Table 6. Effect of induction therapy on the outcomes by post-remission therapies

	5-year OS		5-year RFS	
Consolidation arm	IDR group	DNR group	IDR group	DNR group
Conventional standard-dose	57%	56%	41%	37%
	P=0.759		*P*=0.332	
High-dose Ara-C	58%	58%	42%	44%
	P=0.725		*P*=0.658	
Allogeneic SCT in 1st CR	59%	59%	578%	64%
	P=0.469		*P*=0.394	

Number of patients in the conventional standard-dose arm was 196 in the IDR group and 196 in the DNR group; in the high-dose Ara-C arm 196 and 193, respectively; and in the SCT group 67 and 69, respectively, as listed in Figure 1.

Figure legends

Fig. 1 CONSORT diagram
IDR, idarubicin; DNR, daunorubicin.

Fig. 2a Overall survival
Predicted 5-year OS was 48% for the IDR group (n=532) (red line) and 48% for the DNR group (n=525) (blue line) ($P = 0.54$).

Fig. 2b Relapse-free survival
Predicted 5-year RFS was 41% for the IDR group (n=416) (red line) and 41% for the DNR group (n= 407) (blue line) ($P = 0.97$).

Fig. 3 Hematological recovery

a) Day of recovery from neutropenia after the first induction course
Neutropenia was defined as neutrophil count less than 1.0×10^9/L.
Median duration until recovery was 28 days for the IDR group (red line) and 27 days for the DNR group (blue line) ($P = 0.0011$).

b) Day of recovery from thrombocytopenia after the first induction course
Thrombocytopenia was defined as platelet count less than 100×10^9/L.
Median duration until recovery was 25 days for the IDR group (red line) and 24 days for the DNR group (blue line) ($P = 0.0034$).

Fig. 4 Overall survival of CR patients randomized to receive consolidation therapy in IDR group (a) and DNR group (b).
In IDR group predicted 5-year OS was 58% for the high-dose Ara-C arm (n=196) (red line) and 57% for the conventional standard-dose arm (n=196) (blue line) (P = 0.79). In DNR group predicted 5-year OS was 58% for the high-dose Ara-C arm (n=193) (red line) and 56% for the conventional standard-dose arm (n=196) (blue line) (P = 0.71).
HD-AC arm: high-dose Ara-C arm, Non-HD arm: conventional standard-dose arm

Figure 1

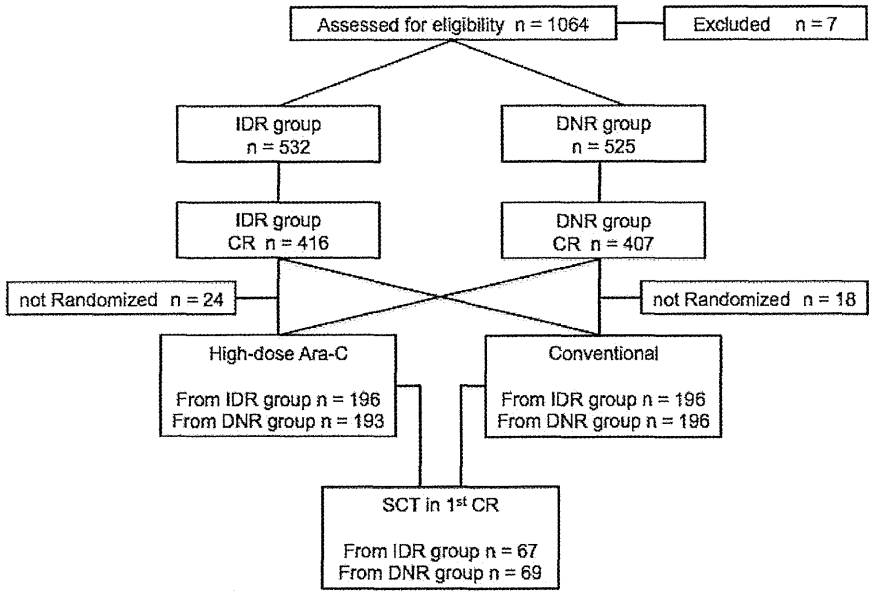


Figure 2a

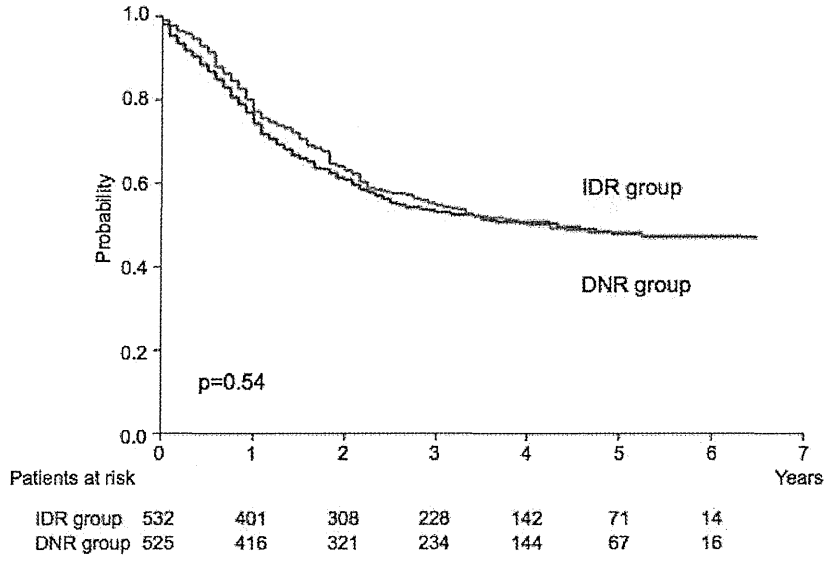


Figure 2b

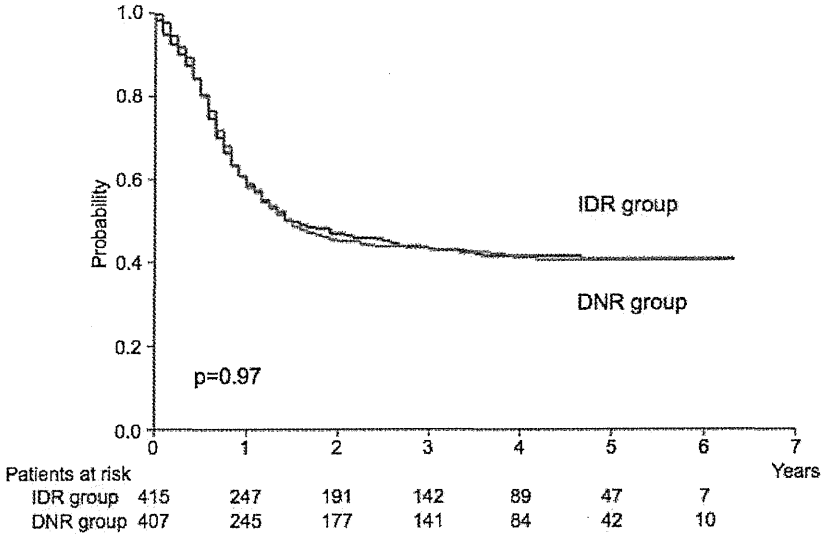


Figure 3a

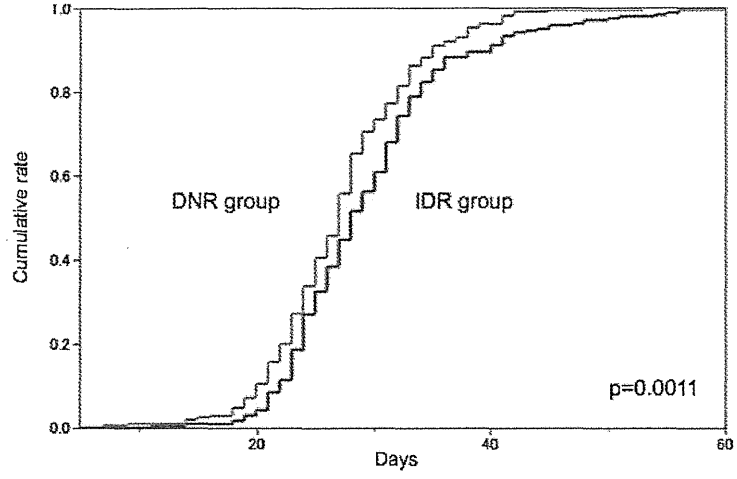


Figure 3b

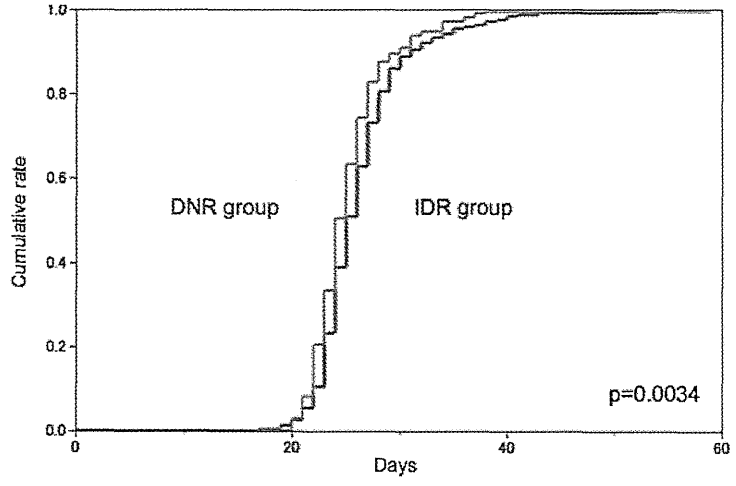


Figure 4a

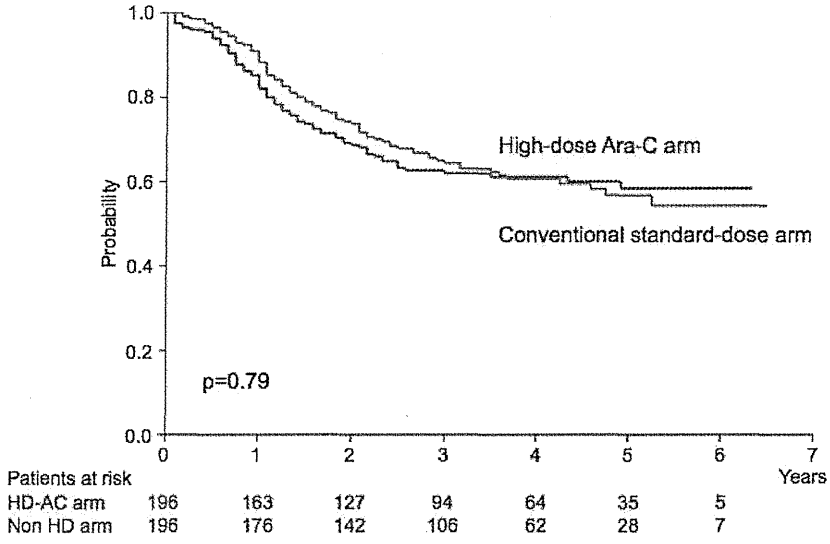
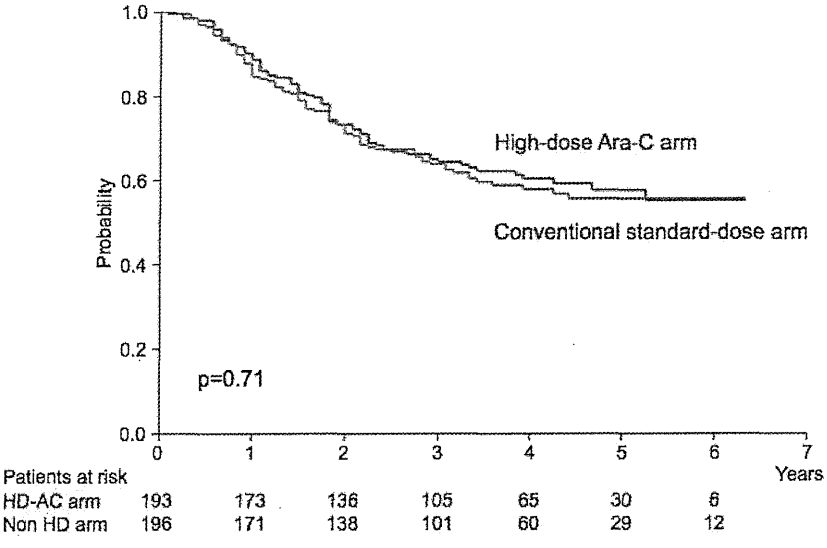


Figure 4b



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ORIGINAL ARTICLE

Intensified consolidation therapy with dose-escalated doxorubicin did not improve the prognosis of adults with acute lymphoblastic leukemia: the JALSG-ALL97 study

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Abstract We designed a treatment protocol for newly diagnosed adult acute lymphoblastic leukemia (ALL) in the pre-imatinib era, employing intensified consolidation therapy with a total of 330 mg/m^2 doxorubicin and adopting slightly modified induction and maintenance regimen of the CALGB 8811 study. Of 404 eligible patients (median age 38 years, range 15–64 years), 298 (74%) achieved complete remission (CR). The 5-year overall survival (OS) rate was 32%, and the 5-year disease-free survival (DFS) rate was 33%. Of 256 Philadelphia chromosome (Ph)-negative patients, 208 (81%) achieved CR and the 5-year OS rate was 39%, and 60 of them underwent allogeneic-hematopoietic stem cell transplantation (allo-HSCT) from related or unrelated donors during the first CR, resulting in 63% 5-year OS. Of 116 Ph-positive patients, 65 (56%) achieved CR and the 5-year OS rate was 15%, and 22 of them underwent

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allo-HSCT from related or unrelated donors during the first CR, resulting in 47% 5-year OS. In Ph-negative patients, multivariate analysis showed that older age, advanced performance status and unfavorable karyotypes were significant poor prognostic factors for OS and higher WBC counts for DFS. The present treatment regimen could not show a better outcome than that of our previous JALSG-ALL93 study for adult ALL.

Keywords Acute lymphoblastic leukemia · A multiinstitutional trial · Doxorubicin · Prognostic factors · The Japan Adult Leukemia Study Group (JALSG)

1 Introduction

The emergence of imatinib therapy for acute lymphoblastic leukemia (ALL) with Philadelphia chromosome (Ph) has markedly changed the therapeutic strategy for ALL [1, 2]; however, the treatment outcome of adult ALL without Ph, which comprises 70–75% of adult patients, is still poorer than that of childhood Ph-negative ALL. Although complete remission (CR) rate exceeds 80% in adult Ph-negative ALL, overall survival (OS) rate decreases below 50% within 5 years in most cooperative group studies [3–9]. Since there was no new breakthrough agents for ALL in 1997, we employed a modification of post-remission therapy as one of the treatment strategies to improve overall therapeutic outcomes of this leukemia in the present study.

ALL is very heterogeneous regarding the underlying genetic abnormality, which is associated with its biological features and treatment outcome. In addition, other prognostic factors, such as age, performance status (PS) and disease progression status at the time of diagnosis, influence the treatment outcome, resulting in complicated evaluation of these factors. Among Ph-negative ALL, there are many types of genetic abnormalities and the proportion of each subset is small, which has hindered the evaluation of prognostic risk by cytogenetics. Recently, the Medical Research Council (MRC) and Eastern Cooperative Oncology Group (ECOG) reported the prognostic impact of more than 20 specific chromosomal abnormalities on the outcome of adult ALL [10]. The Southwest Oncology Group (SWOG) also demonstrated the importance of cytogenetics on the outcome by combining subgroups with similar risk [11]. Although their findings will greatly contribute for the planning of treatment strategy on this leukemia, further clarification of the relationship between cytogenetics and other risk factors is necessary.

In the present JALSG-ALL97 study, which started in the pre-imatinib era, we employed a consolidation therapy similar to that of aggressive non-Hodgkin lymphoma, including frequent administration of vincristine (VCR), glucocorticoid, cyclophosphamide (CPM) and doxorubicin (DOX). The total dose of DOX was 330 mg/m^2 in the consolidation phase. As for induction and maintenance therapy, we adopted the CALGB 8811 study [12], one of the standard regimens for adult ALL, with a slight modification. The primary aim of this study was to evaluate a new treatment protocol with intensified consolidation therapy, and to examine the impact of clinical and biological characteristics, including cytogenetics, on the therapeutic outcome in adult ALL. This report mainly focuses on the outcome of Ph-negative patients. Approximately 30% of Ph-negative patients who achieved CR underwent allogeneic-hematopoietic stem cell transplantation (allo-HSCT) during their first CR; thus, we also added an assessment of its results.

2 Patients and methods

2.1 Patient eligibility criteria

Adult patients with previously untreated ALL were consecutively registered to the JALSG-ALL97 study. Eligible criteria were a diagnosis of ALL (excluding mature B-cell ALL); age from 15 to 64 years; ECOG PS between 0 and 3; and adequate function of heart (no severe abnormalities detected on ECGs and echocardiographs), lung ($PaO_2 >$ 60 mmHg or $SpO_2 > 93\%$), liver (serum bilirubin level $<$ 2.0 mg/dL), and kidney (serum creatinine level $<$ 2.0 mg/dL). ALL was diagnosed according to the French–American–British (FAB) classification [13] using morphology, cytochemistry and immunophenotyping studies at each institution, which was later reevaluated by the Central Review Committee. Surface markers were considered positive when more than 20% of blasts expressed antigens.

Cytogenetic studies on pretreatment bone marrow or unstimulated blood samples were performed using standard banding techniques. Karyotypes were interpreted using the

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International System for Human Cytogenetic Nomenclature [14]. Evaluable cases were classified according to the modified MRC UKALLXII/ECOG E2993ALL cytogenetic subgroups reported by the SWOG [11].

The protocol was approved by institutional review board of each hospital. Written informed consent was obtained from all patients before registration in accordance with the Declaration of Helsinki.

2.2 Treatment

Details of the treatment schedule are described in Table 1. We slightly modified the induction therapy used in the CALGB 8811 study [12] by decreasing the dose of L-asparaginase (L-ASP). In the 1990s, there were two different commercial L-ASP preparations from *E. coli* (L-ASP Medac and L-ASP Bayer) in the United States, and the enzyme activities of the two were significantly different [15]. In Japan, L-ASP Kyowa is the only available preparation and its enzyme activity is much higher than L-ASP Bayer [16].

Induction therapy consisted of five drugs: VCR, daunorubicin, CPM, prednisolone (PSL), and L-ASP. When patients were 60 years or older, the doses of daunorubicin and CPM were reduced and PSL therapy was shortened. If patients did not achieve CR with the first course of induction therapy, consolidation I in Table 1 was applied as the second course of induction therapy. If this also failed, the patients were regarded as failure cases for remission induction.

Consolidation therapy included 8 courses featuring dose-intensified DOX (60 mg/m^2), which was administered by continuous infusion for 24 h on day 1, CPM, and intermediate-dose methotrexate (MTX). Central nervous system prophylaxis was given by intrathecal injection of MTX, cytarabine (Ara-C) and dexamethasone during the consolidation courses. Patients with high initial WBC counts of 50 $\times$ 10^9/L and/or a high LDH level above 5 times of the upper normal limit received prophylactic whole cranial irradiation at a total dose of 20 Gy after 8 consolidation courses. Patients with symptomatic or cytological evidence of central nervous system leukemia received additional intrathecal injections and whole cranial irradiation was given at a total dose of 20 Gy. Subsequent consolidation courses were started immediately after neutrophil counts surpassed 1.5 $\times$ 10^9/L and platelet counts were more than 100 $\times$ 10^9/L. After consolidation, maintenance therapy with daily 6-mercaptopurine, weekly MTX and monthly pulses of VCR and PSL was given until 24 months after the start of induction. All patients were given trimethoprim/sulfamethoxole for pneumocystis prophylaxis. Prophylactic granulocyte-colony stimulating factor was recommended after chemotherapy.

CR was defined as the presence of all of the following: less than 5% of blasts in bone marrow, no leukemic blasts in peripheral blood (PB), recovery of PB values to a neutrophil count of at least 1.5 $\times$ 10^9/L and a platelet count of at least 100 $\times$ 10^9/L, and no evidence of extramedullary leukemia. Relapse was defined as the presence of at least one of the following: recurrence of more than 10% leukemic cells in bone marrow or of any leukemic cells in PB or extramedullary sites.

2.3 HSCT

For patients with Ph or t(4;11) who achieved CR, allo-HSCT was recommended during their first CR if a human leukocyte antigen-matched sibling was available, and allo-HSCT from an alternative donor was allowed. For patients with other types, HSCT was not mandatory. Preparative and post-transplant regimens for HSCT were decided by the institutional guidelines at each hospital.

2.4 Statistical analyses

The cutoff date for analysis was January 1, 2007. The median duration of follow-up was estimated with the reverse Kaplan–Meier method [17]. Continuous data were described as the median and ranges, and compared using the Wilcoxon rank-sum test. Categorical data were compared using the Chi-square test or Fisher's exact test. The main endpoint of this study was OS. The probability of OS was calculated using the Kaplan–Meier estimator, death from any cause was considered an event, and surviving patients were censored at last follow-up [18]. Patients undergoing transplantation were not censored. Statistical comparison of time-to-event curves was completed by the log-rank test. An additional outcome evaluated was disease-free survival (DFS), which was calculated as survival without relapse or death (whichever came first) from the date of first CR. Patients undergoing transplantation were not censored. Univariate and multivariate Cox proportional hazards model [19] was used to determine prognostic factors for OS and DFS and the hazard ratio (HR) estimate was calculated with 95% confidence intervals (CIs). Statistical analyses were performed using SAS (version 9; SAS Japan Institute Inc., Tokyo, Japan). All statistical tests were two sided and conducted at the 5% significance level.

3 Results

3.1 Patient entry and characteristics

Between May 1997 and December 2001, 432 patients from 90 hospitals participating in the JALSG were

Table 1 Treatment schedule for the JALSG-ALL97

Agent	Route	Dose	Day number
Induction			
Vincristine	IV	1.3 mg/m^2	1, 8, 15, 22
Daunorubicin	IV	45 mg/m^2 (30 mg/m^2 [a])	1, 2, 3
Cyclophosphamide	IV	1,200 mg/m^2 (800 mg/m^2 [a])	1
Prednisolone	PO	60 mg/m^2	1–14 (1–7[a]), then tapered
L-Asparaginase	IV	3,000 U/m^2	9, 11, 13, 16, 18, 20
Consolidation(C)-1			
Vincristine	IV	1.3 mg/m^2	1
Doxorubicin	CI for 24 h	60 mg/m^2	1
Cyclophosphamide	IV	1,000 mg/m^2	1
Prednisolone	PO	60 mg/m^2	1–3
CNS prophylaxis (MD[b])	IT		1
C-2			
Methotrexate[c]	CI for 24 h	500 mg/m^2	1
Vincristine	IV	1.3 mg/m^2	2
Doxorubicin	IV	45 mg/m^2	2
Prednisolone	PO	60 mg/m^2	2–4
CNS prophylaxis (MD)	IT		1
C-3			
Vincristine	IV	1.3 mg/m^2	1
Doxorubicin	CI for 24 h	60 mg/m^2	1
Cyclophosphamide	IV	1,000 mg/m^2	1
Prednisolone	PO	60 mg/m^2	1–3
CNS prophylaxis (MAD[d])	IT		1
C-4			
Etoposide	IV	100 mg/m^2	1–4
Cytarabine	CI	200 mg/m^2	1–4
6-Mercaptopurine	PO	60 mg/m^2	1–4
Prednisolone	PO	60 mg/m^2	1–4
CNSprophylaxis (MAD)	IT		1
C-5			
Same as C-1 except for substituting dexamethasone 10 mg/m^2 PO × 3 for prednisolone			
C-6			
Same as C-2 except for substituting dexamethasone 10 mg/m^2 PO × 3 for prednisolone			
C-7			
Same as C-3 except for substituting dexamethasone 10 mg/m^2 PO × 3 for prednisolone			
C-8			
Mitoxantrone	IV	8 mg/m^2	2, 3
Cytarabine	CI	200 mg/m^2	1–4
6-Mercaptopurine	PO	60 mg/m^2	1–4
Dexamethasone	PO	10 mg/m^2	1–4
CNSprophylaxis (MAD)	IT		1
Maintenance			
Vincristine	IV	1.3 mg/m^2	1[e]
Prednisolone	PO	60 mg/m^2	1–5[e]
6-Mercaptopurine	PO	60 mg/m^2	1–28[e]
Methotrexate	PO	20 mg/m^2	1, 8, 15, 22[e]

Maximum dose of vincristine was 2.0 mg/body

IV intravenously, *PO* per os, *CI* continuous infusion, *IT* intrathecally

[a] Doses or schedule for patients 60 y.o. or older

[b] *MD*, methotrexate 15 mg/body + dexamethasone 4 mg/body for IT

[c] 50 mg/m^2 of MTX was administered as IV for 30 min and 450 mg/m^2 of MTX as IV for 23.5 h. After 36 h from the start of MTX infusion, 15 mg/body of leucovorin was administered 8 times every 6 h by IV, subcutaneously (SC), intramuscularly (IM) or PO. When the plasma concentration of MTX at 48 h was 1×10^{-6} M or more, 60 mg/body of leucovorin was added 8 times every 6 h by IV, SC, IM or PO, and when it was $5–10 \times 10^{-7}$ M, 15 mg/body of MTX was added by the same schedule

[d] *MAD* MD + cytarabine 40 mg/body used for IT

[e] Every 4 weeks

enrolled in this study. Sixteen patients were excluded because 13 had been misdiagnosed (6 with acute myeloid leukemia, 4 with mature B-cell leukemia, 2 with blastic crisis of chronic myeloid leukemia and one with non-Hodgkin lymphoma), 2 were not consistent with the eligible criteria and one died before treatment. Evaluable data from 12 were incomplete at the time of analysis; thus, here, we report outcome of 404 eligible patients. Median age was 38 years and there were 208 men (51%) and 196 women. Pretreatment characteristics are summarized in Table 2.

Cytogenetic evaluation was performed in 344 patients (85%); 130 (32%) had normal karyotypes, 214 (53%) showed abnormal karyotypes and 96 (28%) Ph based on conventional banded studies. The fusion gene of *BCR-ABL* was analyzed in 191 patients and 72 (38%) were positive. Twelve patients without Ph had the fusion gene of *BCR-ABL* (9 with normal karyotype; one with monosomy 7; 2 with other karyotypes). We defined patients with Ph and/or *BCR-ABL* fusion gene as Ph-positive (116 patients), and patients without Ph or *BCR-ABL* fusion gene as Ph-negative (256). Thirty-two patients were not assessable for Ph status. Pretreatment characteristics of the Ph-negative group and the Ph-positive one are summarized in Table 2. Age and WBC count were significantly higher in the Ph-positive group ($P < 0.0001$ for both variables). Ph-negative patients were classified according to the modified MRC UKALLXII/ECOG E2993ALL cytogenetic subgroups [11]: the very high risk group ($n = 32$) included t(4;11) ($n = 8$), complex karyotype defined as more than 5 abnormalities without known translocations ($n = 20$), or low hypodiploidy/near triploidy ($n = 4$); the high risk group ($n = 10$) included other *MLL* translocations ($n = 4$), monosomy 7 with less than 5 abnormalities ($n = 2$) or t(1;19) ($n = 4$); the standard-risk group included high hyperdiploidy ($n = 9$); the intermediate risk group ($n = 185$) included normal karyotype ($n = 121$) or other miscellaneous abnormal karyotypes ($n = 64$).

3.2 Response to induction therapy

The results of therapy are summarized in Table 3. Overall, 298 (74%) of 404 evaluated patients achieved CR: 276 (68%) after the first treatment and 22 after additional consolidation course 1. Twenty-one patients (5%) died within 4 weeks after the start of induction therapy before their remission status could be ascertained. The causes of death were sepsis ($n = 14$), pneumonia ($n = 2$), intracranial hemorrhage ($n = 2$), and others ($n = 3$). Eighty-five patients (21%) failed to respond. Among 256 Ph-negative patients, 208 (81%) achieved CR, 12 (5%) died during the induction phase and 36 (14%) were refractory, whereas only 65 (56%) of 116 Ph-positive patients achieved CR.

3.3 Survival

After a median follow-up of 5.8 years (range 2 days to 8.6 years), 146 of 404 eligible patients were alive and 104 were disease-free. The median OS was 23.8 months and the estimated probability of the OS rate at 5 years was 32% (95% CI 27–37%), as shown in Fig. 1a. Among 298 CR patients, 24 died in remission and 170 relapsed. The median DFS was 18.8 months, and the estimated 5-year DFS rate was 33% (95% CI 27–38%), as shown in Fig. 1b. The outcome by Ph status is shown in Table 3. The 5-year OS rates for 256 Ph-negative patients and 116 Ph-positive patients were 39% (95% CI 32–45%) and 15% (95% CI 9–23%), respectively (Fig. 1c).

3.4 Prognostic factors for Ph-negative patients

Univariate analyses for the effects of clinical and biological features on outcome among Ph-negative patients are summarized in Table 4. PS and WBC count were significantly related to CR achievement. The 5-year OS rate for patients who achieved CR was 45% (95% CI 38–52%), whereas that for those who did not reach CR after 2 induction courses was 10% (95% CI 3–21%). Older age, PS 2 or 3, hepatomegaly, WBC count (30×10^9/L or higher) and cytogenetics (the very high/high risk or other miscellaneous abnormal karyotypes) were significantly related to OS. Hepatomegaly, WBC count (30×10^9/L or higher) and cytogenetics (the very high/high risk) were significantly related to DFS. Figure 2a shows OS for Ph-negative patients by age group. Although the OS rate decreased with advancing age, there was no difference between patients of 15–24 and 25–34 years old. When we compared OS between those older and younger than 35 years old, survival of older patients was significantly poorer (HR 1.54, 95% CI 1.12–2.12; $P = 0.008$). In 236 Ph-negative patients with evaluable cytogenetics, there was highly significant heterogeneity of OS among the 5 cytogenetic subgroups ($P = 0.0064$, Fig. 2b). Because of the small number of patients in the high risk group or the standard-risk group, the former was combined with the very high risk group, and the latter with the normal karyotype group. Patients with the very high/high risk karyotype or other miscellaneous abnormal karyotype had significantly poorer OS than those with the standard/normal karyotype (Table 4). DFS of the very high/high risk group was significantly worse than that of the standard/normal karyotype group. Immunophenotype was not a significant prognostic factor for OS (Table 4). The 5-year OS rates for B-lineage patients and for T-lineage were 42% (95% CI 35–49%) and 33% (95% CI 17–49%), respectively ($P = 0.43$). Time to CR was not a risk factor, either. The 5-year OS rate for 191 patients who achieved CR after one course of

Table 2 Clinical and biological features of patients at diagnosis

Parameters	No. (%) or median (range)		
	All	Ph-negative	Ph-positive
No. of patients evaluated	404	256	116
Sex			
Male	208 (51)	120 (47)	69 (59)
Female	196 (49)	136 (53)	47 (41)
Age (years)			
Median (range)	38 (15–64)	30 (15–64)	48 (15–64)
15–24	120 (29)	98 (38)	13 (11)
25–34	63 (16)	43 (17)	11 (10)
35–54	144 (36)	70 (27)	64 (55)
55 or older	77 (19)	45 (18)	28 (24)
Performance status			
0, 1	359 (89)	230 (90)	102 (88)
2, 3	45 (11)	26 (10)	14 (12)
Hepatomegaly			
Yes	87 (22)	58 (23)	25 (22)
No	317 (78)	198 (77)	91 (78)
Splenomegaly			
Yes	75 (19)	49 (19)	20 (17)
No	329 (81)	207 (81)	96 (83)
Lymphadenopathy			
Yes	111 (27)	80 (31)	25 (22)
No	293 (73)	176 (69)	91 (78)
Fever over 38°C			
Yes	126 (31)	78 (30)	43 (37)
No	278 (69)	178 (70)	73 (63)
CNS involvement			
Yes	4 (1)	3 (1)	1 (1)
No	399 (99)	253 (99)	114 (98)
Missing	1 (0.2)		1 (1)
WBC count ($\times 10^9$/L)			
Median (range)	12.6 (0.3–810)	10.5 (0.3–718)	29.2 (1.0–810)
Less than 3	62 (15)	48 (19)	9 (8)
3–10	115 (29)	75 (29)	25 (22)
10–30	90 (22)	62 (24)	25 (22)
30 or higher	136 (34)	71 (28)	56 (47)
Missing	1 (0.2)		1 (1)
FAB classification			
L1	75 (19)	55 (21)	15 (13)
L2	325 (80)	199 (78)	100 (86)
Unknown	4 (1)	2 (1)	1 (1)
Immunologic classification			
B-lineage	330 (82)	199 (77)	108 (94)
T-lineage	38 (9)	35 (14)	0 (0)
Others	36 (9)	22 (9)	7 (6)

CNS central nervous system, *Ph* Philadelphia chromosome

chemotherapy was 48%, compared with 28% for 17 who did after the additional chemotherapy, but this difference was not statistically significant ($P = 0.16$).

Multivariate analyses revealed that advanced age, PS 2 or 3, and cytogenetics (the very high/high risk or other miscellaneous abnormal karyotypes) were independent

prognostic factors for OS and only WBC count (30×10^9/L or higher) was an independent prognostic factor for DFS (Table 4). We developed a simple scoring system for predicting outcome based on the HR of these risk factors for OS of CR patients. A score of one was allocated to each of the following parameters: age $\geq$ 35 years, PS 2 or 3, WBC counts $\geq 30 \times 10^9$/L and other miscellaneous abnormal karyotype, and a score of 2 to the very high/high risk karyotype. OS curves of patients scoring 0, 1, 2, 3, and 4 or more are shown in Fig. 2c. The 5-year OS rate for patients scoring 0 was 60% (95% CI 45–73%). OS decreased with an increasing total score, and 4-year OS rate for patients scoring 4 or more was only 10% (95% CI 1–35%; Table 5).

Table 3 Summary of therapy results

	All patients	Ph-negative	Ph-positive
Patients eligible	404	256	116
Early deaths	21 (5%)	12 (5%)	9 (8%)
Refractory	85 (21%)	36 (14%)	42 (36%)
Dead	70	28	38
Alive	15	8	4
CR achievement (% of all)[a]	298 (74%)	208 (81%)	65 (56%)
Died in CR	24	14	6
Relapse[b]	170	121	38
Dead	143	99	36
Alive	27	22	2
CCR	104	73	21
Total dead	258	153	89
Total alive	146	103	27

CCR continuous complete remission, *CR* complete remission, *Ph* Philadelphia chromosome

[a] CR achievement includes those reached CR by induction therapy and 1st consolidation therapy

[b] Relapse indicates the first relapse after CR achievement including the first relapse after hematopoietic stem cell transplantation (HSCT) among those who received HSCT during CR

3.5 HSCT for Ph-negative patients

Among 208 Ph-negative patients who achieved CR, 60 (29%) underwent allo-HSCT during their first CR (37 from a related donor and 23 from an unrelated donor). The median duration from the time of achieving CR to transplantation was 7.5 months (range 3.1–34.6 months). Patients who received allo-HSCT were significantly younger than those who did not [median (range) 25.5 years (16.0–55.0) vs. 31.0 years (15.0–64.0), $P = 0.02$]. Among 60 patients who received allo-HSCT, 8 (13%) died in remission, 16 (27%) relapsed, and 36 (60%) were in continuous CR (CCR). The 5-year OS rate was 63% (95% CI 49–74%; Fig. 3a), 68% (95% CI 50–81%) from a related donor and 55% (95% CI 32–73%) from an unrelated donor, showing no significant difference ($P = 0.43$). Patients scoring 0 or 1 had significantly better OS [75% (95% CI 55–86%)] than those scoring 2 or more [48% (95% CI 26–67%)] ($P = 0.02$; Fig. 3b).

Among 148 patients who did not receive allo-HSCT during their first CR, 37 (25%) were in CCR, 6 (4%) died in remission (2, therapy-related death; one, other disease; 3, unknown) and 105 (71%) relapsed. Of 105 relapsed, 46 received allo-HSCT for salvage therapy, and 10 were alive in remission after transplantation with a median duration of 3.9 years (range 7 months to 7.1 years). The 5-year OS

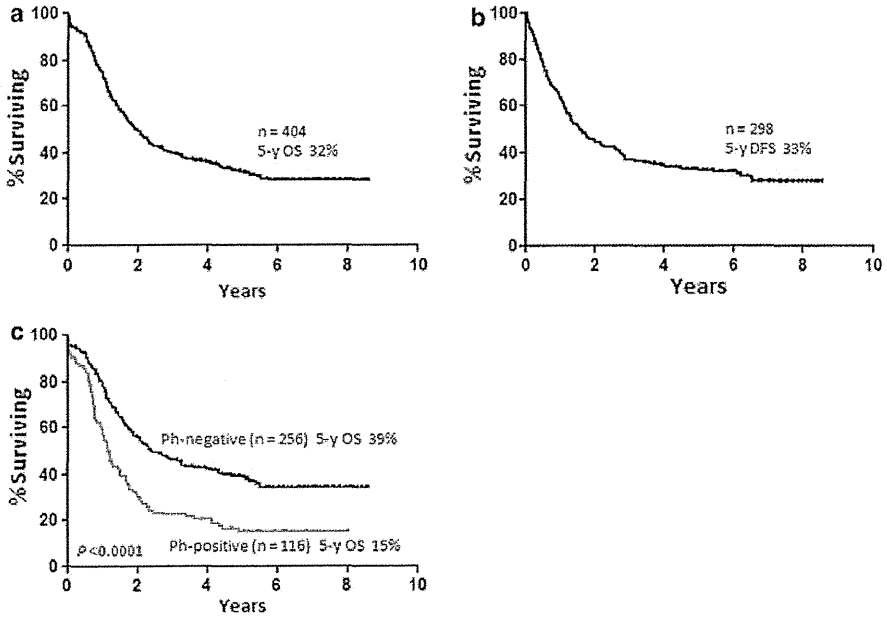

Fig. 1 Survival analysis. **a** Overall survival (OS) of 404 eligible patients. **b** Disease-free survival (DFS) of 298 patients who achieved complete remission. **c** OS of 116 Philadelphia chromosome (Ph)-positive patients and 256 Ph-negative patients

Table 4 Effects of clinical and biological features on outcome among Ph-negative ALL (univariate analyses)

Parameters	No. of patients at diagnosis	CR		OS		DFS	
		%	*P*	No. of events[a]	Hazard ratio (95% CI)	No. of events[b]	Hazard ratio (95% CI)
Total	256	81		153		135	
Sex							
Female	136	85	0.08	82	Ref	80	Ref
Male	120	77		71	1.08 (0.78–1.48)	55	0.86 (0.60–1.23)
Age (years)							
15–24	98	85	0.72	52	Ref	50	Ref
25–34	43	79		23	0.93 (0.57–1.52)	22	0.96 (0.57–1.61)
35–54	70	80		44	1.31 (0.87–1.96)	36	1.06 (0.68–1.65)
55 or older	45	78		34	1.87 (1.21–2.90)	27	1.37 (0.84–2.21)
Performance status							
0, 1	230	83	0.03	133	Ref	123	Ref
2, 3	26	65		20	2.00 (1.25–3.21)	12	1.56 (0.84–2.90)
Hepatomegaly							
No	198	81	0.74	111	Ref	99	Ref
Yes	58	83		42	1.50 (1.05–2.15)	36	1.71 (1.15–2.53)
Splenomegaly							
No	207	83	0.12	120	Ref	110	Ref
Yes	49	74		33	1.29 (0.88–1.91)	25	1.37 (0.88–2.14)
Lymphadenopathy							
No	176	89	0.30	106	Ref	94	Ref
Yes	80	78		47	0.98 (0.69–1.39)	41	1.13 (0.77–1.65)
Fever over 38°C							
No	178	81	0.83	104	Ref	96	Ref
Yes	78	82		49	1.12 (0.80–1.58)	39	0.84 (0.57–1.24)
CNS involvement							
No	253	82	0.09	150	Ref	134	Ref
Yes	3	33		3	3.01 (0.96–9.46)	1	1.40 (0.20–9.99)
WBC count ($\times 10^9$/L)							
Less than 30	185	86	0.002	105	Ref	97	Ref
30 or higher	71	69		48	1.66 (1.17–2.33)	38	1.80 (1.22–2.65)
Immunologic classification							
B-lineage	199	84	0.14	115	Ref	107	Ref
T-lineage	35	74		22	1.20 (0.76–1.92)	19	1.30 (0.78–2.17)
Chromosome category (n = 236), unknown = 20							
Standard risk	9	89	0.49	3	Ref[c]	3	Ref[c]
Normal	121	79		65		58	
Miscellaneous	64	78		44	1.68 (1.14–2.46)	35	1.47 (0.95–2.26)
High risk	10	90		5	1.87 (1.21–2.89)[c]	5	1.82 (1.15–2.89)[c]
Very high risk	32	91		25		24	
Days from treatment start to CR achievement							
≤30 days	85			44	Ref	54	Ref
>30 days	120			66	1.00 (0.68–1.46)	78	1.02 (0.71–1.46)

ALL acute lymphoblastic leukemia, *CNS* central nervous system, *CR* complete remission, *DFS* disease-free survival, *OS* overall survival, *Ph* Philadelphia chromosome

[a] Death

[b] Relapse or death

[c] The standard-risk group was combined with the normal karyotype group, and the high risk group with the very high risk group

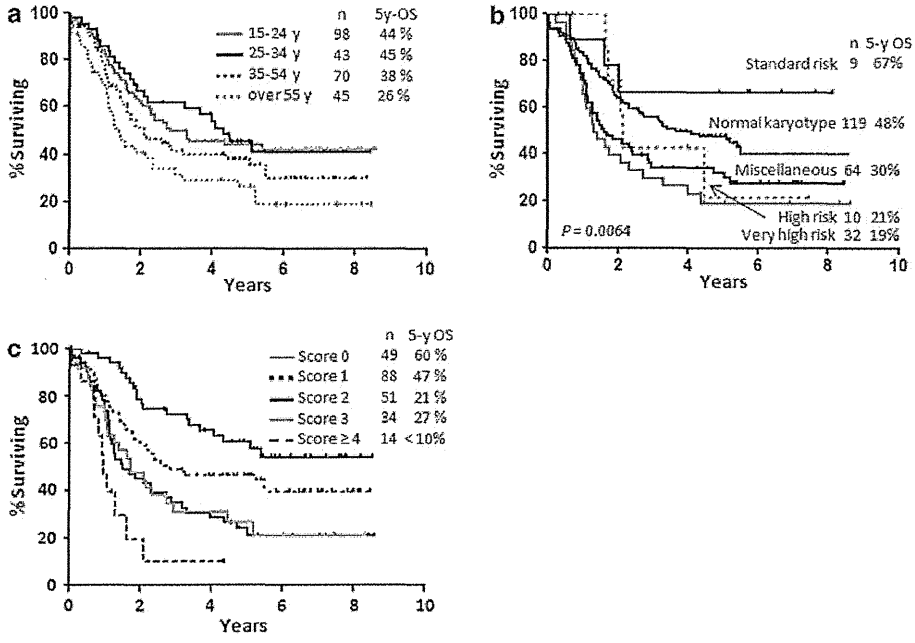

Fig. 2 Survival analysis of Philadelphia chromosome-negative patients. **a** Overall survival (OS) by age group. **b** OS by karyotype category according to the modified MRC UKALLXII/ECOG E2993ALL cytogenetic subgroups: the very high risk group included t(4;11), complex karyotype defined as more than 5 abnormalities without known translocations, or low hypodiploidy/near triploidy; the high risk group included other *MLL* translocations, monosomy 7 with less than 5 abnormalities or t(1;19); the standard-risk group included high hyperdiploidy; other miscellaneous abnormal karyotypes were categorized as intermediate risk. **c** OS by a scoring system that we developed. A score of one was allocated to each of the following parameters; age ≥ 35 years, performance status 2 or 3, WBC counts ≥ 30 × 10^9/L and other miscellaneous abnormal karyotype, and a score of 2 to the very high/high risk karyotype

Table 5 Effects of clinical and biological features on survival among Ph-negative ALL (multivariate analyses)

Parameters	HR (95% CI)		
	OS	OS of CR patients	DFS
Age (years old)			
35 or older (vs. 15–34)	1.74 (1.24–2.44)	1.64 (1.11–2.43)	1.21 (0.83–1.74)
Performance status			
2, 3 (vs. 0, 1)	2.06 (1.26–3.37)	1.94 (1.02–3.69)	1.43 (0.74–2.77)
Hepatomegaly			
Yes (vs. no)	1.26 (0.86–1.85)	1.43 (0.91–2.23)	1.44 (0.94–2.21)
WBC count (×10^9/L)			
30 or higher (vs. less than 30)	1.42 (0.98–2.01)	1.16 (0.73–1.82)	1.63 (1.08–2.48)
Chromosome category			
Miscellaneous group (vs. SR + NK[a])	1.55 (1.05–2.29)	1.56 (0.98–2.50)	1.26 (0.81–1.97)
High and very high risk (vs. SR + NK[a])	1.60 (1.02–2.50)	2.25 (1.37–3.70)	1.49 (0.92–2.41)

ALL acute lymphoblastic leukemia, *CR* complete remission, *DFS* disease-free survival, *HR* hazard ratio, *OS* overall survival, *Ph* Philadelphia chromosome

[a] Standard risk + normal karyotype

rate for all Ph-negative patients who did not receive allo-HSCT during the first CR was 37% (95% CI 29–46%; Fig. 3c). Among those, the 5-year OS rate for patients scoring 0 or 1 was 53% (95% CI 41–63%) and that for patients scoring 2 or more was 19% (95% CI 10–31%), showing a significantly better OS in the former than the latter ($P < 0.0001$; Fig. 3d).

3.6 HSCT for Ph-positive patients

Among 65 Ph-positive patients who achieved CR, 22 (34%) underwent allo-HSCT during their first CR (19 from a related donor and 3 from an unrelated donor). The median duration from the time of achieving CR to transplantation was 4.6 months (range 2.6–12.1 months).

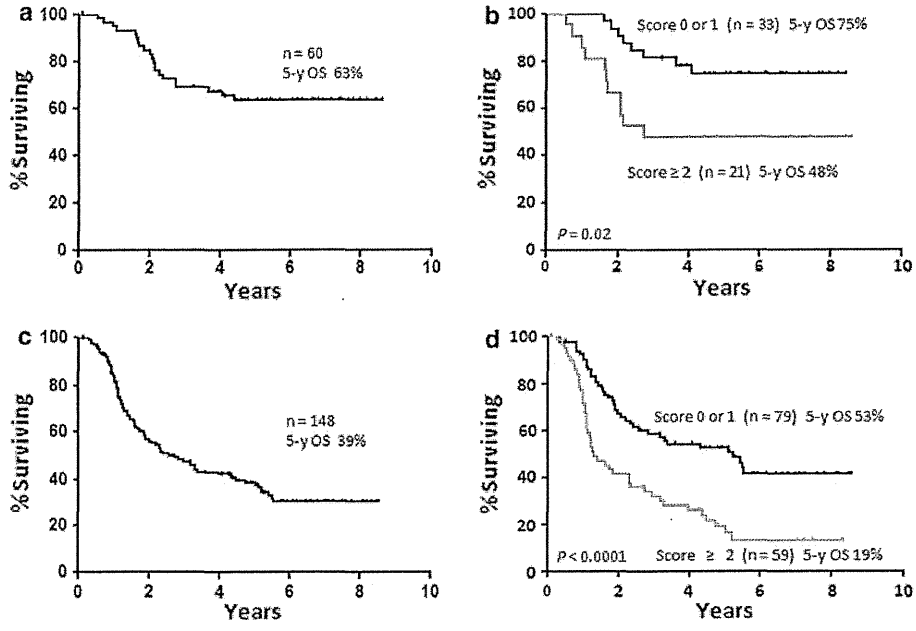

Fig. 3 Survival analysis of Philadelphia chromosome-negative patients with/without allogeneic-hematopoietic stem cell transplantation (allo-HSCT) in first complete remission. **a** Overall survival (OS) in those who received allo-HSCT. **b** OS in those who received allo-HSCT by dichotomized prognostic score group. **c** OS in those who did not received allo-HSCT. **d** OS in those who did not received allo-HSCT by dichotomized prognostic score group

Patients who received allo-HSCT were significantly younger than those who did not [median (range) 41.5 years (15–56) vs. 49.0 years (24–63), $P = 0.02$]. Among 22 Ph-positive patients who received allo-HSCT, 5 (23%) died in remission, 6 (27%) relapsed, and 11 (50%) were in CCR. The 5-year OS rate was 47% (95% CI 24–67%; Fig. 4).

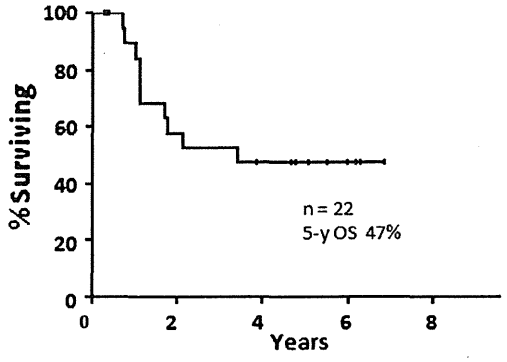

Fig. 4 Overall survival (OS) of Philadelphia chromosome-positive patients who received allo-hematopoietic transplantation in first complete remission

4 Discussion

In the present study, although the CR rate of all 404 evaluable patients did not exceed 80%, the rate was greater in Ph-negative patients (81%) than Ph-positive patients (56%). These results are not so different from our preceding JALSG-ALL93 study [4] (Ph-negative, 83%; Ph-positive, 51%) and from the CALGB 8811 study [12] (Ph-negative, 84%; Ph-positive, 70%). In the JALSG-ALL93 study, we tested an intensified induction therapy mainly using DOX. In the present study, we asked whether a benefit could be achieved by intensifying the consolidation phase of the CALGB 8811 study protocol, mainly using DOX. However, DFS of CR patients did not differ much from that of the CALGB 8811 study or that of the CALGB 9111 study [3] in which the same chemotherapy regimen was used. Besides, the 5-year OS of 45% for Ph-negative patients who achieved CR was similar to that in the MRC UKALL XII/ECOG E2993 study [7], suggesting that the present intensified consolidation therapy resulted in a similar outcome to the standard consolidation regimen, and had little impact on the survival improvement of adult Ph-negative ALL.

Age is a major prognostic factor in ALL. When we compared by age, OS of patients younger than 35 years was significantly better than that of patients aged 35 years or older (5-year OS; 44 vs. 32%, $P = 0.008$); however, there was no significant difference between patients of 15–24 and 25–34 years old. A similar outcome was seen in the MRC UKALL XII/ECOG E2993 study [7], i.e., the 5-year OS rates for Ph-negative patients aged 15–19 and 20–29 years old were 44 and 45%, respectively.

Several retrospective analyses reported improved outcomes for adolescent and young adult ALL treated by the pediatric regimens [20, 21]. Stock et al. [21] reported the outcomes of 321 adolescents and young adults who underwent pediatric (Children's Cancer Group) or adult (CALGB) trials, and the 7-year OS rates were 67 and 46%, respectively. As one potential explanation for these differences, they suggested dose intensification of nonmyelosuppressive drugs, such as glucocorticoids, VCR and

L-ASP, which have been the mainstay of pediatric ALL therapy. The outcome of adolescents and young adults in our study was similar to that of the same cohort in the CALGB study, including the 8811 trial, and we did not use L-ASP during the post-remission therapy. Therefore, to improve the therapeutic outcome of adult ALL, particularly that of adolescent and young adult ALL, pediatric regimens using dose-intensified nonmyelosuppressive drugs should be prospectively tested. Such studies are already underway in several adult cooperative study groups, including the JALSG-202 study, showing promising results [22, 23].

The outcome of T-ALL patients in JALSG-ALL97 study has previously been reported together with T-ALL patients in other JALSG ALL studies [24]. Reportedly, the T-cell phenotype is generally a favorable prognostic factor in adult ALL; however, the outcome of T-ALL patients in our present study was not better than that of Ph-negative precursor B-ALL. T-ALL was said to be benefited from Ara-C and CPM [25]. In our consolidation phase, high doses of anthracycline and CPM were used, but not Ara-C. Thus, T-ALL may not have been benefitted from anthracycline in consolidation therapy. T-ALL therapy may need a higher dose of Ara-C and/or a new drug such as nelarabine, a promising drug for T-cell malignancies [26, 27].

In the present study, we were able to confirm the impact of cytogenetics on the outcome of adult ALL based on the grouping by MRC UKALL XII/ECOG E2993 study [10] and SWOG 9400 study [11]. In addition to Ph, the very high risk group in the present study was t(4;11), complex type and low hypodiploidy/near triploidy, and the outcome (5-year OS, 19%) of this group was very similar to the SWOG 9400 study (22%) and the MRC UKALL XII/ECOG E2993 study (22–28%), suggesting that this grouping is useful for the prediction of poor prognostic group. Normal diploidy is the most frequent karyotype among Ph-negative ALL. In the present study, the 5-year OS rate of patients with a normal karyotype was 48%, which was similar to that of the MRC UKALL XII/ECOG E2993 study (48%) and the SWOG 9400 study (50%). In contrast, the prognosis of other miscellaneous types was worse in the present study than in the SWOG 9400 study. This group includes numerous cytogenetic abnormalities, and the prognostic risk of each type has not been defined because the number of each type is very small. In fact, in the MRC UKALL XII/ECOG E2993 study, the largest study of adult ALL, most other miscellaneous types did not show any significant association with disease outcome, and only a few karyotypes exceeded 45% 5-year OS, showing no conflict to our results. Since the high risk group in the present study, comprising other *MLL* translocations, monosomy 7 or t(1;19), showed a poor prognosis, we combined this group with the very high risk group for statistic analysis, although the outcome of the high risk group in the SWOG 9400 study was not particularly detrimental. It seems difficult to discuss the difference because of the small number of patients in each study (SWOG study, 12 patients vs. present study, 10).

In our previous JALSG-ALL93 study, CR patients under 40 years old with human leukocyte antigen-matched siblings were scheduled to receive allo-HSCT during the first CR. In this study, however, we did not incorporate recommendation for HSCT except for patients with Ph or t(4;11), because the ALL93 study showed no survival difference between patients of age under 40 years with and without a sibling donor, except for Ph-positive patients who benefited from allo-HSCT. However, if patients without a sibling wished to have HSCT, most of them can obtain an unrelated donor through the Japan Marrow Donor Program. Approximately 30% of Ph-negative patients who achieved CR underwent allo-HSCT in their first CR, and 38% of them from unrelated donors. The 5-year OS rate in Ph-negative patients who received allo-HSCT during the first CR was 63% and the transplantation-related mortality rate was only 13%. Notably, the 5-year OS of patients without risk factors, such as older age, advanced PS, a higher WBC count and unfavorable karyotypes, was 75% and very satisfactory despite of marked selection bias in the choice of treatment. Recently, the MRC/ECOG group reported that matched related allo-HSCT for adult ALL in the first CR provided survival benefit for standard-risk patients in prospective sibling donor versus no-donor comparison [28]. The HOVON Cooperative Group also stated that standard-risk ALL patients showed favorable survival following allo-HSCT, due to both a strong reduction of relapse and a modest transplantation-related mortality, although their standard-risk criteria did not include age [29]. These results suggest that allo-HSCT is the most promising treatment modality for adult ALL patients who have achieved CR and have few risk factors.

Multivariate Cox analysis in our Ph-negative patients showed that older age (35 years old or more), advanced PS (PS 2 or 3) and unfavorable karyotypes (very high/high risk or other miscellaneous abnormalities) were independent adverse prognostic factors for OS, and a higher WBC count (30×10^9/L or more) for DFS. The 5-year OS of patients without these risk factors was 60%, whereas that of patients with multiple risk factors was under 30%. Our scoring system worked well for both patients who received HSCT or did not in their first CR. This demonstrates importance to assess prognostic factors, including cytogenetics, when making a treatment plan. Further studies on this scoring system should be performed to prove its usefulness in the individualized therapy on Ph-negative ALL possessing different prognostic scores.

Regretfully, the present study could not show the benefit of intensified consolidation with myelosuppressive drugs in

adult ALL. Dose intensification of nonmyelosuppressive agents such as glucocorticoids, VCR and L-ASP like pediatric regimens and/or incorporation of new agents such as molecule-targeting drugs and monoclonal antibodies would be the next step to be tested in order to increase the cure rate of adult ALL.

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Correlation Between Imatinib Pharmacokinetics and Clinical Response in Japanese Patients With Chronic-Phase Chronic Myeloid Leukemia

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Despite the outstanding results generally obtained with imatinib mesylate (IM) in the treatment of chronic myeloid leukemia (CML), some patients show a poor molecular response. To evaluate the relationship between steady-state trough plasma IM concentration (IM-C_{min}) and clinical response in CML patients, we integrated data from six independent Japanese studies. Among 254 CML patients, the mean IM-C_{min} was 1,010.5 ng/ml. Importantly, IM-C_{min} was significantly higher in patients who achieved a major molecular response (MMR) than in those who did not ($P = 0.002$). Multivariate analysis showed that an MMR was associated with both age (odds ratio (OR) = 0.97 (0.958–0.995); $P = 0.0153$) and with IM-C_{min} (OR = 1.0008 (1.0003–1.0015); $P = 0.0044$). Given that patients with IM-C_{min} values >1,002 ng/ml had a higher probability of achieving an MMR in our large cohort ($P = 0.0120$), the data suggest that monitoring of IM levels in plasma may improve the efficacy of IM therapy for CML patients.

Imatinib mesylate (IM) is a potent and selective inhibitor of the BCR-ABL tyrosine kinase and the autophosphorylation of the tyrosine kinase receptor c-KIT, and it has been approved for the treatment of Philadelphia chromosome–positive chronic myeloid leukemia (CML)[1] and gastrointestinal stromal tumors.[2] Despite the outstanding results generally achieved with IM in CML, there have been cases of treatment failure, as well as cases in which the response to IM was suboptimal.[3] Factors that might be associated with suboptimal responses to IM include (i) biological factors, such as the baseline presence or later emergence of BCR-ABL mutations and other genetic variants; (ii) clinical features, such as the disease status of the patient or the Sokal risk score at baseline; (iii) pharmacokinetics-related interindividual pharmacogenetic variations and/or drug–drug interactions affecting IM metabolism; and (iv) adherence.[4–6]

Several previous studies have investigated whether variations in the concentration of IM in plasma influence the clinical response of IM-treated patients; however, the studies produced varied results (for a summary, see **Table 1**).[6–12] For example, data from three studies suggested a correlation between the trough plasma IM concentration (IM-C_{min}) and clinical response among CML patients.[6–8] Larson *et al.* reported that the IM-C_{min} was significantly higher in patients who achieved a complete cytogenetic response (CCyR) than in patients without a CCyR.[7] In addition, Picard *et al.* reported that an IM-C_{min} of 1,002 ng/ml should be set as an efficacy threshold because this concentration was significantly associated with a major molecular response (MMR) in 68 chronic-phase CML patients.[8] In contrast, Forrest *et al.* did not find any correlation between IM-C_{min} and clinical response among 78 CML patients after a minimum of 12 months of IM therapy.[9] However, as stated by the authors, their results

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