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ORIGINAL ARTICLE

Randomized trial of response-oriented individualized versus fixed-schedule induction chemotherapy with idarubicin and cytarabine in adult acute myeloid leukemia: the JALSG AML95 study

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Abstract A multicenter, prospective, randomized study was conducted to compare a response-oriented individualized remission induction therapy with a standard fixed-schedule induction therapy, using idarubicin (IDR) and cytarabine (Ara-C), in adult patients with acute myeloid leukemia (AML). Newly diagnosed patients with AML of age less than 65 were randomly assigned to receive either of the two schedules. Both groups received IDR (12 mg/m^2) for 3 days and Ara-C (100 mg/m^2) for 7 days. In the individualized group, if the bone marrow on day 8 did not become hypocellular with less than 15% blasts, patients received additional IDR for one more day and Ara-C for 2 or 3 more days. Patients achieving complete remission (CR) received the same post-remission therapy. The CR rate was 79.4% for the individualized group ($n = 209$) and 81.9% for the fixed group ($n = 221$) ($p = 0.598$). At a median follow-up of 81 months, 7-year predicted overall survival was 37% for the individualized group and 39% for

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the fixed group ($p = 0.496$), and 7-year predicted event-free survival was 22% for the individualized group and 23% for the fixed group ($p = 0.546$). Thus, the present study could not demonstrate any advantage of a response-oriented individualized induction therapy over a fixed-schedule induction therapy in this protocol setting.

Keywords Acute myeloid leukemia · Response-oriented individualized induction therapy · Idarubicin · Cytarabine

1 Introduction

In Japan, a response-oriented individualized induction therapy has been used for adult acute myeloid leukemia (AML) since the reporting of the success of DCMP two-step therapy using daunorubicin (DNR), cytarabine (Ara-C), 6-mercaptopurine (6MP) and prednisolone (PSL), by Uzuka et al. in the mid 1970s [1]. They reported a complete remission (CR) rate of more than 80% in adult AML, which is currently not surprisingly high but was remarkable in the mid 1970s even for a single institutional study. A subsequent multi-institutional study conducted at the Koseisho Leukemia Study Group using this DCMP two-step protocol could not replicate the high CR rate, but a subset analysis revealed the first-step alone could induce almost the same CR rate as the two-step therapy [2]. Accordingly, a response-oriented individualized induction therapy, the BHAC-DMP therapy, using enocitabine (BHAC), Ara-C, 6MP, and PSL, was developed, and Ohno et al. [3] reported more than 80% CR in adult AML by a single institutional study.

The multi-institutional AML87 study conducted by the Japan Adult Leukemia Study Group (JALSG) confirmed the high CR rate of response-oriented individualized BHAC-DMP therapy in adult AML, reporting an 80% CR rate [4]. Subsequent JALSG studies, AML89 [5] and AML92 [6], also employed the response-oriented individualized induction therapy, and reported 81 and 77% CR rates, respectively, in adult patients of age less than 65 years with non-M3 type AML. These CR rates were around 10% higher than those reported from cooperative study groups in the USA and Europe, where fixed-schedule induction therapies are used [7]. Therefore, even though the necessity for a randomized study was seriously discussed among JALSG members, it was not possible to find any fixed-schedule regimen worth comparing with the present individualized therapy.

In the above 3 JALSG studies, DNR was used as one of the key drugs. However, in the late 1980s, a new DNR analogue, idarubicin (IDR), was introduced clinically, and in the early 1990s, one single [8] and 2 multi-institutional studies [9, 10] reported that IDR plus Ara-C regimens could produce 70–80% CR rates in adult AML by fixed-schedule therapy, which were significantly higher than the 58–59% CR rates of DNR plus Ara-C regimens.

Consequently, after IDR had been approved in Japan in 1995, a randomized study using IDR and Ara-C was conducted, comparing a response-oriented individualized induction therapy with a fixed-schedule therapy in previously untreated adult patients with AML.

2 Patients and methods

2.1 Patients

From August 1995 to December 1997, 437 newly diagnosed adult patients with AML, aged 15–64 years, were consecutively registered from 79 institutions, which participated in JALSG. The enrolled number of patients per hospital varied from 1 to 23 with median number of 4, and about 60% of patients were registered from major hospitals listed in the institutions of the authors.

AML was diagnosed by the French-American-British (FAB) classification at each institution. Peripheral blood and bone marrow smears from all registered patients were sent to Nagasaki University and examined by May-Giemsa, peroxidase, and esterase staining. Then, diagnosis was reevaluated by the central review committee. FAB-M3 was not registered in this study. Eligibility criteria included adequate functioning of the liver (serum bilirubin level < 2.0 mg/dL), kidney (serum creatinine < 2.0 mg/dL), heart, and lungs, and an Eastern Cooperative Oncology Group performance status between 0 and 3. Patients were not eligible if they had prediagnosed myelodysplastic syndrome (MDS), but were eligible if they had no definite diagnosis of MDS, as confirmed by bone marrow histological analysis even when they had a previous history of

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hematological abnormality. Cytogenetic analyses were performed at either laboratories in participating hospitals or authorized commercial laboratories according to standard methods of G-banding. Cytogenetic abnormalities were grouped by standard criteria and classified according to the MRC classification [11]. The protocol was approved by institutional review board of each hospital. Informed consent was obtained from all patients before registration.

2.2 Treatment regimens

Patients were assigned randomly to receive either a response-oriented individualized induction therapy or a fixed-schedule induction therapy, using a centralized telephone procedure. All patients received IDR (12 mg/m^2/day, intravenously) from days 1 to 3 and Ara-C (100 mg/m^2/day, by 24-h continuous infusion) from days 1 to 7. Examination of bone marrow on the day 8 was evaluated at each participating hospital and the decision was made by the attending physician in charge of the hospital. In the individualized group, bone marrow aspiration was performed on day 8, and if the marrow was not severely hypoplastic and had more than 15% blasts, additional IDR was given on day 8 and Ara-C on days 8 to 10, or if the marrow was severely hypoplastic and had more than 15% blasts, additional IDR was given on day 8 and Ara-C on days 8 and 9. If patients suffered from documented infection on day 8, cancellation of additional chemotherapy was permitted according to the judgment of the attending physician (Fig. 1). The main aim of the individualized therapy was to give highly intensive but not too toxic doses of anti-leukemia drugs, especially IDR, to make the bone marrow severely hypoplastic, reduce the percentage of blasts to less than 5% within 10 days and obtain CR by the first course of induction therapy. In the fixed-schedule group (fixed group), patients did not receive additional doses regardless of their marrow status at day 8. If patients did not achieve CR by the first course, the same induction therapy was repeated at approximately 3- to 4-week intervals. If patients did not achieve CR with two courses, they were judged as failure cases.

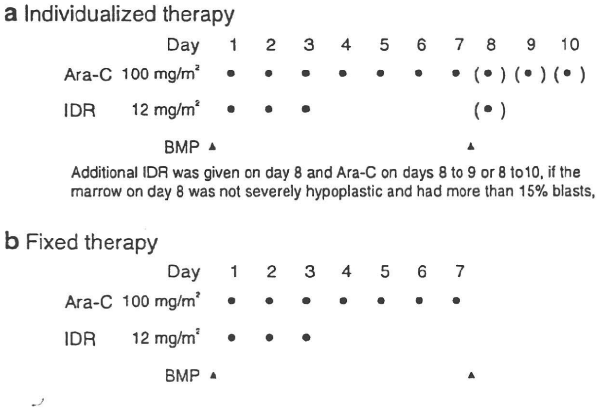

Fig. 1 Treatment scheme of induction therapy

All patients in both groups who had achieved CR planned to receive the same 3 courses of consolidation therapy. The first course consisted of mitoxantrone (MIT; 7 mg/m^2 by 30-min infusion on days 1–3) and Ara-C (200 mg/m^2 by 24-h continuous infusion on days 1–5). The second consisted of BHAC (200 mg/m^2 by 3-h infusion on days 1–7), DNR (50 mg/m^2 intravenously on days 1–3), 6MP (70 mg/m^2 orally on days 1–7), and etoposide (ETP; 100 mg/m^2 by 1-h infusion on days 1–5). The third consisted of BHAC (200 mg/m^2 on days 1–7) and aclarubicin (ACR; 14 mg/m^2 intravenously on days 1–7). Each consolidation course was given as soon as possible after WBC and platelet counts had recovered to more than 3,000/μL and 100,000/μL, respectively. Intrathecal methotrexate (15 mg), Ara-C (40 mg), and PSL (10 mg) were given after the second consolidation therapy for the prophylaxis of central nervous system leukemia.

After the completion of consolidation therapy, all patients planned to receive 6 courses of maintenance/intensification therapy every 2 months. The first course consisted of BHAC (170 mg/m^2 on days 1–5), DNR (40 mg/m^2 on days 1 and 4), and 6MP (70 mg/m^2 on days 1–7). The second consisted of BHAC (170 mg/m^2 on days 1–5) and MIT (5 mg/m^2 on days 1 and 2). The third consisted of BHAC (170 mg/m^2 on days 1–5), ETP (80 mg/m^2 on days 1, 3, and 5), and vindesine (2 mg/m^2 intravenously on days 1 and 8). The fourth consisted of BHAC (170 mg/m^2 on days 1–5), ACR (14 mg/m^2 on days 1–4) and 6MP (70 mg/m^2 on days 1–7), the fifth was the same as the first, and the sixth was the same as the third. Each course was given at 2-month intervals.

Best supportive care, including administration of antibiotics and platelet transfusion from blood cell separators, was given if indicated. When patients had life-threatening infections during neutropenia, the use of granulocyte colony-stimulating factor was permitted.

2.3 Response criteria and statistical analysis

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, recovery of peripheral neutrophil counts over 1,000/μL and platelet counts over 100,000/μL, and no evidence of extramedullary leukemia. CR had to continue for at least 4 weeks, but the date of CR was defined as the first day when these criteria were fulfilled. Relapse was defined as the presence of at least one of the following: recurrence of more than 10% leukemic cells in bone marrow, any leukemic cells in peripheral blood, and appearance of extramedullary leukemia.

Overall survival (OS) was calculated from the first day of induction therapy to death by any cause and censored at the last follow-up. Event-free survival (EFS) was computed from the first day of induction therapy to relapse or death by any cause and censored at the last follow-up, and the survival time of patients who did not achieve CR was defined as 0 days. Relapse-free survival (RFS) for patients who achieved CR was measured from the date of CR to relapse or death by any cause and censored at the last follow-up. Patients who underwent allogeneic bone marrow transplantation (BMT) were censored at the date of BMT or not censored according to the object of the analysis. Kaplan–Meier product-limit estimates were used to determine OS, EFS, and RFS. To test factors to predict CR, χ^2 test and Wilcoxon rank-sum test were used for univariate analysis and the multiple logistic regression model for multivariate analysis. For comparison of OS, EFS, and RFS, the log-rank test was used for univariate analysis and Cox's proportional hazard model for multivariate analysis. JMP software (SAS Institute Inc., Cary, NC, USA) was used for the analysis; p values less than 0.05 (two-sided) were considered statistically significant. Analysis was done on an intent-to-treat basis.

3 Results

3.1 Patient population and characteristics

Of 437 patients registered, 7 patients were judged as ineligible by the central review committee because of other diseases: one refractory anemia with excess of blast, 5 mixed-lineage leukemia, and one acute lymphoblastic leukemia (ALL), with 430 patients considered evaluable. Two hundred nine patients received the individualized therapy and 221 the fixed-schedule therapy. Pretreatment characteristics are presented in Table 1. There were no major imbalances between the two randomized groups. Overall, the median age was 44 years, and 154 patients (36%) were of age 50 years or older. Cytogenetic analysis was reported in 414 patients (96%), and the cytogenetic prognostic groups were equally distributed in both arms.

3.2 Overall treatment results

Of 430 evaluable patients, 347 (80.7%) achieved CR. Of 209 patients in the individualized group, 166 (79.4%) achieved CR, and of 221 in the fixed group, 181 (81.9%) obtained CR ($p = 0.516$) (Table 2). CR rates related to FAB classification, age, and cytogenetics are shown in Table 2, and there were no statistically significant differences between the two groups. In the individualized group, of 41 patients with favorable chromosomes, 39 (95%) achieved CR, of 133 with intermediate chromosomes, 109 (79%) achieved CR, and of 28 with adverse chromosomes, 17 (61%) achieved CR. In the fixed group, of 49 patients with favorable chromosomes,

Table 1 Pretreatment characteristics

	Individualized group ($n = 209$)	Fixed group ($n = 221$)
Median age (range)	44 years (15–64)	44 years (15–64)
PS 0	34.9%	38.5%
PS 1	42.6%	45.2%
PS 2	14.4%	9.5%
PS 3	8.1%	6.8%
Leukocyte counts > 50,000/μL	17.7%*	29.9%*
Peroxidase positivity ≥ 50%	62.8%	64.2%
Presence of Auer body (%)	37.5%	46.1%
Presence of trilineage dysplasia	25.4%	21.2%
LDH ≥ 500 IU/L	65.9%	69.1%
Cytogenetics		
Favorable	19.6%	22.2%
Intermediate	63.6%	59.7%
Adverse	13.4%	14.0%
Unknown	3.3%	4.1%

* $p < 0.05$

Table 2 CR rates related to FAB classification, age, and cytogenetics

	All cases		Individualized group		Fixed group	
	No.	CR (%)	No.	CR (%)	No.	CR (%)
FAB						
M 0	16	62.5	8	62.5	8	62.5
M 1	80	85.0	41	85.4	39	84.6
M 2	192	82.3	95	77.9	97	86.6
M 4	108	78.7	55	80.0	53	77.4
M 5	20	90.0	5	100.0	15	86.7
M 6	8	50.0	2	50.0	6	50.0
M 7	6	66.7	3	66.7	3	66.7
Age						
15–19	40	90.0	19	100.0	21	81.0
20–29	65	78.5	29	75.9	36	80.6
30–39	71	81.7	41	75.6	30	90.0
40–49	100	83.0	45	77.8	55	87.3
50–59	105	77.1	53	79.2	52	75.0
60–64	49	77.6	22	77.3	27	77.8
Cytogenetics						
Favorable	90	93.3	41	95.1	49	91.8
Intermediate	265	80.8	133	78.9	132	82.6
Adverse	59	62.7	28	60.7	31	64.5
Unknown	16	75.0	7	71.4	9	77.8
Total	430	80.7	209	79.4	221	81.9

45 (92%) achieved CR, of 132 with intermediate chromosomes, 109 (83%) achieved CR, and of 31 with adverse chromosomes, 20 (65%) achieved CR.

In the individualized group, 149 patients (71%) achieved CR after the first course, and 79 (38%) patients who had received additional chemotherapy during the first course, 56 (71%) achieved CR. In the fixed group, 159 (72%) achieved CR after the first course (Table 3; Fig. 2). CR rates between patients who had equal to or more than 15% of blasts in bone marrow on day 8 and those had less than 15% were not significantly different in the individualized group (75 and 63%, respectively; $p = 0.09$), but were significantly different in the fixed group (81 and 56%, respectively; $p < 0.001$).

Myelosuppression judged by the nadir of leukocyte counts and the period of leukocyte count less than 1,000/μL after the first course of induction therapy was significantly more severe in the individualized group, as shown in Table 4. Early death within 30 days occurred in 10 (4.8%) in the individualized group and 4 (1.8%) in the fixed group ($p = 0.105$). There were no statistically significant differences in the distribution or frequency of complications between the two groups.

Significant favorable prognostic features for the achievement of CR were cytogenetic risk group (favorable or intermediate), blast peroxidase positivity of 50% or more, and pretreatment LDH value of less than 500 IU/L. These features were independent by the logistic regression analysis and not different between the two groups.

All courses of consolidation therapy were administered to 72% of patients in the individualized group and 80% in the fixed group ($p = 0.087$), and all courses of maintenance therapy were administered to 36 and 41% ($p = 0.365$), respectively. The most common reason for these cancellations was relapse in both groups (34 and 42 patients, respectively). The second common reason was BMT in the first remission (22 and 12 patients, respectively).

At a median follow-up of 81 months, 23 patients underwent BMT in the first remission, 29 after relapse and 4 without remission in the individualized group, and 15, 32 and 7 patients, respectively, in the fixed group. If patients who underwent BMT were censored at the date of transplantation to decrease the influence of BMT, 7-year predicted OS was 37% for the individualized group and 39% for the fixed group ($p = 0.496$) (Fig. 3a), and 7-year predicted EFS was 22 and 23%, respectively ($p = 0.546$) (Fig. 3b). If patients who underwent BMT were not censored, 7-year predicted OS was 35 and 35%, respectively

Table 3 Effect of individualized induction therapy

	Patients (%)	CR after first course	
		n	%
Individualized group	209	149	71
Additional chemotherapy −	130 (62)	93	72
Additional chemotherapy +	79 (38)	56	71
Fixed group	221	159	72

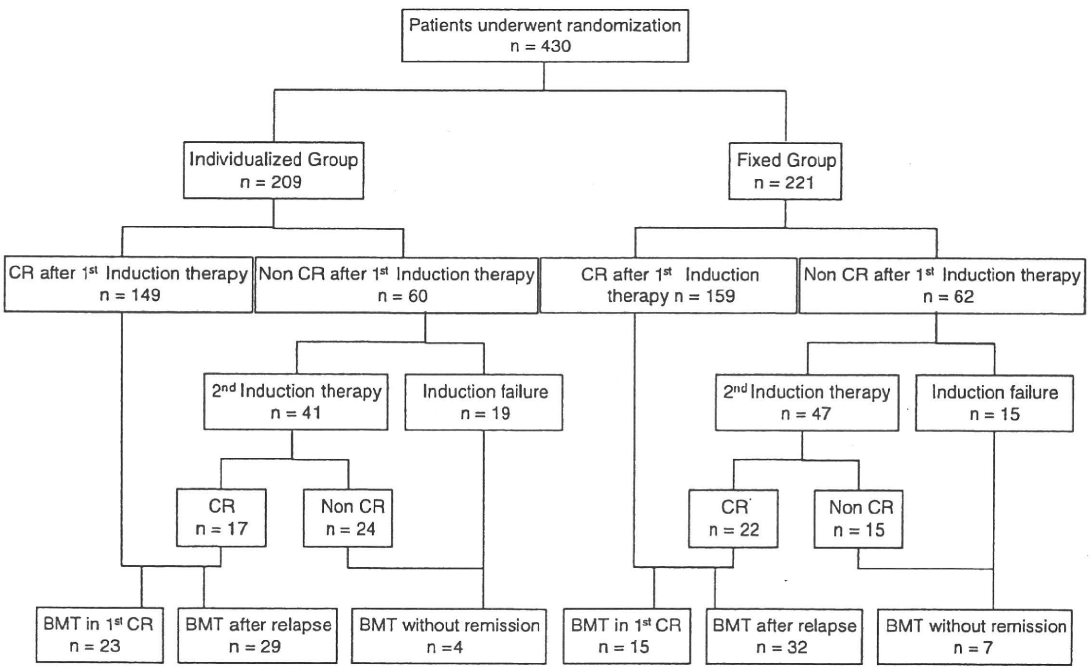

Fig. 2 Flow diagram: study design and outcome

Table 4 Comparison of treatment outcome

	Individualized group ($n = 209$)	Fixed group ($n = 221$)	p
CR rate (%)	79.4	81.9	0.516
After the first course	71.3	71.9	
After the second course	8.1	10.0	
Marrow blasts at day 8	12.9 ± 17.8%	11.1 ± 18.4%	0.021
Nadir of WBC[a]	328 ± 205/μL	394 ± 215/μL	0.0002
Period of WBC < 1,000/μL[a]	19.6 ± 9.8 days	17.8 ± 8.5 days	0.024
Days to CR[a]	38.9 ± 17.5	38.5 ± 16.2	0.802
Days till the consolidation therapy	49 ± 22	46 ± 18	0.157
Early death rate			
Within 30 days	4.8%	1.8%	0.105
Between 30 and 60 days	0.9%	1.4%	
Overall survival at 7 years	37%	39%	0.496
Event-free survival at 7 years	22%	23%	0.546

Data with ± denotes mean ± standard deviation

[a] After the initial course of induction therapy

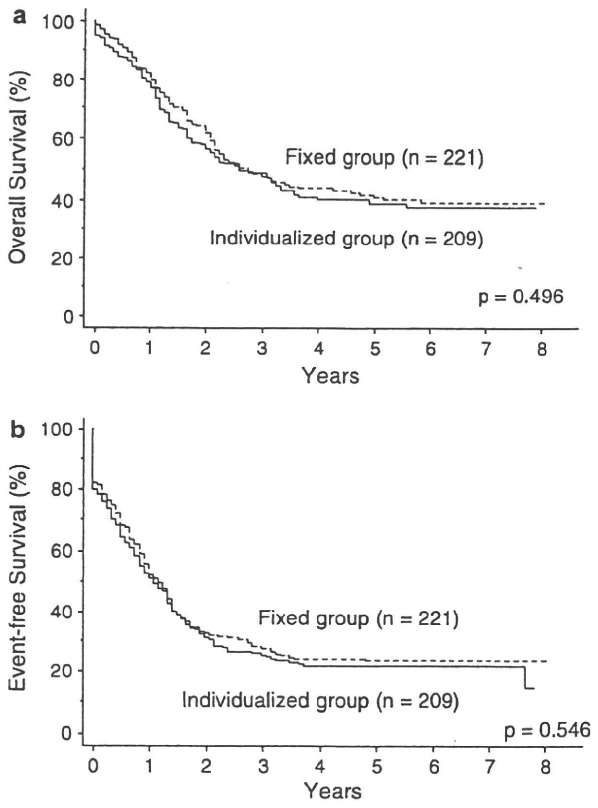

Fig. 3 Overall survival (**a**) and event-free survival (**b**). Predicted 7-year OS was 37% for the individualized group ($n = 209$) (*solid line*) and 39% for the fixed group ($n = 221$) (*dotted line*) ($p = 0.496$), and EFS was 22% for the individualized group (*solid line*) and 23% for the fixed group (*dotted line*) ($p = 0.546$)

($p = 0.840$), and 7-year predicted EFS was 23 and 24%, respectively ($p = 0.717$). Significant adverse prognostic features for OS were absence of Auer body, cytogenetic risk group (adverse), and age more than 30 years, and those for EFS were blast peroxidase positivity less than 50%, cytogenetic risk group (adverse), pretreatment LDH value equal or more than 500 IU/L, and FAB classification (M0, M6, or M7). When patients who underwent BMT were censored, RFS of CR patients was 27% for the individualized group and 29% for the fixed group ($p = 0.712$). Significant adverse prognostic features for RFS of CR patients were cytogenetic risk group (adverse) and FAB classification (M0, M6, or M7). There were no significant differences in these prognostic features between the two groups. However, among patients of age 50 years or older, the individualized group had significantly lower RFS (17%) than the fixed group (34%, $p = 0.026$), but there was no such difference of RFS (34 and 25%, respectively, $p = 0.194$) among patients of age less than 50 years.

4 Discussion

Most drug therapies are generally carried out in a response-oriented and individualized manner. Physicians adjust the dosage and treatment period depending on the response of patient's disease to the administered drugs. The reason why cancer chemotherapy is generally carried out by fixed dosage and period is because myelosuppression, the most important toxic effect of cytotoxic drugs, appears 7–10 days after the discontinuation of drugs. Myelosuppression is usually judged by leukocyte or platelet counts in the peripheral blood. However, if it is judged by bone marrow itself it is possible to obtain information on myelosuppression directly and earlier. Although the present individualized therapy requires frequent bone marrow aspirations and a prompt decision by attending physicians, well-trained hematology oncologists have little difficulty in

making such a decision. In addition, the present protocol states that, if the decision is difficult due to equivocal findings, additional drugs should be given.

It was considered that the higher CR rates of previous JALSG studies for adult AML: AML87 [4], AML89 [5] and AML92 [6], were due to response-oriented individualized therapy, giving highly intensive but not too toxic doses of anti-leukemia drugs, especially IDR, to make the bone marrow severely hypoplastic, reduce the percentage of blasts to less than 5% within 10 days, and aim to obtain CR by the first course of induction therapy. For example, in the AML89 study, the primary objective of which was to compare Ara-C with BHAC in remission induction therapy, 130 (82%) of 159 patients in the DNR + Ara-C + 6MP + PSL group achieved CR by this individualized induction therapy [5]. It is clear that without a prospective randomized study, one cannot argue whether the individual therapy is superior to a standard fixed-schedule remission induction therapy. However, it is noteworthy, that in the 3 randomized studies in the USA mentioned in Sect. 1, which compared IDR plus Ara-C with DNR plus Ara-C, the fixed-schedule therapy with DNR plus Ara-C resulted in merely 57–58% CR rates, while IDA plus Ara-C regimens produced 70–80% CR rates [8–10].

Disappointingly, the present study could not demonstrate that response-oriented individualized therapy was superior to the fixed-schedule therapy. Both regimens resulted in almost the same CR rates: 79 and 82%, respectively. Actually, both therapies produced very good CR rates. The results were interpreted as follows: IDR is a good but very powerful drug, therefore, additional IDR and Ara-C on day 8 or later may not be necessary and gave too much myelosuppression. In fact, in the individualized group, leukocytopenia was significantly more severe and its duration was significantly longer, and early death within 30 days tended to occur more frequently. From the present study it is suggested that response-oriented individualized therapy could be successful in cases where DNR is used as a key drug. Usui et al. [12] reported that the optimal dose of DNR in the induction therapy for newly diagnosed adult AML was approximately 280 mg/m^2 (40 mg/m^2 for 7 days), which was more than its conventional dose of 40–60 mg/m^2 for 3 days.

It is very interesting that among patients of age 50 years or older, the individualized group had significantly lower RFS than the fixed group, but there was no such difference in younger patients. However, we cannot clearly explain the real reason of this observation. There may be potential sources of bias in our subset analysis of clinical data that have many confounding factors. Therefore, we must be cautious in drawing a conclusion from this observation.

So far, CR rates around 80% for newly diagnosed adults of age less than 65 years with non-M3 AML seems to be the upper limit by currently available anti-leukemia drugs in multi-institutional studies [7]. To increase the CR rates and improve treatment outcomes, novel drugs other than cytotoxic ones such as all-*trans* retinoic acid (ATRA) for acute promyelocytic leukemia (APL) are needed. With ATRA in combination with conventional cytotoxic drugs such as IDR and Ara-C, CR rates around 95% and more than 80% overall survival for APL with PML/RARα can be obtained [13, 14]. The remarkable success of molecule targeting therapy with ATRA against APL as well as imatinib mesylate against chronic myeloid leukemia [15] and Philadelphia chromosome-positive ALL [16] with BCR/ABL is a good example. Specific molecule targeting therapy should be developed against pathogenic molecules responsible for leukemogenesis. Meanwhile, it is necessary to explore separate treatment regimens for prognostically different subtypes of AML with conventionally available modalities in order to increase the cure rate of adult leukemia.

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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

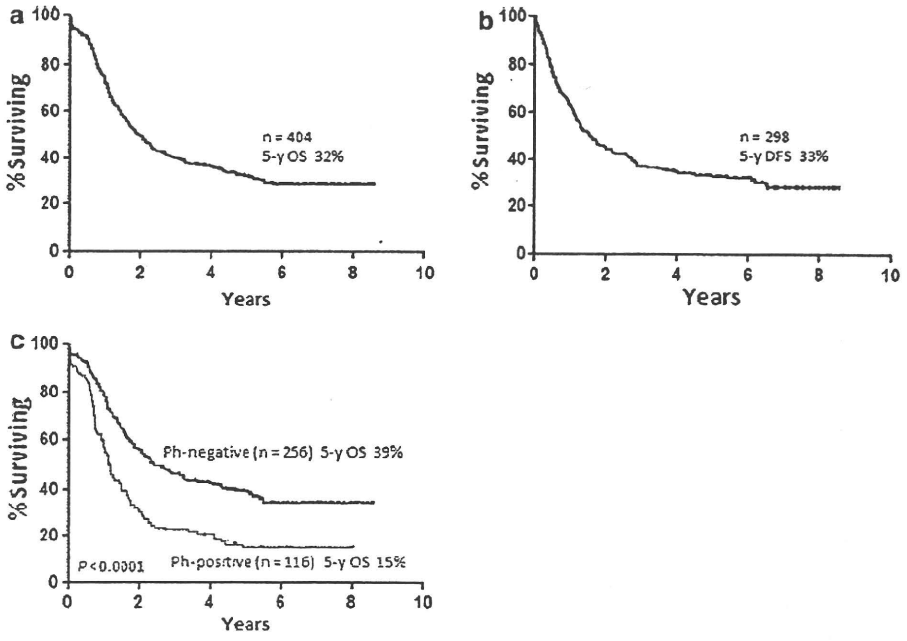

Fig. 1 Survival analysis. **a** Overall survival (OS) of 404 eligible patients. **b** Disease-free survival (DFS) of 298 patients who achieved complete remission. **c** OS of 116 Philadelphia chromosome (Ph)-positive patients and 256 Ph-negative patients

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

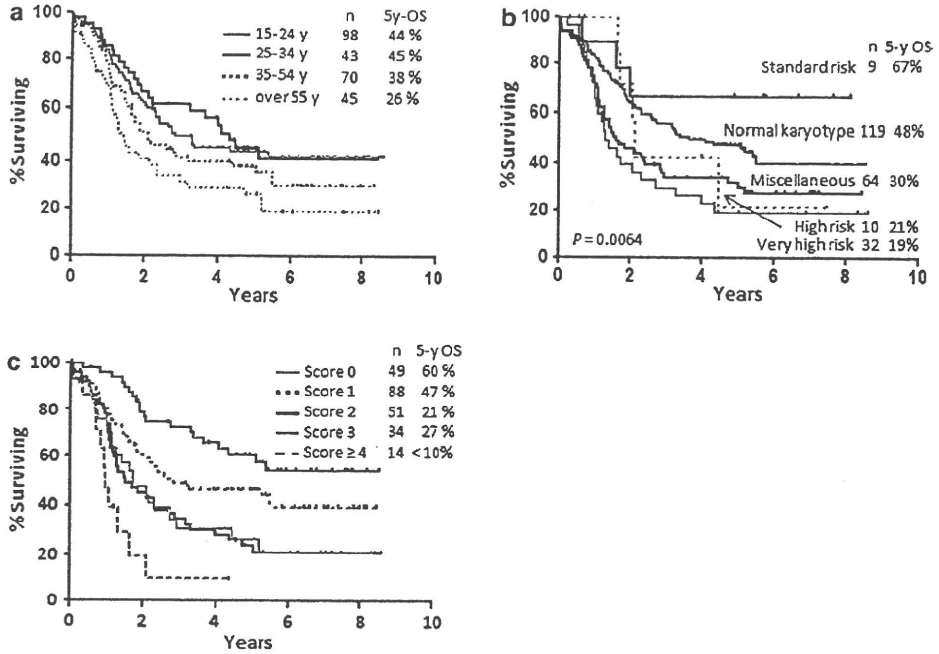

Fig. 2 Survival analysis of Philadelphia chromosome-negative patients. **a** Overall survival (OS) by age group. **b** OS by karyotype category according to the modified MRC UKALLXII/ECOG E2993ALL cytogenetic subgroups: the very high risk group included t(4;11), complex karyotype defined as more than 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).

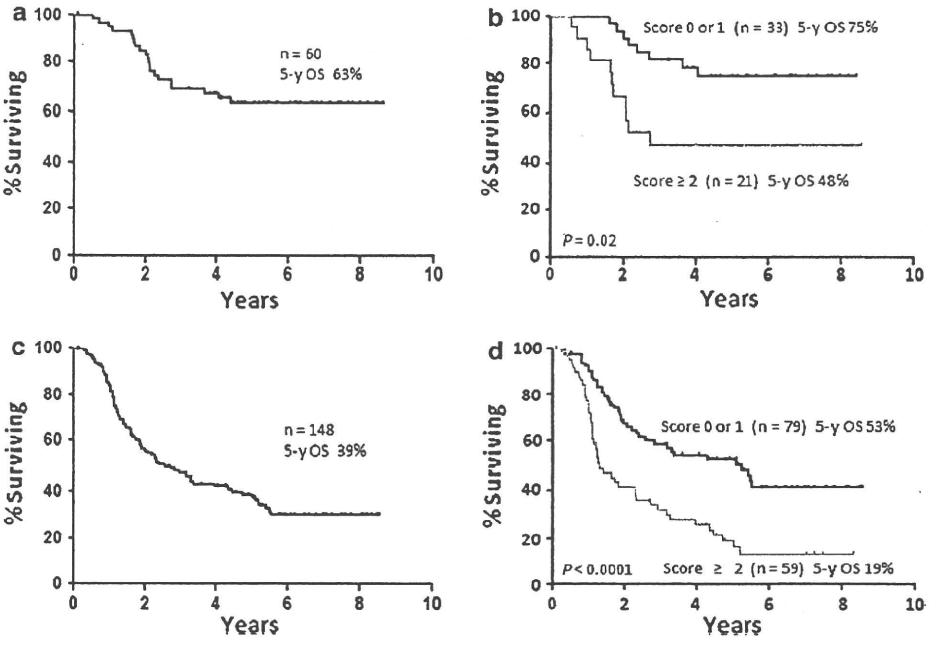

Fig. 3 Survival analysis of Philadelphia chromosome-negative patients with/without allogeneic-hematopoietic stem cell transplantation (allo-HSCT) in first complete remission. **a** Overall survival (OS) in those who received allo-HSCT. **b** OS in those who received allo-HSCT by dichotomized prognostic 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).

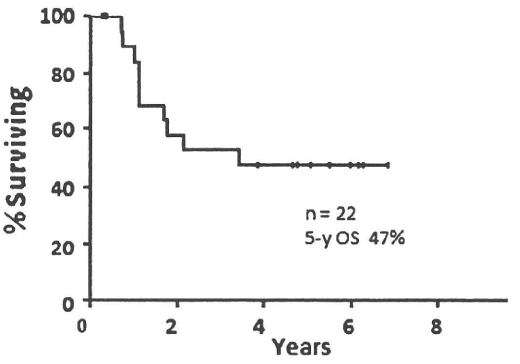

Fig. 4 Overall survival (OS) of Philadelphia chromosome-positive patients who received allo-hematopoietic transplantation in first complete remission

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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