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ORIGINAL REPORT

Prospective Study of a Pirarubicin, Intermediate-Dose Cytarabine, and Etoposide Regimen in Children With Down Syndrome and Acute Myeloid Leukemia: The Japanese Childhood AML Cooperative Study Group

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ABSTRACT

Purpose
To evaluate a less intensive chemotherapeutic regimen specifically designed for patients with Down syndrome (DS) and acute myeloid leukemia (AML), and to determine the prognostic factors for event-free survival.

Patients and Methods
Seventy-two patients with AML-DS were treated with remission induction chemotherapy consisting of pirarubicin (25 mg/m^2/d for 2 days), cytarabine (100 mg/m^2/d for 7 days), and etoposide (150 mg/m^2/d for 3 days). Patients received four courses of intensification therapy of the same regimen. Prophylaxis for CNS leukemia was not included.

Results
All but two patients were younger than 4 years, and 67 of the 72 patients (93%) were diagnosed as acute megakaryoblastic leukemia (AMKL). Seventy of the 72 patients (97.2%) achieved a complete remission (CR), and the estimated 4-year event-free survival (EFS) rate was 83% ± 9%. Nine patients relapsed, and one died as a result of pneumonia during CR. Multivariate analysis revealed that the presence of monosomy 7 was a greater risk factor of adverse outcome (odds ratio = 5.67; P = .027).

Conclusion
A less intensive chemotherapeutic regimen produces excellent outcomes in standard-risk AML-DS patient. Risk-oriented therapy should be considered for future trials in AML-DS.

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INTRODUCTION

Patients with Down syndrome (DS) have a 10- to 20-fold increased risk of developing acute leukemia.[1,2] In particular, the relative risk of developing acute megakaryoblastic leukemia (AMKL) is estimated to be 500 times higher in children with DS than in those without DS.[3]

Before the 1990s, most patients with acute myeloid leukemia (AML)-DS were treated outside clinical trials and received suboptimal therapy, resulting in dismal outcomes.[4,5] The first report that there was a significantly better outcome for children with AML-DS came from the Pediatric Oncology Group (POG) in 1992.[6] After recognition of the favorable outcome when patients were treated with protocols of the cooperative study groups for childhood AML, there has been an increase in recruitment to collaborative protocol studies.[7-10] However, it has become apparent that induction failure and relapse are rare, but treatment-related deaths are frequent in most series. Since then, several collaborative groups have adapted their AML protocols for AML-DS by reducing the dose of chemotherapeutic agents.[11,12] In recent reports, the 5-year event-free survival (EFS) has exceeded 80%, largely because of the reduction in treatment-related deaths, with a fall from 30% to 40% in the early 1990s to 3% to 5% in recent studies.[13-15]

A treatment regimen specifically designed for AML-DS has been used in Japan since the mid-1980s.[16,17] The regimen is less intensive and does not include high-dose cytarabine and prophylaxis against CNS leukemia. On the basis of encouraging results, since 1999, we have conducted a prospective multi-institutional study for AML-DS using a

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slightly modified protocol. In the present study, we present the outcome of this study in 72 patients with AML-DS and analyze the prognostic risk factors for survival.

PATIENTS AND METHODS

Patients with AML-DS aged less than 18 years were eligible for treatment according to the DS protocol proposed by the Japanese Childhood AML Cooperative Study Group. Neonates with transient myeloproliferative disorder (TMD), defined as appearance of myeloid blasts within the first months of life, and those with spontaneous remission were not included. The protocol was approved by the institutional review board, and written informed consent was obtained from the parents of all patients.

The diagnosis of AML was classified according to the French-American-British (FAB) cooperative group criteria.[18] The diagnosis of AMKL, corresponding to FAB M7, was made irrespective of the initial blast count, which was often less than 30%. For the assessment of megakaryocytic lineage, at least 10% of the blast cells needed to be positive for one or more of the platelet-specific antigens such as CD36, CD41, CD42, and CD61. Immunophenotyping was performed at the reference laboratories. Morphology of bone marrow or peripheral blood smears and results of karyotyping were centrally reviewed.

Remission induction chemotherapy consisted of pirarubicin (25 mg/m^2/d, on days 1 and 2), which was estimated to be equivalent as 25 mg/m^2/d of daunomycin (DNR), cytarabine (100 mg/m^2/d on day 1 through 7), and etoposide (150 mg/m^2/d on day 3 through 5). Each drug was administered over a 1-hour infusion. Patients who achieved complete remission (CR) received four courses of intensification therapy of the same regimen. Prophylactic therapy for CNS leukemia was not included in the protocol.

Estimation of survival was performed using the Kaplan-Meier method, and the differences were compared using the log-rank test.[19] EFS was defined as time from diagnosis to any event (induction failure, relapse, or death) and overall survival (OS) was defined as the time from diagnosis to death from any cause. Statistical differences were analyzed using the χ^2 test. We used the Cox regression model in a multivariate analysis of predictive factors for EFS. *P* values less than.05 were considered significant.

Table 1. Clinical and Laboratory Characteristics of AML Patients With Down Syndrome (N = 72)

Characteristic	No.	%
Age, months		
Median, months	12	
0-12	8	11
12-24	34	47
24-36	23	32
36-48	5	7
≥ 48	2	3
Sex		
Male	44	61
Female	28	39
WBC, $\times 10^9$/L		
Median	5.8	
Range	1.9-107.0	
Hb, g/dL		
Median	8.4	
Range	3.5-15.7	
Pl, $\times 10^9$/L		
Median	31	
Range	1.0-240.0	
FAB classification		
M1	1	1.4
M2	1	1.4
M5	1	1.4
M6	1	1.4
M7	67	93.0
Unclassified	1	1.4
Cytogenetics		
Trisomy 8	10	14
Monosomy 7	6	8
Additional 21	5	7
t(9;11)	1	1.4

Abbreviations: AML, acute myeloid leukemia; FAB, French-American-British.

RESULTS

Between January 2000 and June 2004, 72 patients with AML-DS were enrolled onto the study. The interim analysis was performed in December 2005. The median follow-up period was 44 months, ranging from 19 months to 70 months. Characteristics of the 72 patients are summarized in Table 1. Their median age was 22 months (range, 7 to 88 months). All but two patients were younger than 4 years. Forty-four patients were male and 28 were female. Major congenital heart anomalies were present in eight patients. Nine patients had a history of TMD as neonates, and 8 had a history of myelodysplastic syndrome. The WBC counts ranged from 1.9 to 107 $\times$ 10^9/L (median, 5.8 $\times$ 10^9/L), the hemoglobin levels from 3.5 to 15.7 g/dL (median: 8.4 g/dL), and the platelet counts from 1 to 240 $\times$ 10^9/L (median, 31 $\times$ 10^9/L). At the time of initial presentation, 38 patients had less than 30% of leukemic blasts in the bone marrow. However, the percentage of leukemic blasts increased within a short period, and they were finally diagnosed as FAB M7. The distribution of FAB subtypes showed a predominance of M7 (93%). One patient each was classified as FAB M1, M2, M5a, or M6. One patient with low blast counts could not be classified. Cytogenetic results were available for 71 patients. In addition to the constitutional aberrations, an additional chromosome was found, involving chromosomes 8 (n = 10) and 21 (n = 5). Six patients had monosomy 7.

A total of 70 of the 72 patients (97.2%) achieved a CR: 65 patients after one cycle of the induction course; four patients after receiving a further cycle of consolidation after the induction course; and one of the three patients with M3 marrow after induction course who then achieved a CR after intensified reinduction therapy containing high-dose cytarabine. Two patients received unrelated cord blood transplantation (UCBT) during the first CR; both survived. These two patients had a chromosomal abnormality of t(9;11) or monosomy 7 and both were excluded at the time of transplantation.

Nine patients relapsed in the bone marrow and one of these nine had a CNS relapse simultaneously. The patient who had CNS relapse had megakaryoblastic leukemia. No patient suffered from isolated CNS relapse. Eight of the nine patients relapsed during chemotherapy. All patients with relapse during chemotherapy and resistant disease died without achieving a second CR. One patient who relapsed after cessation of the chemotherapy received bone marrow transplantation (BMT) from an human leukocyte antigen–matched sibling donor and successfully achieved a second CR. However, he died of pneumonia 2 years after BMT. Chemotherapy-related mortality was low; only one patient died as a result of pneumonia during the second course of intensification. Fifty-eight patients remain in the first CR, with a median duration of 43 months (range, 18 to 69 months). The 4-year EFS was 83.3% $\pm$ 9.1% and the 4-year OS was 83.7% $\pm$ 9.5% (Fig 1).

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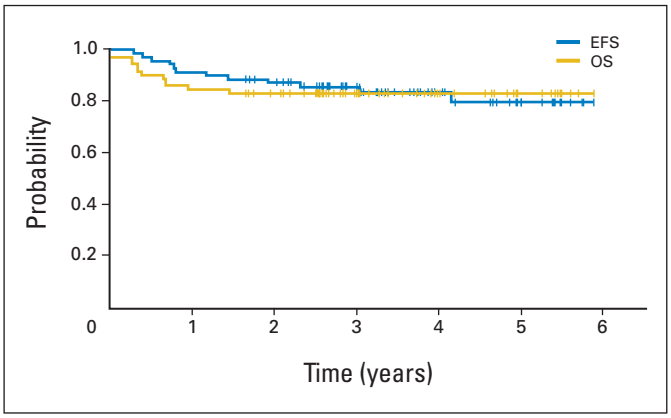

Fig 1. Actuarial survival rate for the AML99 Down syndrome protocol. Among the 72 patients, 70 achieved complete remission (CR). Nine patients relapsed. One patient died as a result of pneumonia during the first CR. Two patients received cord blood transplantation in first CR. Fifty-eight patients remained in first CR. The 3-year overall survival (OS) was 84% and the 3-year event-free survival (EFS) 83%, respectively.

We evaluated the predictive factors for EFS in 70 patients, excluding the two patients who received UCBT during the first CR. There was no difference in outcome with respect to age group. The 40 patients who were aged 2 years or younger had a 4-year EFS of 85% ± 11.8%, compared with the 30 patients older than 2 years, who had a 4-year EFS of 80% ± 15.7% ($P = .478$). We also compared the EFS of the 63 patients who were aged 3 or younger and the seven patients older than 3 years. The 4-year EFS was 84.1% ± 9.6% and 71.4% ± 28.6%, respectively ($P = .282$). Only two patients were older than 4 years: one with FAB M5a and t(9;11), who received UCBT and is still living, and the other with FAB M2, who also remains in the first CR.

Table 2 shows the outcomes for the six patients with monosomy 7. Five of these six patients were diagnosed as FAB M7 and the other as FAB M1. Five of the six patients achieved a CR, but two then relapsed and received hematopoietic stem-cell transplantation (HSCT); however, both of them died. One patient who received UCBT in the first CR is alive and well. Only two of the five patients who did not undergo HSCT are alive with no evidence of disease. Excluding the patient who received UCBT in the first CR, three of the other five patients experienced induction failure or relapse. The 3-year EFS in the five patients with monosomy 7 was significantly worse than in the 65 patients without monosomy 7 (40,0% ± 26.3% *v* 86.2% ± 8.8%; $P = .007$; Fig 2).

In the multivariate analysis, we evaluated the predictive factors for EFS (Table 3). The presence of monosomy 7 was a greater risk factor of adverse outcome (odds ratio = 5.67; $P = .027$). There was no difference in outcome between the patient groups of age older than 1.8 years and 0 to 1.8 years (odds ratio = 2.640; $P = .170$).

The regimen-related toxicities were relatively tolerable. Table 4 shows the duration of neutropenia and incidence of grade 3 or 4 toxicity during induction and each intensification phase of therapy. Only one patient died as a result of pneumonia in the second course of intensification. Subclinical cardiac dysfunction was revealed by echocardiography in four patients after the induction therapy. Reduction of chemotherapy dose was required in one of them. All but one patient received all scheduled courses of therapy without dose reduction. Although the patients were treated with the same regimen, the duration of neutropenia was longer during the induction phase than during the other courses of intensification.

DISCUSSION

During the last decade, several large collaborative studies have reported the experience of AML-DS children treated using standard AML protocols.[6-10] The most remarkable finding of these studies has been the lower incidence of induction failure and relapse compared with non-DS children with AML. Consistent with the clinical results, in vitro studies have demonstrated that DS leukemic cells are more sensitive to several chemotherapy drugs compared with non-DS leukemic cells.[20-22] Zwaan et al demonstrated a 12-fold increase in sensitivity to cytarabine in DS-AML cells compared with non-DS AML cells, as well as increased sensitivity to anthracyclines (two- to seven-fold) and etoposide (20-fold).[23] Mutation of the *GATA-1* gene is the hallmark of DS-AML.[24] Taub and Ge[25] provided the evidence for the potential linkage of the *GATA-1* mutation and the increased sensitivity to cytarabine resulting from effects on *cytidine deaminase* gene expression.

Conventional treatment of AML-DS has been associated with excessive treatment-related mortality (TRM). Thus, several collaborative study groups have adapted their standard AML protocol for AML-DS by reducing the dose of drugs or prolonging the interval between chemotherapy courses. In the Children's Oncology Group

Table 2. Outcome of AML-DS Patients With Monosomy 7

UPN	Age (months)	Sex	Karyotype	CR	Relapse	HSCT	Duration of Survival (months)	Cause of Death
A097	20	Female	47,XX,−7,−16, +21, +r1, +mar	Yes	Yes	UCBT (2nd CR)	27	Leukemia
A357	32	Male	47,XY,−4,−7,−13,−16, +21, add(22)(p13), +r1, +r2, +mar	No	NA	No	3	Leukemia
A408	21	Female	90,XXXX,−3,−7,−9, del(11)(q?),−18, +21, +21	Yes	No	No	> 30	
A425	22	Female	48,XX,−7, +21, +21, +r1	Yes	NA	UCBT (1st CR)	> 30	
A467	39	Male	48,XY,−7, +8, +21, +r1	Yes	No	No	> 29	
A538	15	Male	48,XY,−7, +21	Yes	Yes	Sib-BMT (non-CR)	49	Leukemia

Abbreviations: AML-DS, acute myeloid leukemia–Down syndrome; UPN, unique patient number; CR, complete remission; HSCT, hematopoietic stem-cell transplantation; UCBT, unrelated cord blood transplantation; Sib-BMT, bone marrow transplantation from human leukocyte antigen–matched sibling; NA, not assessable.

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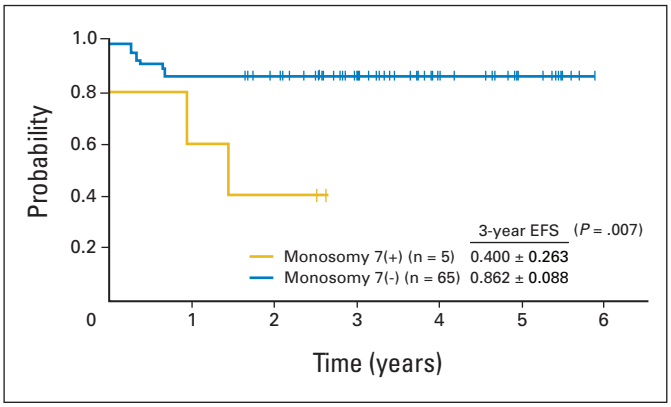

Fig 2. Actuarial survival rate by monosomy 7 status. The 3-year event-free survival (EFS) in the five patients with monosomy 7 was 40.0%, compared with 86.2% in the 65 patients without monosomy 7 ($P = .007$). Multivariate analysis revealed that the presence of monosomy 7 was a greater risk factor of adverse outcome (odds ratio: 5.67; $P = .027$).

(COG) trial A2971 (n = 130),[12] etoposide, dexamethasone, and the maintenance course were eliminated from the previous CCG2891 protocol. The outcome in COG A2971 was not different to that in CCG2891: the 3-year EFS was 79% versus 77%. In the AML-BFM98 study (n = 66),[11] AML-DS patients were treated with reduced doses of anthracyclines and cytarabine compared with the previous AML-BFM93 protocol (n = 44). The cumulative doses of anthracyclines and cytarabine were 220 to 240 mg/m^2 and 23 to 29 g/m^2 in the BFM98 study, and 440 mg/m^2 and 23.3 g/m^2 in the BFM93 study, respectively. Outcome improved significantly for patients treated in the BFM98 study, with a 3-year EFS of 91% ± 4% versus 70% ± 7% in the BFM93 study ($P = .001$). In the BFM98 study, three patients died in CR and three relapsed. The treatment related deaths equaled those caused by disease, which suggested that further reduction in dose-intensity may be justified. Accordingly, the major question in therapy of AML-DS is the intensity of chemotherapy that may be further reduced while maintaining the current high cure rate.

Among the several multi-institutional studies of AML-DS, the Japanese trial is unique in that it has been specifically designed for AML-DS from the beginning using the least dose-intensive regimen. Originally, each chemotherapy course consisted of daunorubicin (25 mg/m^2/d for 2 days), cytarabine (100 mg/m^2/d for 7 days), and etoposide (150 mg/m^2/d for 3 days). The protocol did not include prophylaxis against CNS leukemia. Between 1987 and 1997, 33 patients were treated with the same regimen in 12 hospitals.[17] The CR and 8-year EFS rates were 100% and 80% ± 7%, respectively, which is comparable to the outcome reported in other recent studies. During remission, two patients died of cardiac toxicity and one died of septicemia. Three children relapsed, one of whom was rescued by reinduction therapy containing high-dose cytarabine. Of the 28 patients with cytogenetic analysis, four had monosomy 7. It is of note that two of the three patients who relapsed had monosomy 7.

Table 3. Multivariate Analysis of Prognostic Factors Without Planned-SCT Patients (disease-free survival, n = 68)

Variable	Hazard Ratio	95% CI	*P*
Age > 1.8 years	2.640	0.6642 to 10.49	.170
Log_{10} (WBC)	1.020	0.1990 to 5.23	.980
FAB M7	0.264	0.0529 to 1.31	.100
Female sex	2.399	0.6845 to 8.40	.170
Monosomy 7	5.672	1.2209 to 26.35	.027

Abbreviations: SCT, stem-cell transplantation; FAB, French-American-British classification.

The main aims of the present study were to reduce regimen-related toxicity, in particular cardiotoxicity, and to identify prognostic factors for EFS with a uniform treatment. The present AML 99 DS protocol used pirarubicin instead of the original daunorubicin and fixed the number of treatment courses to five. Pirarubicin is much less cardiotoxic and more myelosuppressive than daunorubicin.[26-28] The cardiotoxicity of pirarubicin should be calculated as 0.8× compared with daunorubicin.[28]

Cytarabine and anthracyclines have been key drugs for the AML. However, the use of anthracyclines is limited by cardiomyopathy, which is irreversible with both acute and subacute manifestations.[26,27,29] One of the problems associated with the treatment of AML-DS is the high frequency of congenital heart anomalies. In a recent report from POG,[30] 57 patients with AML-DS were enrolled in the 9421 protocol, which includes 135 mg/m^2 of daunorubicin and 60 to 100 mg/m^2 of mitoxantrone. Twelve of the 57 patients (21%) had documented congestive heart failure (CHF) requiring chronic diuretics and/or inotropes with diminished fractional shortening on echocardiogram. In the study, four patients died of CHF. In the present study, cardiac dysfunction was observed in four patients (5.9%) during the induction therapy, but all recovered after the induction therapy. Thus, a cumulative pirarubicin dose of 250 mg/m^2 may be tolerable for patients with AML-DS, even those with congenital heart anomalies.

As for other types of leukemia, risk-oriented therapy is proposed if any prognostic factors are identified in AML-DS. In the CCG2891 study,[13] patients with AML-DS who were 2 years old or younger had a 6-year EFS of 86% compared with those older than 2 years, who had a 6-year EFS of 64% ($P = .002$). Multivariate analysis in that study showed that AML-DS patients older than 2 years had an increased risk of relapse (odds ratio = 4.9; $P = .006$). However, subsequent studies did not confirm these findings. In the BFM98 study, there was no difference in outcome between those 2 years or younger and those older than 2 years (EFS; 83% ± 4%, 81% ± 7%, respectively). The present study also did not identify age older than 2 years as a risk factor in the multivariate analysis. Even in the CCGA2971 study, which reduced the dose-intensity from the CCG2891 study, the 3-year EFS was 83% in those younger than 2 years and 79% in those older than 2 years, with no statistically significance difference.[12]

The distribution of age at diagnosis skews to a younger age in patients with AML-DS. Only 10% (seven of 72) and 3% (two of 72) of patients were older than 3 years and 4 years, respectively, in the present study. No detailed data have previously been available that separately analyzes the 2 to 3, 3 to 4, and older than 4 age groups. In the present study, two of five patients experienced induction failure or relapse in the 3 to 4 year age group. Only two patients were older than 4 years: one with FAB M5 who received UCBT and is alive, and the other with FAB M2 who remains in CR. In the CCG2891 study, the EFS was only 28% in nine patients older than 4 years.[13] In the BFM study, three of four patients older than 4 years were classified as FAB M1/M2, and only one patient with FAB M7 remained in the first CR.[11] A better age cut may be beyond 3 or 4 years to discriminate the prognosis in AML-DS patients.

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Table 4. Incidence of GradeIII/IV Treatment-Related Toxicity During Induction and Intensification Phases of Therapy

Measure	Induction Phase	Intensification Phase			
		1	2	3	4
No. of assessed patients	68	65	64	62	59
Sepsis, %	7.3	7.7	1.6	6.5	3.4
Infection of any site, %	10.3	9.2	6.3	1.6	1.7
Pulmonary, %	3.0	1.5	3.0	0	1.7
Cardiac, %	5.9	0	0	0	0
Liver, %	5.9	3.1	6.3	3.2	0
GI, %	1.5	0	0	0	0
Patients who required reduction of drug dose, %	0	1.5	1.6	1.6	1.7
Duration of ANC $< 0.5\times10^9$, days	22.4	16.0	13.9	13.8	14.4
Duration of ANC $< 0.2\times10^9$, days	13.1	8.0	6.6	6.6	7.1

Abbreviation: ANC, absolute neutrophil count.

We would like to emphasize that the TRM in the current study was only 1.4% (one of 72 patients) which is much lower than those of previous reports.[7-9,16] On the other hand, relapse and induction failure were found in 11 of 72 patients (14%), which is more frequent than in other reports with intensive regimens.[6,8,13] On the basis of the results of the present study, we have designed a risk-oriented therapy protocol for our next trial with AML-DS. The patients with M1 marrow after induction therapy should be classified into a standard-risk group and receive the same dose of pirarubicin and cytarabine regimen. In POG 8498, daunorubicin was used only in induction, with a total dose of 135 mg/m^2, and high-dose cytarabine in consolidation. Although this study included only small cohort of 14 DS patients, all were alive as last updated in 2005.[31] We will include high-dose cytarabine for patients with M2 or M3 marrow after induction therapy, classified into a high-risk group, who might have adverse prognostic factors such as age older than 3 and the presence of monosomy 7.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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