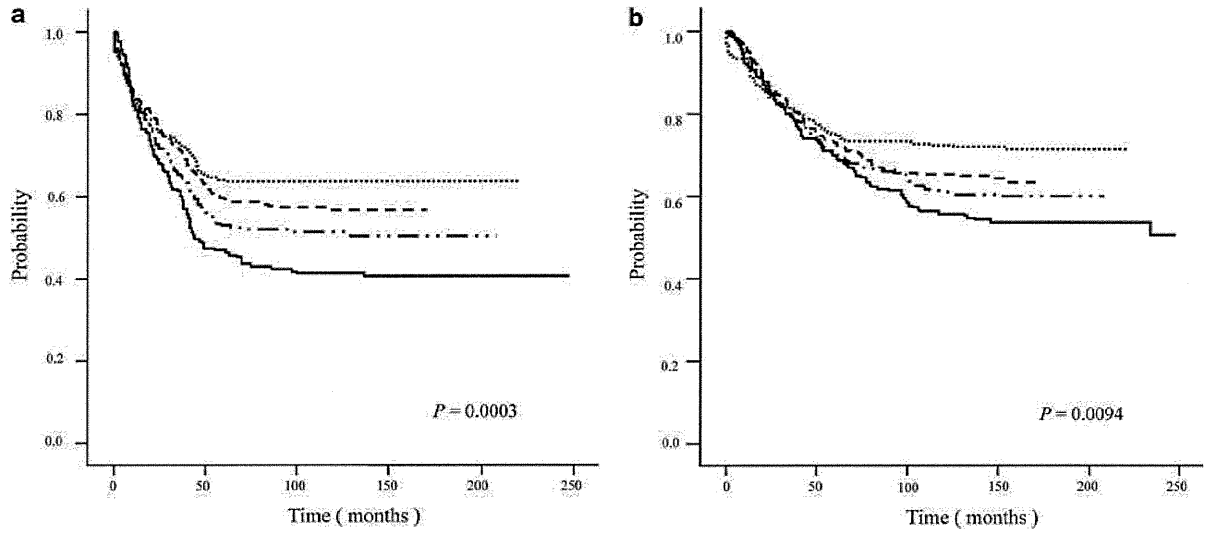

Figure 1 Kaplen–Meier curves for EFS (**a**) and OS (**b**) according to ALL studies ALL811 (——); ALL841 (– · –· ·); ALL874 (- - - -) and ALL911 (· · · ·). ALL, acute lymphoblastic leukemia; EFS, event-free survival; OS, overall survival.

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 ($\times 10^9$/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 ($\times 10^9$/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 × 10^9/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 ($\times 10^9$/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 ($\geqq 100 \times 10^9$/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 (≧100 × 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	25 230	0	0	0	34 125	8100	18	0	0
SR-B	86	0	25 230	0	0	0	50 750	2940	18	0	0
HR-A	60	1200	17 280	0	300	0	22 750	0	6.1	0	0
HR-B	110	7800	20 490	0	540	0	23 325	1500	0	0	0
ALL841											
LR-A	86	0	25 230	0	0	0	34 125	5850	30	0	0
LR/IR-B	86	0	25 230	98	0	0	34 125	5850	30	0	0
IR-C	108	0	16 830	20	540	0	21 875	0	10.5	0	0
HR-A	72	1200	17 430	0	240	0	22 750	0	183	0	0
HR-B	108	7800	14 150	0	460	0	23 100	1320	27	0	0
ALL874											
LR-A	86	0	25 230	20	0	0	34 125	8775	0	0	0
LR-B	86	0	25 230	20	0	0	34 125	8100	6	0	0
IR-A	94	0	15 030	64	420	0	19 250	225	92	0	0
IR-B	88	0	13 680	64	450	0	18 375	0	105.5	0	0
HR-A	84	2400	22 270	38	225	0	31 290	6750	7.5	0	3600
HR-B	84	3600	22 270	38	225	0	26 250	6750	7.5	0	18 000
ALL911											
LR	60	0	17 430	24	0	450	29 250	6900	6	0	0
IR	92	1600	24 370	44	0	450	33 110	7650	0	0	2400
HR	88	2400	23 470	44	225	240	33 425	7200	0	0	3600
HHR	66	2400	16 870	44	225	180	23 415	4725	0	3600	10 800

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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Pediatr Blood Cancer 2010;55:1287–1295

Minimal Residual Disease-Based Augmented Therapy in Childhood Acute Lymphoblastic Leukemia: A Report From The Japanese Childhood Cancer and Leukemia Study Group

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Background. The majority of minimal residual disease (MRD)-positive patients with acute lymphoblastic leukemia (ALL) have poor outcomes. The ALL2000 study was performed to evaluate the efficacy of augmented chemotherapy based on MRD-restratification in childhood ALL. ***Procedure.*** Between 2000 and 2004, 305 eligible patients with precursor B or T-cell ALL were enrolled in the ALL2000 study. The ALL941-based therapy protocol utilized PCR MRD assays using Immunoglobulin and T-cell receptor gene rearrangements. They were initially stratified into three risk-groups according to leukocyte count and age, and MRD levels were measured at weeks 5 (TP1) and 12 (TP2) for a second stratification. From week 14, patients with MRD levels $\geqq 10^{-3}$ received an increase in therapy (one risk group higher), while the remainder continued to receive the initial risk-adapted therapy. ***Results.*** The overall 5-year event-free survival (EFS) rate for ALL2000 was 79.7 ± 2.4%. MRD stratification was feasible for 234 of 301 patients (77%) who achieved complete remission. The EFS rate of the MRD stratifiable (MRD) group was 82.5 ± 2.6%, considerably superior to the 74.7 ± 5.7% of MRD non-stratifiable (Non-MRD) group ($P = 0.084$) and the 74.4 ± 2.1% for ALL 941 ($P = 0.012$). MRD-positive patients at TP2 showed inferior outcomes as compared with MRD-negative cases, but the difference did not reach a statistically significant level in any risk groups or immunophenotypes. ***Conclusions.*** These results suggest that augmented therapy for MRD-positive patients at TP2 contributed to better outcomes of the ALL2000 study. Pediatr Blood Cancer. 2010;55:1287–1295. © 2010 Wiley-Liss, Inc.

Key words: augmented therapy; childhood ALL; minimal residual disease; MRD stratification

INTRODUCTION

Children with acute lymphoblastic leukemia (ALL) are usually treated according to risk-groups defined by both clinical and laboratory features such as leukocyte count and age at the time of diagnosis [1]. Early response measurements by morphological recognition of leukemic cells have shown a consistent feasibility for risk-stratification in childhood ALL [2,3]. However, even patients assigned to good responder groups by morphological definition may have minimal residual disease (MRD) that can only be detected by highly sensitive methods, such as polymerase chain reaction (PCR) or multi-color flow cytometry after induction therapies [4,5]. In recent years, relatively large prospective studies have revealed that children with MRD-negative levels ($<10^{-3}$ or $<10^{-4}$) during an early treatment period (5–12 weeks after the start of therapy) can be expected to demonstrate excellent outcomes, but children with MRD-positive levels are associated with very high relapse rates [4,6–11]. MRD levels, more importantly, retain statistically significant prognostic values independently of other relevant factors in multivariate analyses [4,6]. We retrospectively analyzed the relationship between molecular MRD levels at weeks 4 and 12 of therapy and survival outcomes in the ALL911 study, which showed very poor outcomes in MRD-positive ($\geqq 10^{-3}$) patients across risk groups according to leukocyte count and age [12]. Thus, MRD information is redefining remission status, and a variety of ongoing or planned clinical trials in childhood ALL are aiming to design new treatment strategies based on MRD levels [13–16]. Positive results from such clinical trials may pave the way towards a much higher degree of individualized treatment. This manuscript presents original results from an MRD-based intervention in the treatment of childhood ALL, the ALL2000 clinical trial, which restratified patients according to MRD levels during the early treatment phase and showed that an increase in therapy based on MRD can be effective in high-risk groups but not for non-high-risk patients [17].

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PATIENTS AND METHODS

Study Design and Diagnostic Criteria

The ALL2000 study was a prospective nonrandomized trial that investigated the feasibility and efficacy of augmented chemotherapy in childhood ALL based on PCR-MRD levels 12 weeks after the start of treatment. The primary aim of this study was to improve outcomes of patients enrolled in the ALL2000 study by using augmented therapy (dose-intensified chemotherapy) for MRD-positive patients as compared to those of the previous ALL941 study. Between January 2000 and June 2004, newly diagnosed B-cell precursor ALL (B-ALL) or T-cell ALL (T-ALL) patients aged between 1 and 15 years of age were enrolled in the study, which was conducted across 18 hospitals, all members of the Japanese Childhood Cancer and Leukemia Study Group (JCCLSG). The protocol was approved by each institution's review

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TABLE I. Risk Classification of Acute Lymphoblastic Leukemia at Diagnosis

	Age (years)			
WBC count/μl	1–3	4–5	6–9	≧10
<5,001	SR (LR)	SR (LR)	SR (IR)	HR
5,001–10,000	SR (LR)	SR (IR)	HR	HR
10,001–50,000	SR (IR)	SR (IR)	HR	HR
50,001–100,000	HR	HR	HR	HR
>100,000	HHR	HHR	HHR	HHR

SR, standard-risk; LR, low-risk; IR, intermediate-risk; HR, high-risk; HHR, high-high-risk.

board, and written informed consent was provided by patients or legal guardians before treatment. ALL was diagnosed when ≥25% lymphoblastic cells were present in bone marrow (BM) samples by cytomorphology based on the French-American-British (FAB) criteria and cytochemistry. Flow cytometric immunophenotyping was performed at the central (Aichi Medical University) or local laboratory. Patients with mature B-cell ALL (FAB, L3 morphology) or Philadelphia chromosome positive ALL (Ph+ ALL) were excluded.

Stratification Criteria

Patients were initially stratified, according to leukocyte count and age at the time of diagnosis, into four risk groups: low-risk (LR), intermediate-risk (IR), high-risk (HR), and high-high-risk (HHR) (Table I) [18]. In this study, we defined initial risk groups of LR and IR to be standard-risk (SR), because these patients received identical treatments except for the length of the maintenance therapy as described below. MRD levels in patients that had achieved complete remission were measured at two time points: point 1 (TP1, week 5) and point 2 (TP2, week 12) of therapy. These results were used in a second stratification, and from week 14, patients with MRD levels $\geqq 10^{-3}$ at TP2 received an augmented therapy (of one risk group higher), while the remainder continued to receive the initial risk-adapted therapy.

Treatments

The treatment framework (Fig. 1) of the ALL2000 protocol used chemotherapy schedules (Table II) almost identical to the ALL941 protocol except for the addition of doxorubicin (DOX) to the LR group [19]. Treatment consisted of induction (Ind-1/Ind-2/Ind-3), intensification (Int-1/Int-2/Int-3), reinduction (Re-2/Re-3/Re-4), and maintenance (M-1/M-2/M-3) phases. Induction therapy for the SR and HR groups consisted of vincristine (VCR), prednisolone (PSL), L-asparaginase (LASP, Kyowa, Japan), and DOX. Etoposide (VP16) and cytarabine (Ara-C) were added to the induction regimen of the HHR group. After achieving complete remission, they received intensification therapy which consisted of the alternate use of eight drugs in three blocks at 2-week intervals. HR/HHR patients received reinduction therapy at week 14, followed by intensification including a weekly LASP therapy until week 30. The HHR patients with MRD levels $\geqq 10^{-3}$ at TP2 were assigned to the salvage arm. Maintenance therapy consisted of the cyclic administration of 9 drugs for the early phase (M-1) followed by 5/6 drugs for the late phase (M-2/M-3) starting in week 14 (SR), 30 (HR/HHR), or 40 (salvage) and lasting until week 104 (LR) or 156 (IR, HR, HHR, salvage). In this phase, a tetrahydropyranyl derivative of doxorubicin (pirarubicin, THP) was used because of its lower cardiotoxicity compared with doxorubicin [20,21]. For CNS prophylaxis, SR patients underwent extended intrathecal injections of three drugs (TIT) which started on day 1, and which were repeated every 6 weeks in the first year, every 8 weeks in the second year, and every 12 weeks in the third year. The HR and HHR patients received 18 Gy cranial radiotherapy (CRT) plus six doses of TIT injections until week 22 of therapy.

MRD Quantification

High-molecular weight DNA extracted from heparinized bone marrow cells was initially screened for the major rearrangement patterns of TCRγ TCRδ and Igκ chain genes, and secondarily for Ig heavy chain (IgH) gene rearrangements using previously described primers [12,22]. We performed a two-step (nested) PCR for MRD quantification by ASO-primers based on the sequence of PCR screening products, which had clonal recombinations by

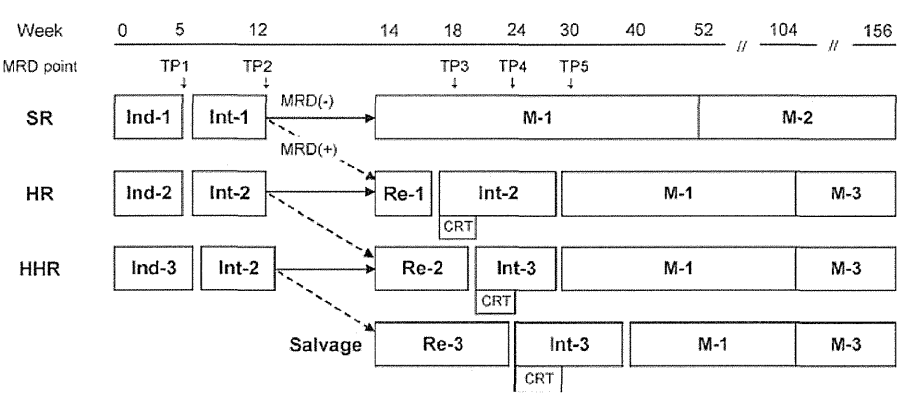

Fig. 1. Treatment framework and MRD stratification of the ALL2000 MRD study. SR, standard-risk; HR, high-risk; HHR, high-high-risk; CRT, cranial radiotherapy. Patients with MRD levels $\geqq 10^{-3}$ at TP2 received augmented therapy of one risk group higher (broken lines), while the remainder continued to receive the initial risk-adapted therapy (solid lines). Time points of MRD cell sampling at TP3, TP4, and TP5 were different by risk groups: SR, weeks 18, 24, 30; HR, weeks 18, 24, 52; HHR, weeks 22, 28, 52. Treatment schedules are shown in Table II.

TABLE II. Drug Dosage and Schedules for ALL2000 Protocols

	Regimen	Daily dose	Administration	Days
Induction phase				
Ind-1 (VPLA)	Vincristine	2 mg/m^2	IV	1, 8, 15, 22
	Prednisolone	60 mg/m^3	Oral	1–28
	L-Asparaginase	2,000 U/m^2	IV	8–26 (3/w)
	Doxorubicin	25 mg/m^3	IV	1
Ind-2 (VPLA′)	Same as in Int-I except for Dox (25 mg/mg^2 × 3 at days 1, 18, 15)			
Ind-3 (VPLA′ + EC)	Etoposide	150 mg/m^2	IV	22, 29, 36
	Cytarabine	300 mg/m^2 × 2	IV	22, 29, 36
Intensification phase				
Int-1	Pirarubicin	20 mg/m^2	IV	1
	Vincristine	2 mg/m^2	IV	1
	Prednisolone	120 mg/m^2	Oral	1–5
	6-Mercaptopurine	250 mg/m^2	Oral	1–5
	Cyclophosphamide	400 mg/m^2	IV	15
	Cytarabine	50 mg/m^2 × 2	IV	15–18
	6-Mercaptopurine	125 mg/m^2	Oral	15–19
	Methotrexate	500 mg/m^2	IV	29
	L-Asparaginase	2,000 U/m^2	IV	30, 31
Int-2	Same as in Int-1 except for LASP (6,000 U/m^2, weekly for 12 weeks)			
Int-3 (Int-2 + EC)	Etoposide	100 mg/m^2	IV	43–45
	Cytarabine	2 g/m^2 × 2	IV	43–47
CNS prophylaxis				
TIT	Methotrexate	12 mg/m^2	IT	
	Cytarabine	30 mg/m^2	IT	
	Hydorocortisone	50 mg/m^2	IT	
Reinduction phase				
Rc-1 (VPLA″)	Vincristine	2 mg/m^2	IV	1, 8, 15, 22
	Prednisolone	60 mg/m^2	Oral	1–28
	L-Asparaginase	2,000 U/m^2	IV	1, 8, 15, 22, 29
	Pirarubicin	25 mg/m^2	IV	8, 15, 22
Rc-2 (VPLA″ + EC)	Etoposide	150 mg/m^2	IV	22, 29, 36
	Cytarabine	300 mg/m^2 × 2	IV	22, 29, 36
Rc-3 (VPL + EC + M)	Etoposide	300 mg/m^2	IV	8, 22, 36
	Cytarabine	300 mg/m^2 × 2	IV	8, 22, 36
	Mitoxantrone	10 mg/m^2	IV	50, 57, 64
Maintenance phase				
M-1 (VPMA-CCM-ML)	Pirarubicin	20 mg/m^2	IV	1
	Vincristine	2 mg/m^2	IV	1
	Prednisolone	120 mg/m^2	Oral	1–5
	6-Morcaptopurine	250 mg/m^2	Oral	1–5
	Cyclophosphamide	400 mg/m^2	IV	15
	Cytarabine	50 mg/m^2 × 2	IV	15–18
	6-Mercaptopurine	125 mg/m^2	Oral	15–19
	Methotrexate	225 mg/m^2	IV	28
	L-Asparaginase	2,000 U/m^2	IV	29
M-2 (VPM-ML)	Vincristine	2 mg/m^2	IV	1
	Prednisolone	120 mg/m^2	Oral	1–5
	6-Mercaptopurine	250 mg/m^2	Oral	1–5
	Methotrexate	225 mg/m^2	IV	14
	L-Asparaginase	2,000 U/m^2	IV	15
M-3 (VPMA-ML)	Same as in M-2 except for pirarubicin (20 mg/m^2 at day 1)			

IV, intravenous; IT, intrathecal.

heteroduplex analyses. DNA extracted from bone marrow samples after treatment was amplified simultaneously with the leukemic DNA extracted at diagnosis and its four serial dilutions (10-fold step, 10^{-2}–10^{-5}), which were done in buffy coat DNA taken from eight healthy volunteers. The buffy coat DNA was also amplified at the same time as the background of the assay, that is the nonspecific amplification of comparable Ig/TCR gene arrangements present in normal cells. The MRD was quantified by comparing the intensities of band-signals on an agarose gel stained with ethidium bromide without amplification of the background.

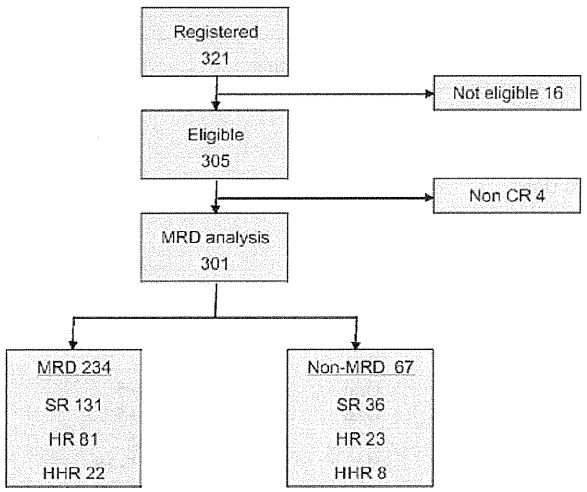

Fig. 2. Patient flow chart. CR, complete remission; MRD, MRD stratifiable group; Non-MRD, MRD nonstratifiable group; SR, standard-risk; HR, high-risk; HHR, high-high-risk, Each number shows the number of patients.

Statistical Analysis

Final statistical analyses were performed based on data obtained in June 2008. Overall survival (OS) was defined as the time between 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 second malignant neoplasm. For patients who did not experience an event, EFS was defined as the time to the last follow-up. The patients who had undergone hematopoietic stem cell transplantation (HSCT) during first remission were defined as a major protocol violation and excluded from analyses of events and outcomes. Survival curves were prepared using the Kaplan–Meier life table method, and the significance of differences in survival outcomes was determined by means of the log-rank test. Characteristics of patients across the MRD stratifiable group and the MRD nonstratifiable group were compared using the Mann–Whitney–Wilcoxon *U*-test for values of age and leukocyte count at the time of diagnosis or Fisher's exact test for distributions of sex, immunophenotype, initial risk, and chromosomal abnormalities. SPSS statistical analysis software (SPSS 12.0J, Japan Inc., Tokyo, Japan) was used for all computations.

RESULTS

Patient Characteristics

From January 2000 to June 2004, a total of 321 children were enrolled in the ALL2000 MRD study, and 305 children with B-ALL or T-ALL were evaluable in this study. Ages ranged from 1 to 15.8 years of age with a median of 5.3. There were 172 males and 133 females, for a sex ratio of 1.29:1. Immunophenotypes of blast cells were B-ALL in 275 (precursor B in 267 and not specified stage in 8) and T-ALL in 30. For the first stratification, patients were assigned to one of four risk groups according to leukocyte count and age as follows: 167 in SR (94 in LR and 73 in IR), 105 in HR, and 33 in HHR. Four patients (1 HR, 3 HHR) failed to achieve complete remission (Fig. 2).

MRD Measurements

In 234 (78%) of 301 patients who achieved CR, at least one target was detected: TCRγ, TCRδ, Igκ, and IgH rearrangements were found in 64, 61, 50, and 59 patients respectively. Among the remaining 67 patients, 32 had no clonal Ig/TCR targets, and 35 had insufficient DNA. In this study, we defined the 234 MRD stratifiable patients as the MRD group, and the 67 MRD nonstratifiable patients as the non-MRD group (Fig. 2). At TP2, MRD-negative ($<10^{-3}$) patients numbered 193 (82.5%) and MRD-positive patients numbered 41 (17.5%). The percentages of MRD-positive cases by initial risk group and immunophenotype were 19.8% (26/131) in SR, 8.6% (7/81) in HR, 36.3% (8/22) in HHR, and 16.5% (35/211) in B-ALL and 30% (6/20) in T-ALL. Thus, the frequency of MRD-positive cases in the SR group was unexpectedly high, and that of T-ALL was about two times higher than for B-ALL. Of MRD-positive patients at TP2, two refused to receive an augmented therapy, and the other two refused cranial irradiation for CNS prophylaxis. The aforementioned patients were included in the MRD group for statistical analyses.

Events

All events except for induction failure are shown in Table III. Eleven patients who had undergone HSCT during first remission were removed from the table. Among the remaining 290 patients, there were 52 relapses and 4 deaths. Relapse sites were BM (42), BM and CNS (3), BM, CNS, and testis (1), isolated CNS (2), testis (1), others (3). The deaths were due to asthma attack (1), cardiac insufficiency (1), and septic infections (2). A 7-year-old female in the HR group developed acute myeloid leukemia with mixed lineage leukemia gene rearrangements during a maintenance therapy,

TABLE III. Summary of Events and Outcomes of the Various Subgroups for 290 Patients

Risk group	SR	HR	HHR	Total
MRD group				
No. of patients	131	80	18	229
MRD^- at TP2	105	74	13	192
Relapse	17	10	3	30
Death	0	1	0	1
Second cancer	0	1	0	1
MRD^+ at TP2	26	6	5	37
Relapse	6	1	1	8
Death	0	0	1	1
5y-EFS MRD^-	86.2 ± 3.4	83.2 ± 4.4	74.1 ± 13.0	84.3 ± 2.7
5y-EFS MRD^+	73.6 ± 9.2	83.3 ± 15.2	60.0 ± 21.9	70.3 ± 7.5
P^a	0.204	0.779	0.641	0.047
Non-MRD group				
No. of patients	35	20	6	61
Relapse	5	8	1	14
Death	0	0	2	2

SR, standard-risk; HR, high-risk; HHR, high-high-risk; EFS, event-free survival. [a]*P*-value was calculated for the difference in survival rates between MRD^- and MRD^+. Four cases who did not achieve complete remission and 11 cases who had undergone hematopoietic stem cell transplantation during first remission were removed from analyses.

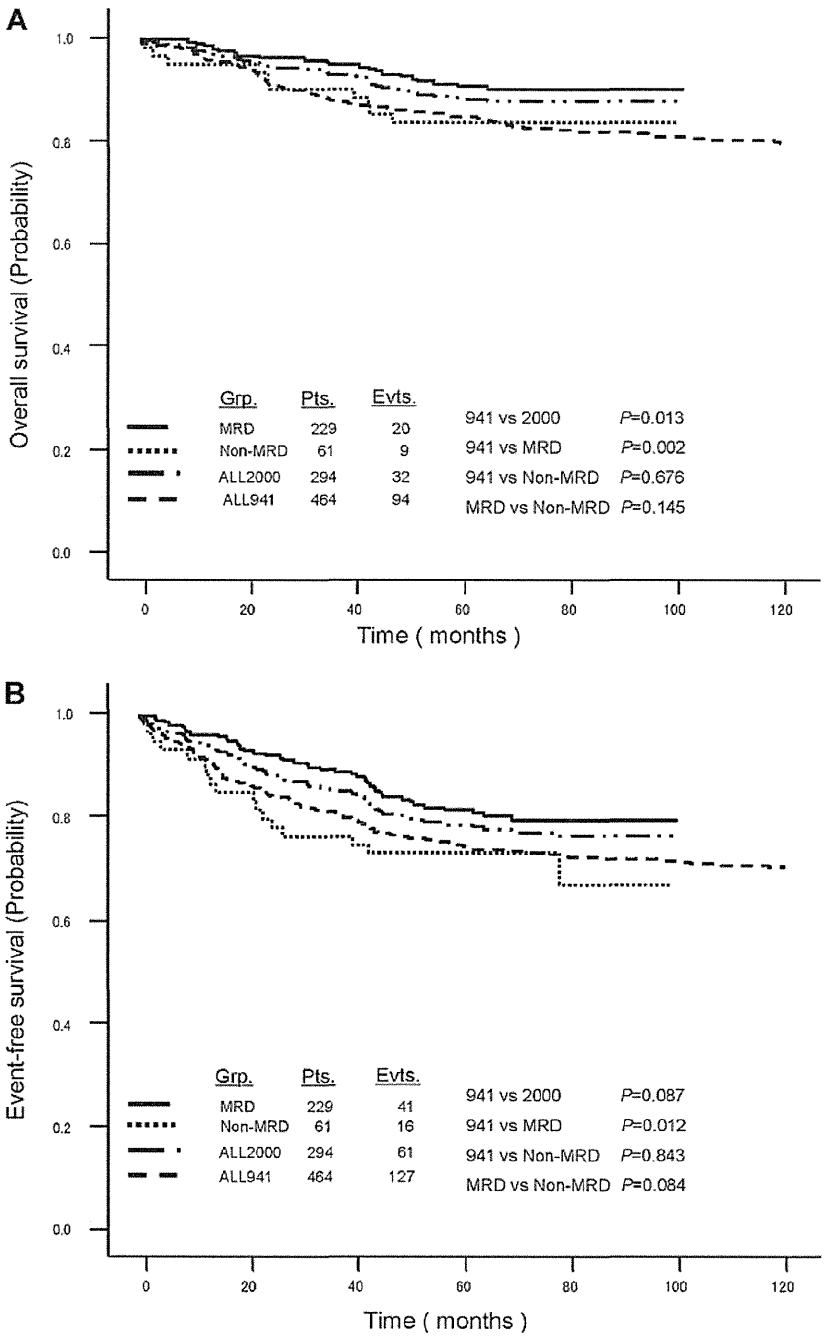

Fig. 3. Kaplan–Meier curves for overall survival (**A**) and event-free survival (**B**) in ALL941 and ALL2000. MRD, MRD stratifiable group in ALL2000; Non-MRD, MRD nonstratifiable group in ALL2000; Grp, group; Pts, patients; Evts, events.

22 months after the start of treatment. Since her MRD level was negative at TP2, she had no history of receiving augmented therapy including etoposide.

Survival Outcomes

The median follow-up time for survival was 67 months with a range of 45–101 months. The survival curves for the ALL2000 and ALL941 studies are shown in Fig. 3A,B. The 5-year OS and EFS rates for ALL2000 were 89.2 ± 1.8% and 79.7 ± 2.4%. When we analyzed the rates by feasibility of MRD stratification, the OS and EFS rates were 91.4 ± 1.9% and 82.5 ± 2.6% for the MRD group, and 85.3 ± 4.5% and 74.7 ± 5.7% for the non-MRD group; EFS for the MRD group was significantly superior to the rate of 74.4 ± 2.1% for ALL941, but that for the non-MRD group was almost identical to ALL941.

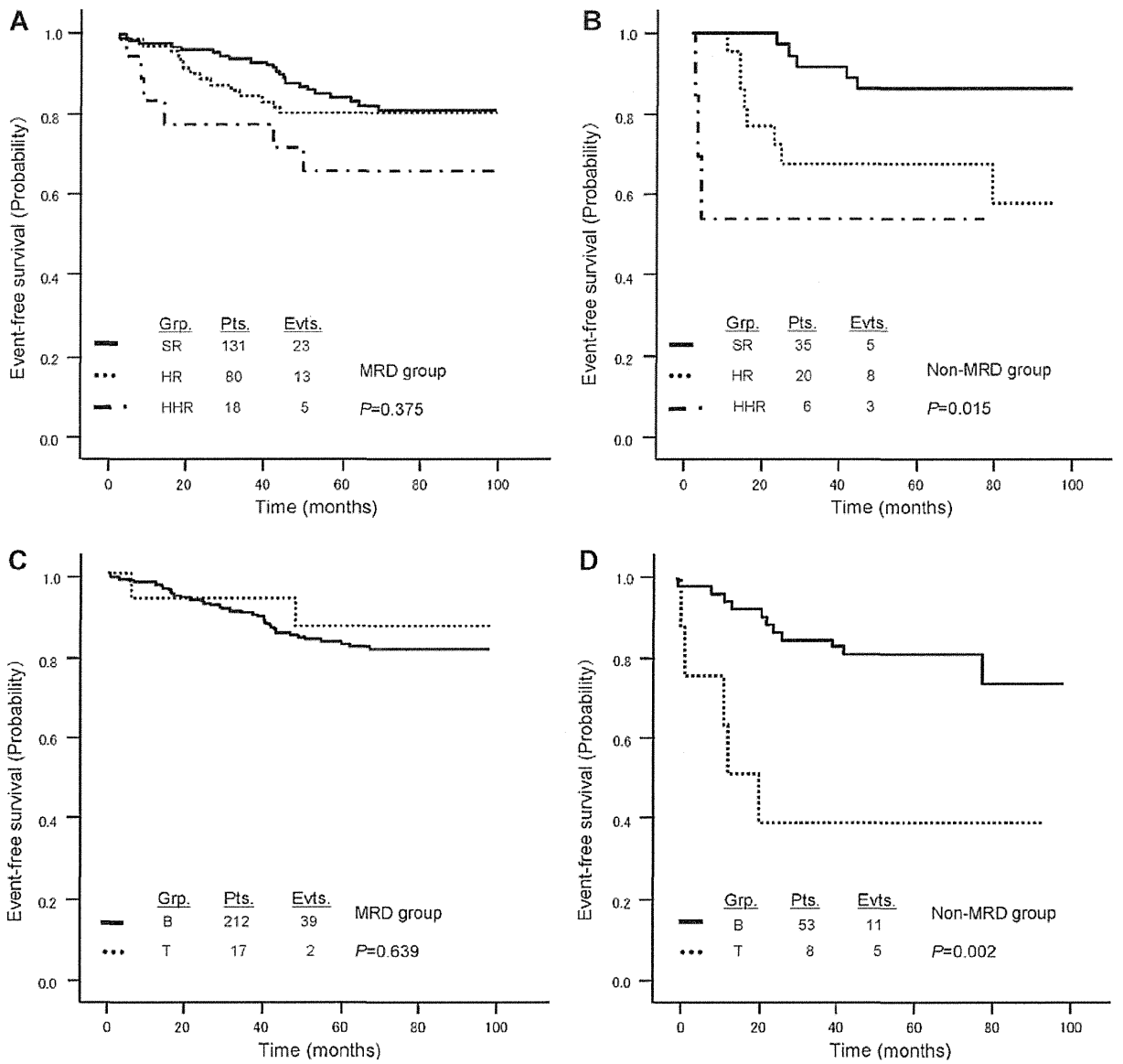

Fig. 4. Kaplan–Meier curves for event-free survival in ALL2000. SR, standard-risk; HR, high-risk; HHR, high-high-risk; B, B-ALL; T, T-ALL; Grp, group; Pts, patients; Evts, events. There was no significant difference for either risk group (**A**), or immunophnetype (**C**) in MRD (MRD stratifiable) group. On the other hand, significant difference was observed for both risk group (**B**), and immunophenotype (**D**) in Non-MRD (MRD nonstratifiable) group.

Further analysis of the survival rates according to initial risk group or immunophenotype across the MRD and non-MRD groups showed a considerable difference. In the MRD group, there was no significant difference for either risk group (Fig. 4A), or immunophenotype (Fig. 4C). On the other hand, in the non-MRD group, a significant difference was observed for both risk group (Fig. 4B), and immunophenotype (Fig. 4D).

In addition, we compared survival outcomes of the initial risk groups by MRD positivity at TP2 (Table III). As expected, MRD-negative cases showed higher EFS rates than MRD-positive cases, but the individual group differences did not reach statistically significant levels. Similar findings on the survival rates between the MRD-negative and MRD-positive cases were observed in the immunophenotypic groups: 84.4% ± 2.8% (MRD^-, n = 179) versus 69.9% ± 8.4% (MRD^+, n = 33) in B-ALL ($P = 0.068$); 82.5% ± 11.3% (MRD^-, n = 13) versus 100% (MRD^+, n = 4) in T-ALL ($P = 0.458$).

MRD and Non-MRD Groups

Since patients in the non-MRD group were not a control for the MRD group, we compared relapse outcomes and various features of cases between both groups. As shown in Table IV, there were no significant differences in either patients' characteristics or cumulative

TABLE IV. Treatment Outcome and Characteristic of Patients Between the MRD and Non-MRD Groups for 301 Patients

	MRD	Non-MRD	*P*-Value
No. of patients	234	67	
Age (years)			
Median	5.0	5.0	0.133
Range	1.0–15.3	1.2–15.8	
Sex			
Male	132	37	0.890
Female	102	30	
Immunophenotype			
B	214	58	0.243
T	20	9	
WBC count (/μl)			
Median	29,700	61,500	0.586
Range	300–552,430	600–454,000	
Initial risk			
SR	131	36	0.825
HR	81	23	
HHR	22	8	
Chromosome findings			
Successful	176	42	
Hyperdiploid (>50)	33 (18.7%)	6 (14.3%)	0.655
SR	28/98 (28.6%)	5/18 (27.7%)	n.d.
HR	5/60 (8.3%)	1/19 (5.2%)	n.d.
HHR	0/18 (0%)	0/5 (0%)	n.d.
Hypodiploid (<45)	1	0	n.d.
t(4;11)	0	1 (HHR)	n.d.
t(1;19)	2 (HR/HHR)	1 (HR)	n.d.
t(12;21)	1 (SR)	0	n.d.
5-year EFS ± SE (%)	82.5 ± 2.6	74.7 ± 5.7	0.085
5-year cumulative risk of BM relapse ± SE (%)	13.4 ± 2.4	21.3 ± 5.8	0.123
5-year cumulative risk of BM + CNS relapse ± SE (%)	1.5 ± 0.1	0	0.394
5-year cumulative risk of isolated CNS relapse ± SE (%)	0.9 ± 0.1	0	0.479

n.d., not done; EFS, event-free survival; BM, bone marrow; CNS, central nervous system. Survival outcomes were analyzed on the 290 patients except 11 cases who had undergone hematopoietic stem cell transplantation dining first remission.

risk by relapse site across the two groups. For genetic factors, our study looked only at chromosome ploidy and three translocations of t(4;11), t(1;19), and t(12;21), and these appeared to have no impact on the outcome.

TEL/AML1 gene rearrangements were not mandatory due to the high cost of the study.

MRD Monitoring

In 94 patients, MRD levels were monitored through 5 follow-up time points, and results of 92 patients (having excluded 2 cases who had undergone HSCT in first remission) are shown in Table V. At TP2, there were 73 MRD-negative and 19 MRD-positive patients. A considerable change of MRD positivity after TP2 was observed in the MRD-positive group: At TP5, MRD became negative in 13, and MRD was still positive in 6, while their relapse rates were 7.7% and 66.6% respectively.

Toxicity

Although data were only available for 74% of patients in ALL2000, MRD-negative patients (n = 193) and MRD-positive patients (n = 29) showed similar toxicity profiles during treatment:

TABLE V. MRD Levels and Relapses in 92 Patients

Time points		TP5	
Group	TP2	MRD$^-$	MRD$^+$
MRD-negative	73	72	1
relapse		13 (18.1%)[a]	0
MRD-positive	19	13	6
relapse		1 (7.7%)[a]	4 (66.6%)[a]
Total	92	85	7

[a]Percentages were calculated based on population at TP5.

The percentages of the three major toxicities (infection, hepatotoxicity, and pancreatitis) with grade 3 (4) (National Cancer Institute-Common Toxicity Criteria) were 55% (6%), 45% (1%), and 4% (2%), respectively, for MRD-negative, and 48% (13%), 38% (0%), and 7% (0%), respectively, for MRD-positive cases. For severe late adverse effects, 1 second cancer was reported as described above, but with no cardiotoxicity.

Total cumulative doses of chemotherapy drugs according to MRD level in the three risk groups are given in Table VI. This shows that everyone except MRD-negative SR patients received high cumulative doses (405–715 mg/m^2) of anthracycline, espe-

TABLE VI. Total Cumulative Doses of Chemotherapy Drugs According to MRD Level in the Three Risk Groups in ALL2000

Risk group/MRD[a]	PSL (g)	6MP (g)	LASP (ku)	Ara-C (g)	DOX (mg)	THP (mg)	MIT (mg)	VP16 (mg)	CPM (g)	IT (doses)
SR (LR/IR)										
MRD$^-$	(15.0/22.8)	(32.5/48.8)	(6.8/9.4)	3.2	25	160	—	—	3.2	16/20
MRD$^+$	(13.2/21.0)	(30.0/46.3)	13.4	6.4	25	(380/640)	—	—	6.4	6
HR										
MRD$^-$	21.0	46.2	18.8	6.4	75	640	—	—	6.4	6
MRD$^+$	21.7	45.6	19.2	26.9	75	640	—	750	6.0	6
HHR										
MRD$^-$	20.4	46.3	19.4	27.8	75	640	—	1,200	6.4	6
MRD$^+$	21.1	42.5	21.6	27.4	75	540	30	1.650	5.6	9

SR, standard-risk; LR, low-risk: IR, intermadiate-risk; HR, high-risk; HHR, high-high-risk; PSI, prednisolone; 6MP, 6-mercaptopurine; LASP, L-asparaginase; Ara-C, cytarabine; DOX, doxorubicin; THP, pirarubicin; MIT, mitoxantrone; VP16, etoposide; CPM, cyclophosphamide; IT, intrathecal therapy. All drug doses were shown per square meter of body surface area. [a]MRD$^-$ patients at TP2 received the initial risk-directed therapy and MRD$^+$ cases received an augmented therapy (of one-risk group higher).

cially pirarubicin (THP). In addition, dose intensities of treatments for MRD-positive and MRD-negative patients were considerably different by risk group. In the SR group, doses of four drugs (LASP, Ara-C, THP, and CPM) were about two times higher for MRD-positive cases than MRD-negative cases. In the HR group, high-dose Ara-C and etoposide were newly employed for MRD-positive cases, but the doses of other drugs were little different from those for MRD-negative cases.

DISCUSSION

In the present study, 41 out of 234 (17.5%) patients received augmented therapy based on MRD levels at TP2, and the most valuable finding was observed for this group: patients with higher MRD levels $\geqq 10^{-3}$ at TP2 achieved a favorable outcome, with EFS rates of 60–80%, which were apparently superior to those of MRD-positive patients (i.e., MRD high-risk in the MRD category) reported by previous studies [4,6–11]. In addition, comparisons between the MRD group (who were restratified according to MRD level at TP2) and the non-MRD group (who continued to receive the initial risk-adapted therapy) on their survival rates, combined with the similar toxicity profiles of MRD-positive and MRD-negative patients, suggest that treatment intervention based on MRD level at week 12 of therapy may have contributed to better outcomes for the MRD group, with no increase in toxicity.

To confirm that the characteristics of patients between the MRD and the non-MRD groups was indeed identical, we compared clinical and biological features between the two groups. We found that there was no significant difference in any characteristics although data for cytogenetic abnormalities were limited.

To clarify how the augmented therapy contributed to favorable outcomes of MRD-positive patients, we studied the relationship between MRD levels after TP2 and relapse outcomes. The results of MRD monitoring suggest that the effectiveness of augmented therapy for MRD-positive cases is closely associated with the change of MRD levels to $<10^{-3}$ after TP2.

Contrary to expectation, the proportion (19.8%) of MRD-positive SR patients at TP2 was high compared with the 8.6% of HR patients in ALL2000 or the 8% of MRD-high risk patients ($\geqq 10^{-3}$) in the International Berlin-Frankfurt-Muenster (I-BFM) MRD studies [15]. These findings may be explained by the low intensity therapy provided to SR patients during the first 12 weeks in the ALL2000 protocol. Indeed, the total doses of cytotoxic drugs used in the early treatment phase (*Ind-1* + *Int-1*) for SR group are much smaller compared with the induction phase (*Protocol Ia* + *Ib*) in BFM2000 (anthracycline: 45 mg/m^2 vs. 120 mg/m^2; cyclophosphamide: 400 mg/m^2 vs. 2,000 mg/m^2).

Interestingly, improved outcomes by augmented therapy were evident exclusively in HR/HHR or T-cell, but not SR or B-cell patients. The reason for the absence of any benefit from intensive therapy in MRD-positive SR patients might be related to the high intensity of maintenance therapy for the SR group: The maintenance therapy with cyclic administration of five to nine drugs is more intensive when compared with a standard maintenance therapy of oral methotrexate and 6-mercaptopurine [23]. Furthermore, large prospective studies have shown that intensification by antimetabolites failed to show additive effects on outcomes of non high-risk or B-lineage ALL [24–26], and a German group has achieved favorable outcomes for standard-risk ALL with reduced intensities of treatment [24,27]. Additionally, improved outcomes of MRD-positive patients in the HR/HHR group suggest the effectiveness for such patients of newly incorporated drugs (high-dose Ara-C and etoposide), especially because the dose intensity of other drugs did not vary. This finding is in line with the recent report by Seibel et al. [28], who suggested that effectiveness of post-induction therapy for high-risk patients depended on intensity rather than duration.

We also showed that outcomes of MRD-positive T-ALL patients were strikingly improved, reaching comparable levels with MRD-negative T-ALL cases. Although the number of patients is small, this finding is promising when compared with that of Willemese et al. [9], who showed that survival outcomes of MRD-positive T-ALL at TP2 were very disappointing, and it suggests that the augmented therapy for MRD-positive patients is effective for T-ALL.

It should be noted that we did not use MRD levels to identify a potentially low-risk MRD group that could receive reduced therapy because of the low sensitivity of MRD measurements in our study [4,9]. This matter remains to be resolved by ongoing trials using a more quantitative real-time (RQ) PCR method [15,16,29].

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Original Article

Survey of childhood cancer survivors who stopped follow-up physician visits

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Abstract ***Background***: Childhood cancer cure rates have increased remarkably; however, survivors face an increased risk of morbidity and mortality. Survivors may benefit from anticipatory guidance and periodic surveillance to minimize morbidity and mortality.

Methods: Subjects included 114 5-year survivors of childhood cancer who were diagnosed and treated in three hospitals in Nagoya between 1975 and 2001 and who stopped follow-up physician visits during the preceding 2 years. We conducted a survey of their socioeconomic status, knowledge about their diagnosis and late effects of treatment received, and current hospital attendance patterns.

Results: Eighty-eight of 114 subjects replied. Sixty-six survivors knew about their disease, but only 26 knew about possible late effects of cancer treatment. Although 78 respondents indicated they were healthy and had no trouble in their daily lives, 46 had at least one chronic condition. In response to the question regarding why they did not visit the hospital regularly, many subjects responded that the physician-in-charge told them they did not need to visit the hospital anymore; others thought it was unnecessary to consult a physician because they were in good health.

Conclusions: Some cancer survivors who stop follow-up physician visits may still be suffering from cancer-related illnesses. Both survivor-related and physician-related barriers contribute to cancer survivors stopping follow-up physician visits. To ensure that survivors undergo appropriate follow-up visits, it is necessary to educate survivors, their families, and medical staff about the late effects of cancer and its treatment and the importance of long-term follow up.

Key words childhood cancer, clinic attendance, late effects, long-term follow up, survivors.

Childhood cancer cure rates have increased remarkably over the past three decades, with overall 5-year survival rates now approximately 80%.[1] However, a large number of survivors are suffering from the long-term health consequences of treatments for childhood cancer and are at risk of mortality.[2] Survivors may benefit from anticipatory guidance and periodic surveillance to minimize morbidity and mortality. In Japan, few childhood cancer survivors receive risk-oriented follow-up care, and many survivors do not continue to consult with a physician who has been educated about the potential late effects of cancer or its treatment.

We conducted a survey of current health status, socioeconomic status, and hospital attendance patterns of childhood cancer survivors who stopped follow-up physician visits. The purpose of this study was to analyze factors that influence hospital attendance among childhood cancer survivors who stop follow-up physician visits and to contribute to developing a long-term follow-up system for cancer survivors in Japan.

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Methods

The subjects of this study were 5-year survivors of childhood cancer who stopped follow-up physician visits during the preceding 2 years The selection procedure for subjects was as follows: a total of 964 children younger than 16 years were diagnosed and treated for childhood cancer at Nagoya University Hospital, Japanese Red Cross Nagoya First Hospital, and Nagoya Medical Center between 1975 and 2001. We reviewed the medical records of these patients for data on patient gender, age at diagnosis, diagnosis, year and month of diagnosis, last physician visit and late effects diagnosed until the last visit. Of the 964 patients, we confirmed that 687 were alive with follow-up physician visits at the time of 5 years from diagnosis; of these 687 patients, 46 died after 5 years from diagnosis, 245 continue follow-up physician visits, and 396 stopped follow-up physician visits during the preceding 2 years as of 1 October 2006. We excluded 102 patients because we could not identify their guardians' name or address (51 patients), they had maintained contact with their

physician-in-charge via personal letters (38 patients), or they were thought to be inappropriate candidates for this survey (13 patients: nine with Down syndrome and four whose guardians indicated that they did not want to visit the hospital any more). Finally, 294 subjects who were 5-year cancer survivors were candidates for this study.

As previously described,[3] we conducted a two-step preliminary survey using a postal questionnaire in order to avoid accidental disclosure of their diseases because some survivors may have been without notice of their disease. The outline of the entire investigation is shown in Figure 1. First, we sent a questionnaire to the 294 guardians to ask whether they agreed to have further contact; 144 guardians and six survivors agreed. Second, we asked 144 guardians about the current health condition of their child, whether they told their child about their disease, whether they would be willing to cooperate in the third main survey, and whether they would agree to send a questionnaire directly to their child. Six survivors that responded in the first preliminary survey and 108 guardians agreed to the third main survey, in which 68 guardians agreed to access survivors directly. As a result, 114 subjects, including 74 survivors and 40 guardians, agreed to the third main survey, and are the topic of this report. In Table 1, the clinical characteristics of 114 subjects for the third main survey are shown compared with that of 282 non-participants who stopped follow-up physician visits during the preceding 2 years.

Eighty of 114 subjects (70.2%) were affected by hematological malignancies and 32 (28.1%) underwent hematopoietic stem cell transplantation. The median age at the survey of the 114 subjects was 24 years (range, 9–37 years), and among them, 85 survivors (74.6%) were aged 20 or older. Thus, we sent a questionnaire to 74 childhood cancer survivors and 40 guardians. Among the 40 guardians, 16 had children younger than 16 years old at the time of the study, and 24 did not agree to contact a child aged 16 years or older but were willing to complete the survey themselves.

The questionnaire was divided into six sections (Table 2): (1) socioeconomic background; (2) whether survivors had received any explanation about their disease; (3) whether survivors had received any explanation about the late effects of cancer treatment; (4) present health condition; (5) late effects and chronic health conditions; and (6) current hospital attendance.

This study was approved by the institutional review board of the National Hospital Organization Nagoya Medical Center. Response to the questionnaire was presumed to represent consent to participate in the survey.

Statistical analysis was as follows. The Student's *t*-test was used to calculate differences between 114 subjects who agreed to the third main survey and 282 non-participants, and between 88 respondents and 26 non-respondents in age at study, and time from diagnosis. The χ^2-test was used to calculate differences in gender, diagnosis between the aforesaid groups and the rate of response between survivors and guardians. Results were considered significant at the $P < 0.05$ level.

Results

Eighty-eight (77.2%) of 114 subjects responded, including 58 (78.4%) of 74 survivors and 30 (75.0%) of 40 guardians. Forty-three of 88 respondents were male. There were no significant differences in response rates between survivors and guardians. Of the 114 subjects and 88 respondents, the median age of survivors at the time of the study was 24 years (range 9–37 years), and median time from diagnosis was 17 years (range 8–29 years). Of the 26 non-respondents, 14 were male, the median age was 26 years (range 12–34 years), and median time from diagnosis was 18 years (range 10–25 years). As shown in Table 1, there were significant differences in the proportions of survivors diagnosed as having acute lymphoblastic leukemia ($P = 0.0245$) and Wilms's tumor ($P = 0.0304$) in 114 subjects who agreed to the third main survey and 282 non-participants who stopped follow-up physician visits during the preceding 2 years. There was a difference in the time from diagnosis between 114 subjects (mean 17.3 ± 5.2 years) and 282 non-participants (mean 18.9 ± 5.9 years) ($P = 0.0141$). There were no significant differences in gender, age at study, survival time or cancer diagnosis between respondents and non-respondents.

Socioeconomic status

Data regarding socioeconomic status were received from 67 survivors aged 20 years or older. At the time of study, three survivors had finished graduate school, 30 had graduated from college or junior college, 10 had finished vocational school, seven were college students, one was studying at vocational school, 14 had finished high school, and one had left high school. One survivor did not respond to the question regarding academic background.

Of the 67 survivors, 14 were married and two were engaged at the time of study. Ages ranged from 27 to 36 years for six men and 28 to 36 years for eight women. The primary diseases of married survivors were as follows: acute lymphoblastic leukemia, eight; acute myeloid leukemia, two; and Hodgkin's disease, Wilms's tumor, germ cell tumor, and liposarcoma, one each. Two of these survivors (both female) received hematopoietic stem cell transplantation. In terms of work, among the 67 survivors, 41 worked full-time, eight worked part-time, 10 were students, four were housewives, and four were unemployed.

In terms of economic dependence, 10 of 67 survivors were excluded because they were students at the time of the study. Among the remaining 57 survivors, 37 were economically independent of their parents, 13 were partially supported by their parents, and five depended on their parents completely. Two survivors did not respond to this question.

Explanation about their disease

Forty-five (77.6%) of 58 survivors aged 16 or older had been told about their disease and 11 (19.0%) had not. One said that he could not remember whether he had heard about his disease. One survivor did not respond to this question. Among the guardians, 21 (70%) of 30 guardians had told their children about the disease. Three survivors, aged 16 or older, who had not been told about their disease learned the truth themselves and one saw his disease listed in his medical chart by chance. Two guardians who had not told their children about their disease believed that their children's disease was a past event. Another three reported that

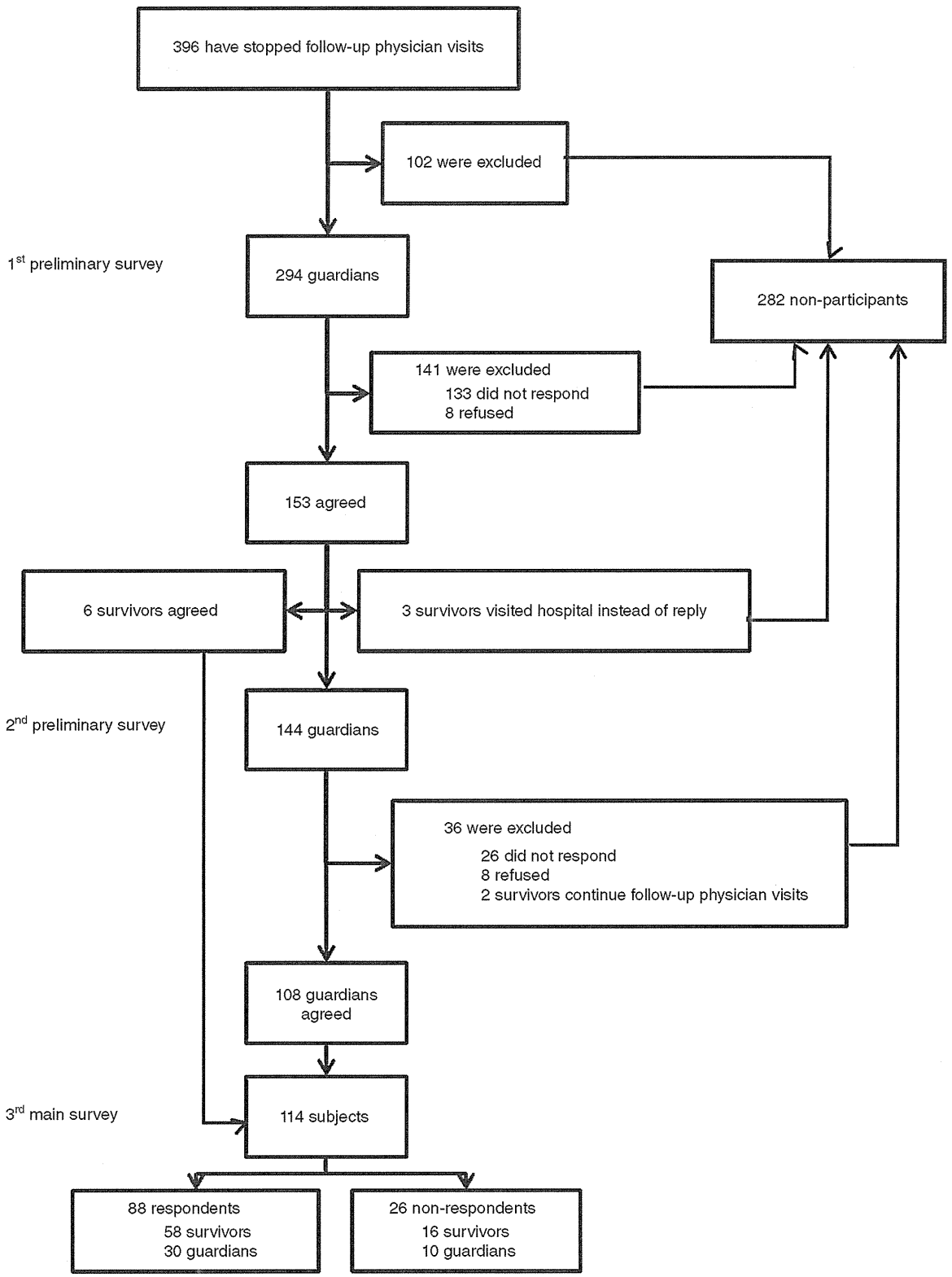

Fig. 1 Schematic representation of the studies done.

Table 1 Patient characteristics

	Non-attendants ($n = 396$)	Subjects ($n = 114$)	Respondents ($n = 88$)	Non-respondents ($n = 26$)	Non-participants ($n = 282$)
Gender (Male / Female)	205/191	57/57	43 /45	14/12	148/134
Age (median)	7–41(25)	9–37(24)	9–37(24)	12–34(26)	7–41(25)
Time from diagnosis (years) (median)	7–32(18)	8–29(17)	8–29(17)	10–25(18)	7–32(19)
Diagnosis					
ALL/AUL	188	44	36	8	144
AML	44	14	12	2	30
Lymphoma	59	20	12	8	39
CML	2	2	2	0	0
Neuroblastoma	29	9	8	1	20
Wilms's tumor	14	8	7	1	6
Germ cell tumor	12	5	5	0	7
LCH	12	3	1	2	9
Bone tumor	8	3	1	2	5
Hepatic tumor	5	2	2	0	3
Other	23	4	2	2	19

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AUL, acute unclassified leukemia; CML, chronic myelogenous leukemia; LCH, Langerhans cell histiocytosis.

they had had no opportunity to tell the truth. Three guardians worried whether they should tell their children about their disease.

Explanation about late effects of cancer treatment

A total of 18 (31.0%) of 58 survivors had received an explanation about possible late effects of cancer treatment; only eight (26.7%) of 30 guardians explained the possible late effects to their children. Guardians who did not share information on possible late effects of cancer treatment indicated that they did not share this information because they did not want their children to worry.

Table 2 Contents of questionnaire

1. Socioeconomic status
   What is your current academic background?
   Are you married?
   What is your occupation?
   What is your work situation?
   Full-time, part-time, housewife, unemployed, unable to work, other
   What is your economic base?
   Fend for yourself, economic assistance from parents, depend on your parents
2. Explanation about their disease
   Have you ever received any explanation about your disease?
3. Explanation about late effects of cancer treatment
   Have the possible late effects of your cancer treatment ever been explained to you?
4. Present health condition
   What is your present health condition?
   Are you able to actively participate in the community and have good relationships with families, friends, and coworkers?
5. Late effects and chronic health conditions
   What, if any, late effects have been diagnosed thus far?
6. Current hospital attendance
   Have you undergone regular health checkups besides school or office medical examinations?
   Is there a medical institution that you visit regularly?
   If yes, why do you visit the clinic?
   If no, why don't you regularly consult a physician?
   What do you think of regular consultations in the future?
   If you would consult a physician regularly, what kind of medical institution do you prefer?

Present health condition

Seventy-eight (88.6%) of 88 respondents answered that they were healthy and had no trouble in their daily lives. Eighty-five (96.6%) responded that they could actively participate in the community and have good relationships with families, friends and coworkers.

Late effects and chronic health conditions

Late effects of cancer treatment and chronic health conditions are shown in Table 3.

Among 88 respondents, 46 (52.3%) reported having at least one chronic condition. Three (3.4%) survivors reported suffering from serious conditions such as having received valve replacement or renal transplantation.

Current hospital attendance

Thirty-one (35.2%) of 88 respondents attend a hospital regularly; 56 (63.6%) do not consult any physician regularly. One

Table 3 Late effects and chronic health conditions

Late effects and chronic health conditions	Number of respondents
Gonadal dysfunction	10
Short stature	6
Hepatitis type C	6
Alopecia	4
Thyroid dysfunction	4
Osteoporosis	4
Abnormal development of permanent teeth	2
Renal dysfunction	2
Heart failure	1
Blindness	1
Defective hearing	1