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Table 1. Patient characteristics

	IDR group (n = 532)	DNR group (n = 525)	*P* value
Age (year)*	47 (15 - 64)	47 (15 - 64)	0.781
=< 50	310	306	0.996
> 50	222	219	
WBC ($x10^9$/L)*	13.7 (0.1 - 382)	15.3 (0.1 - 334)	0.769
=< 20	304	297	
20 < =< 50	95	104	0.427
> 50	125	121	
unknown	8	3	
FAB type (no. of patients)			
M0	30	30	
M1	95	94	
M2	232	233	
M4	100	100	0.997
M5	56	51	
M6	17	16	
M7	2	1	
Cytogenetic group (no. of patients)			
good	128	119	
intermediate	335	346	0.561
adverse	49	44	
unknown	20	16	
MPO positive blast (%)			
< 50	169	187	
>= 50	307	292	0.330
unknown	56	46	
Performance status			
0, 1, 2	512	509	0.524
3	20	16	

* : Number indicates the median, and numbers in parentheses the range

Table 2. Results of induction therapy

	IDR group		DNR group	
	no.	%	no.	%
Patients	532		525	
CR	416	78.2	407	77.5
CR by 1 course	341	64.1	321	61.1
CR by 2 courses	75	14.1	86	16.4
95% CI	74.5 - 81.5		73.8 - 80.9	

Table 3. CR rates by induction therapy

	IDR group (n = 532)	DNR group (n = 525)	*P* value
FAB type	(%)	(%)	
M0	43	63	0.195
M1	86	79	0.236
M2	80	82	0.718
M4	81	79	0.86
M5	77	75	0.96
M6	76	38	0.037
M7	50	100	0.999
Cytogenetic Group			
Favorable	91	96	0.134
Intermediate	79	76	0.359
Adverse	51	43	0.534
unknown	50	69	0.257
Age			
=< 50	83	77	0.108
> 50	73	78	0.225
MPO positive blast (%)			
< 50	68	66	0.709
>= 50	87	88	0.699
WBC at diagnosis ($x10^9$/L)			
=< 20	79	76	0.767
20 < =< 50	82	82	0.993
> 50	74	77	0.824
Performance status			
0, 1, 2	79	78	0.762
3	80	75	0.999

Table 4. Factors to predict CR in all evaluable patients by multivariate analysis

variables		odds ratio	*P* value
Cytogenetic Group	Favorable	10.39	< 0.0001
	Intermediate	4.67	< 0.0001
MPO positive blast	>= 50 %	2.64	< 0.0001
Induction therapy	IDR arm	0.97	0.854

Table 5. Adverse events (WHO Grades 3 to 5) after the start of induction therapy

	IDR group		DNR group		
	no. of patients	%	no. of patients	%	*P* value
Sepsis	46	8.7	26	4.9	0.021
Early Death*	25	4.7	11	2.1	0.026
Bleeding	19	3.6	23	4.4	0.532
Febrile neutropenia	416	78.2	406	77.4	0.761
Acute cardiac toxicity	10	1.9	4	0.8	0.112
Late onset cardiac failure	2	0.38	2	0.38	0.998

*: death within 60 days after the start of induction therapy

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

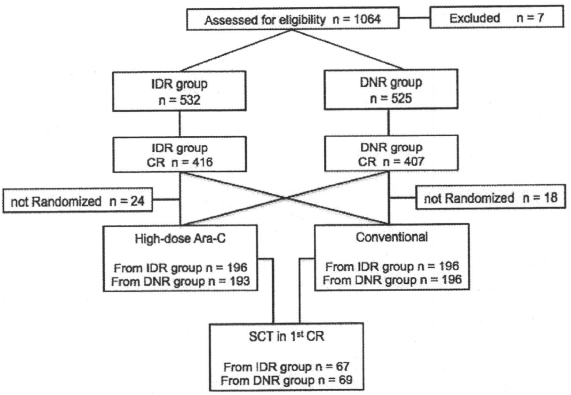

Figure 2a

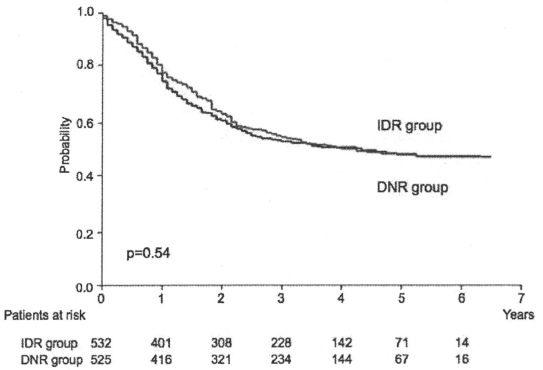

Figure 2b

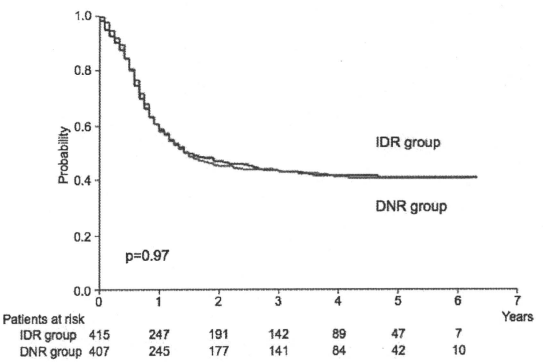

Figure 3a

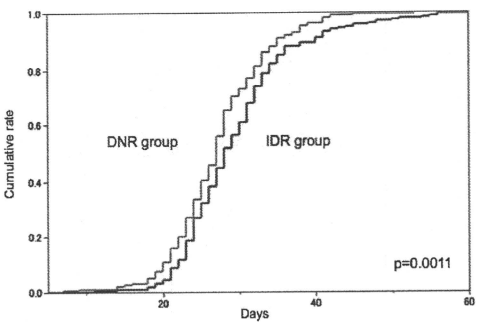

Figure 3b

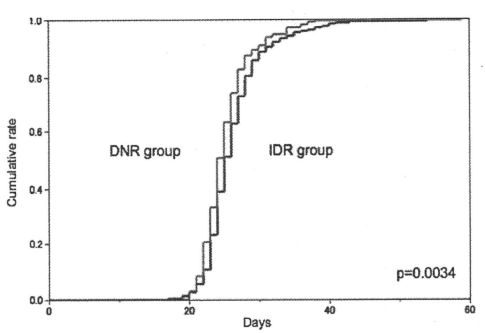

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Figure 4a

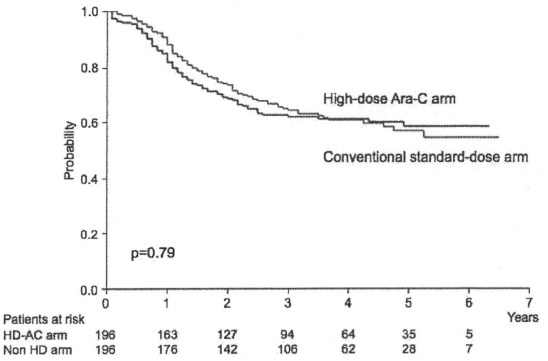
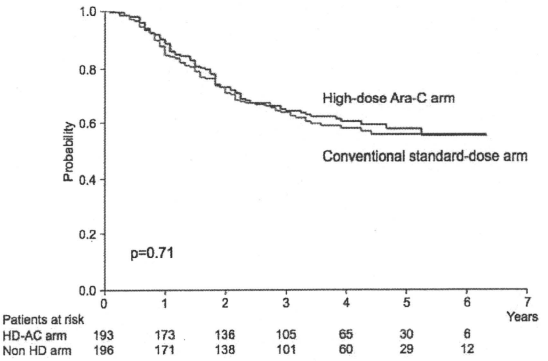


Figure 4b



Int J Hematol (2010) 92:490–502
DOI 10.1007/s12185-010-0672-z

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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Received: 25 March 2010 / Revised: 16 August 2010 / Accepted: 17 August 2010 / Published online: 10 September 2010

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 50×10^9/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 1.5×10^9/L and platelet counts were more than 100×10^9/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 1.5×10^9/L and a platelet count of at least 100×10^9/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