VOLUME 27 · NUMBER 24 · AUGUST 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Risk-Stratified Therapy and the Intensive Use of Cytarabine Improves the Outcome in Childhood Acute Myeloid Leukemia: The AML99 Trial From the Japanese Childhood AML Cooperative Study Group

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Submitted July 4, 2008; accepted February 23, 2009; published online ahead of print at www.jco.org on July 20, 2009.

Supported by a grant-in aid for cancer research and a grant for clinical cancer research from the Ministry of Health, Labor and Welfare, Japan.

Presented in part in the 47th Annual Meeting of the American Society of Hematology, Atlanta, GA, December 10-13, 2005.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2724-4007/$20.00

DOI: 10.1200/JCO.2008.18.7948

ABSTRACT

Purpose
To improve the prognosis in children with newly diagnosed acute myeloid leukemia (AML) by introducing a dose-dense intensive chemotherapy regimen and an appropriate risk stratification system.

Patients and Methods
Two hundred forty children with de novo AML were treated with continuous cytarabine-based induction therapy and stratified to three risk groups based on the initial treatment response, age, and WBC at diagnosis and cytogenetics. All of the patients were treated with intensive consolidation chemotherapy including three or four courses of high-dose cytarabine. Allogeneic hematopoietic stem-cell transplantation (HSCT) was indicated for only the intermediate-risk patients with matched related donors and for all the high-risk subsets.

Results
Two hundred twenty-seven children (94.6%) achieved a complete remission (CR). Four children demonstrated induction death. The median follow-up of the live patients was 55 months (range, 37 to 73 months). The 5-year overall survival of all 240 children was 75.6% (95% CI, 70.3% to 81.4%) and event-free survival was 61.6% (95% CI, 55.8% to 68.1%). The 5-year disease-free survival in each risk group were 71.3% (95% CI, 63.4% to 80.2%) in the low-risk group (n = 112), 59.8% (95% CI, 50.6% to 70.7%) in the intermediate-risk group (n = 92), and 56.5% (95% CI, 39.5% to 80.9%) in the high-risk group (n = 23). Eight children died during the first CR, including four after HSCT.

Conclusion
A high survival rate, 75.6% at 5 years, was achieved for childhood with de novo AML in the AML99 trial. The treatment strategy was well tolerated with only 1.7% induction death rate and 3.5% remission death rate. Low-risk children were successfully treated with chemotherapy alone.

J Clin Oncol 27:4007-4013. © 2009 by American Society of Clinical Oncology

INTRODUCTION

The use of intensive chemotherapy and hematopoietc stem-cell transplantation (HSCT) with better facilities for supportive care over the last two decades has achieved dramatic improvements in the treatment outcome for children with acute myeloid leukemia (AML). Approximately 80% to 90% of these children now achieve a complete remission (CR) and the 5-year overall survival (OS) and event-free survival (EFS) rates are 50% to 60% and 40% to 50%, respectively.[1,2] However, when the results are compared with those of pediatric acute lymphoblastic leukemia (ALL), they are not so favorable and further improvements are necessary. HSCT may be the treatment of choice for improving the outcome in children with AML.[3,4] However, considering acute regimen-related toxicities and long-term adverse effects of HSCT, the indications for HSCT during the first CR should be restricted.[5,6]

We conducted a nationwide cooperative clinical protocol AML99 investigation, in which a risk-stratified strategy and dose-dense intensive chemotherapy were introduced. In risk stratification, low-risk patients were treated with chemotherapy alone and allogeneic (Allo) HSCT was indicated only for the intermediate-risk patients with a matched related donor and for all of the high-risk

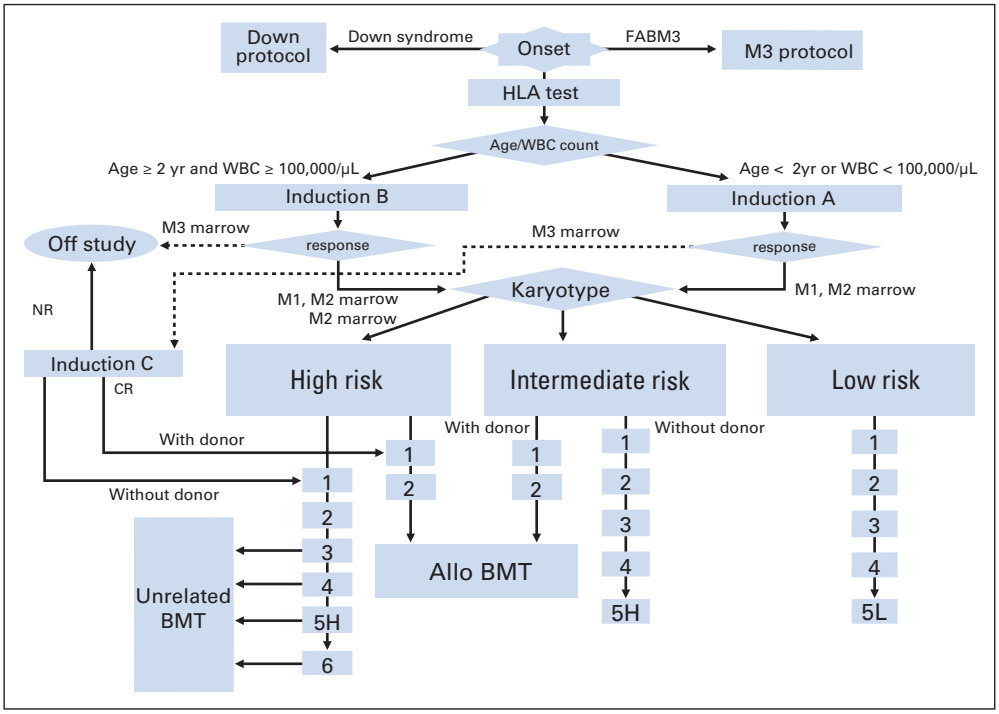

Fig 1. Scheme and details of the Japanese cooperative study AML99. Refer to the Appendix (online only) for further explanation. Abbreviations: FABM3, French-American-British classification M3; Allo, allogenic; NR, no response; CR, complete remission; BMT, bone marrow transplant; HLA, human leukocyte antigen.

patients. In dose-dense intensive chemotherapy, either continuous or high-dose cytarabine was adopted in all courses of chemotherapy. This report describes the improved treatment results of the AML99 protocol for children with de novo AML.

PATIENTS AND METHODS

Between January 2000 and December 2002, a total of 260 children age 0 to 18 years with newly diagnosed AML, excluding children with Down's syndrome and acute promyelocytic leukemia, were enrolled in the AML99 trial by 98 centers, which covered approximately two thirds of the Japanese pediatric population. The French-American-British classification was used for the initial diagnosis of AML. Ten children were excluded from further analysis because of the following reasons: misdiagnosis (n = 4), natural killer (NK) cell/myeloid leukemia (n = 2), granulocytic sarcoma (n = 1), and death before initiation therapy (n = 3). Ten other children with secondary AML were also excluded from this analysis.

Treatment Design of the AML99 Trial

The schema and details of the AML99 protocol are shown in Figure 1. Children younger than age 2 years or those with a WBC lower than 100,000/μL at diagnosis were treated with induction A. Children older than age 2 years and with WBC of 100,000/μL or higher were treated with induction B. Induction C was a rescue regimen for children who showed M3 marrow after induction A. Consolidation therapy consisted of five (for low- and intermediate-risk group) or six (for high-risk group) courses and triple intrathecal therapy was given as a part of each course. After consolidation course 1 (the second course of therapy) or induction C, patients in remission were stratified into three risk groups: low-risk children were defined as those with t(8;21) and a WBC lower than 50,000/μL, inv(16), or an age younger than 2 years without high-risk factors; high-risk children were those with CR after consolidation course 1 or induction C or with abnormalities of monosomy 7,[7] 5q-[7], t(16;21),[8] t(9;22) (Philadelphia chromosome [Ph1])[9]; intermediate-risk children were those who were not in either a low-risk or high-risk group. Low-risk children were treated only with chemotherapy, regardless the availability of a suitable HSCT donor. All high-risk children were allocated to Allo-HSCT in the first remission, including unrelated bone marrow transplantation (BMT). Matched related BMT was recommended for intermediate-risk children with a HLA-matched-related donor (MRD), whereas the remainder of the children was randomly assigned between four courses of consolidation chemotherapy plus autologous BMT (A-BMT) versus five courses of chemotherapy. However, the random assignment was stopped and the protocol was amended to eliminate the A-BMT arm in June 2002, because of a very low consent rate for this random assignment. Only five patients underwent A-BMT and these patients were included in the chemotherapy group in the current analysis. No prophylactic cranial irradiation was included in the protocol. Patients were treated on an inpatient basis during each treatment phase. The protocol was approved in

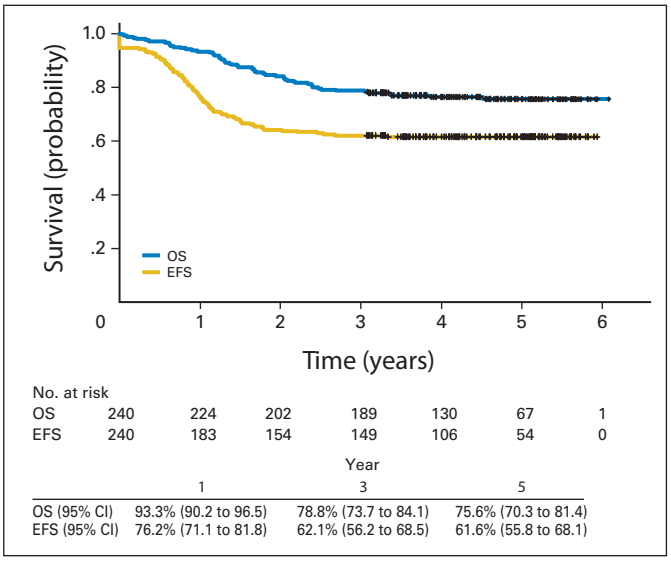

Fig 2. Probability of overall survival (OS) and event-free survival (EFS) in the Japanese cooperative study AML99.

Table 1. Patient and Disease Characteristics

Characteristic	Patients No.	Patients %
Patients enrolled	260	
Patients analyzed	240	100
Age, years		
< 2	45	19
2-9	116	48
≥ 10	79	33
Sex		
Male	128	53
Female	112	47
WBC, $\times 10^3/\mu L$		
< 20	115	48
20-< 50	60	25
50-< 100	29	12
≥ 100	36	15
CNS involvement		
Yes	7	3
No	233	97
FAB type		
M0	10	4
M1	36	15
M2	84	35
M4	39	16
M5a	27	11
M5b	17	7
M6	3	1
M7	20	8
Unclassifiable/not known	4	2
Cytogenetics		
t(8;21)	77	32
inv16	12	5
11q23 abnormalities	41	17
t(9;11)	15	6
Other 11q23 abnormalities	26	11
Normal	53	22
Others	56	23
Unknown	1	< 1

Abbreviation: FAB, French-American-British.

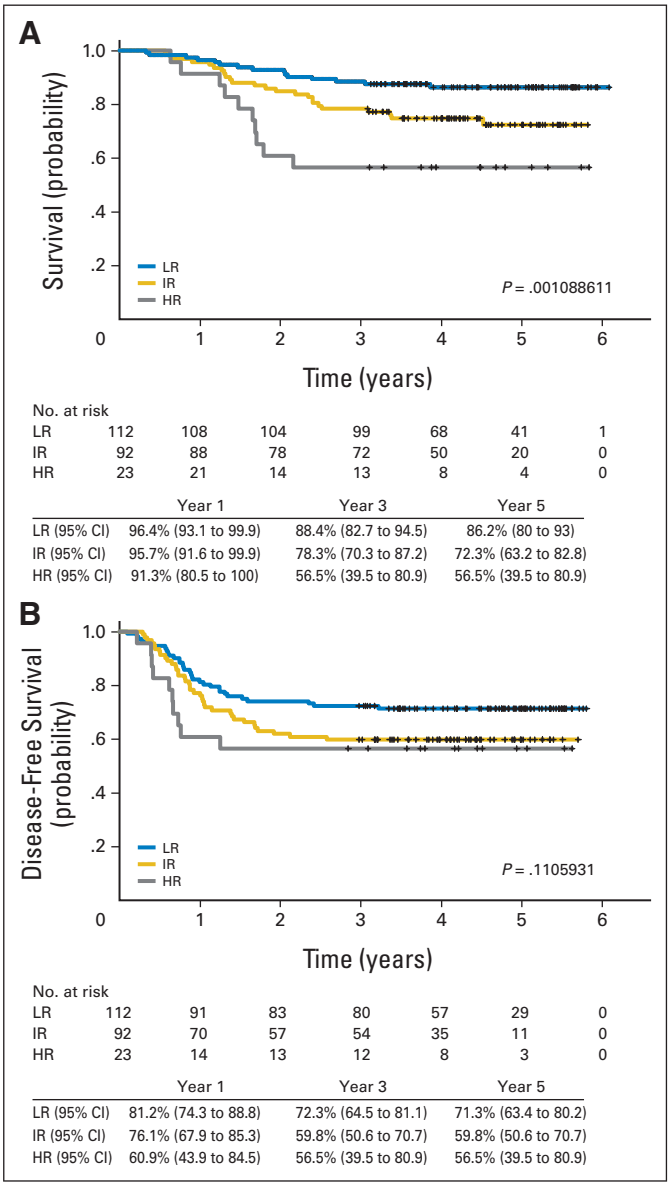

Fig 3. Probability of survival by risk group in the Japanese cooperative study AML99: (A) overall survival and (B) disease free survival. LR, low risk; IR, interediate risk; HR, high risk.

the institutional review board and written informed consent was obtained from the parents or guardians of all patients.

Statistical Analysis

CR was defined by fewer than 5% blast cells in the bone marrow aspirate and the absence of extramedullary involvement (EMI) and had to be achieved before starting of consolidation course 2. CR rates were compared between induction A and B using the Mantel-Haenzel test for trend and Fisher's exact test. The estimation of survival was performed using the Kaplan-Meier method and the curves were compared by means of the log-rank test. The OS was defined as time from the start of treatment to death from any cause or last follow-up. The EFS was defined as time from the start of treatment to first event (induction failure, relapse, or death from any cause) or the last follow-up. The disease-free survival (DFS) was defined as time from the date of remission to first event (relapse or death from any cause) or last follow-up. The CIs were calculated according to Greenwood's formula.

RESULTS

A total of 240 children with newly diagnosed de novo AML, excluding children with Down's syndrome and acute promyelocytic leukemia, were eligible in the current analysis. The median follow-up of the surviving patients was 55 months (range, 37 to 73 months). The characteristics of the patients and the diseases are listed in Table 1.

Overall Results

The bone marrow response rate (< 5% blasts in bone marrow after initial induction course) was 87.1% (209 of 240) and the CR rate (after the first consolidation course or induction C) was 94.6% (227 of 240). Four patients demonstrated induction death (1.7%) and eight children had resistant disease. Eight children with resistant disease were treated with Allo-HSCT, and four of these patients were still alive at the first CR. In one patient, induction chemotherapy was stopped because of toxicity, and this patient was treated with chemotherapy only and still alive in the first CR. Of the 240 children, 214 children were treated with induction A and 26 were treated with induction B.

Table 2. Outcome Data of the Recent Studies for Pediatric AML From Major Groups

Study Group	No. of Patients	Early Death Rate (%)	CR Rate (%)	Time of Evaluation	CR Rate (%) After One Course of Chemotherapy	Induction Regimen (/m^2)	No. of Courses
EORTC-CLG 58,921[11,12]	177	2	84	After 2 courses	69	Ara-C 100 mg 24 hours cont IV days 1-2, 100 mg/12 hours days 3 to 8; VP-16 150 mg IV day 3-5; MIT or IDA 10 mg days 6 to 8	4 Maintenance
LAME-91[13,14]	247	4	91	After 2 courses	84	Ara-C 200 mg 24h cont IV days 1 to 7; MIT 12 mg IV days 1 to 5	3 Maintenance
BFM-93[15-17]	427	7	83	After 4 courses	ND	Ara-C 100 mg 24 hours cont IV days 1 to 2, 100 mg/12 hours days 3 to 8; VP-16 150 mg IV days 6 to 8; DNR 60 mg or IDA 12 mg IV days 3 to 5	4 Maintenance
BFM-98[18,19]	473	3	88	After 4 or 5 courses	ND	Ara-C 100 mg 24 hours cont IV days 1 to 2, 100 mg/12 hours days 3 to 8; VP-16 150 mg IV days 6 t o 8; IDA 12 mg IV days 3 to 5	4 or 5 Maintenance
MRC-AML10[20,21]	303	4	93	After 4 courses	68	Ara-C 100 mg/12 hours IV days 1 to 10; DNR 50 mg IV days 1, 3, 5; 6-TG 75 mg/12 hours PO days 1 to 10 or VP-16 100 mg IV days 1 to 5	4
MRC-AML12[22,23]	455	4	92	After 4 courses	ND	Ara-C 100 mg/12 hours IV days 1 to 10; VP-16 100 mg IV days 1 to 5; DNR 50 mg IV days 1, 3, 5 or MIT 12 mg IV days 1, 3, 5	4 or 5
NOPHO-AML93[24,25]	223	2	92	After 2 or 3 courses	65	Ara-C 200 mg 24 hours cont IV days 1 to 4; VP-16 100 mg 24 hours cont IV days 1 to 4; DOX 75 mg 8 hours IV day 5; 6-TG 100 mg/12 hours PO days 1 to 4	6-8
POG-8821[26,27]	511	4	77	After 2 courses	ND	Ara-C 100 mg 24 hours cont IV days 1 to 7; DNR 45 mg IV days 1 to 3; 6-TG 100 mg PO days 1 to 7	9
CCG-2891[28,29]	750	4	78	After 2 courses	74	DEX 6 mg/12 hours; Ara-C 200 mg cont IV; 6-TG 100 mg/12 hours; VP-16 100 mg cont IV; DNR 20 mg cont IV days 0 to 4, 10 to 14, or 14 to 18	8
TCCSG AML M91-13 and M96-14[10]	192	3.6	88	ND	ND	Ara-C 200 mg 12 hours cont IV days 6 to 12; VP-16 150 mg 2 hours IV days 1 to 5; MIT 5 mg IV days 6 to 10	7 or 9
AML99	240	1.7	94	After 2 courses	86	Ara-C 200 mg 12 hours cont IV days 6 to 12; VP-16 150 mg 2 hours IV days 1 to 5; MIT 5 mg IV days 6 to 10	6

(continued on following page)

The bone marrow response rate, the CR rate, and induction death rate of these two groups were 88.8% (n = 190), 95.8% (n = 205) and 1.4% (n = 3) with induction A, and 73.1% (n = 19), 84.6% (n = 22), and 3.9% (n = 1) with induction B, respectively. The 5-year OS and EFS for all 240 children was 75.6% (95% CI, 70.3% to 81.4%) and 61.6% (95% CI, 55.8% to 68.1%), respectively (Fig 2).

The cumulative risk of relapse was 32.2% (95% CI, 38.1% to 25.7%). The relapse sites were predominantly (86.3%; 63 of 73) located in the bone marrow (BM). Ten patients suffered from EMI or combined BM plus EMI. Although no prophylactic cranial irradiation was included in this protocol, CNS relapses occurred only in three patients (three of 227; 1.3%). One patient suffered a CNS relapse with a BM relapse, one patient a BM relapse and a skin relapse, and one patient a testicular relapse. Although AML99 was a highly intensive protocol, only eight children (3.5%) died in the first CR, four during chemotherapy and four after HSCT.

Results According to Risk Stratification

Among those who achieved first remission, 112 children were stratified to the low-risk group, 92 to the intermediate-risk group, and 23 to the high-risk group. The 5-year OS and DFS in each of the risk groups were 86.2% (95% CI, 80.0% to 93.0%) and 71.3% (95% CI, 63.4% to 80.2%) in the low-risk group, 72.3% (95% CI, 63.2% to 82.8%) and 59.8% (95% CI, 50.6% to 70.7%) in the intermediate-risk group, and 56.5% (95% CI, 39.5% to 80.9%) and 56.5% (95% CI, 39.5% to 80.9%) in the high-risk group (Fig 3).

Among the low-risk children, 96 of 112 underwent five courses of consolidation chemotherapy without any event. Six patients relapsed and three died of infection in CR during chemotherapy. In seven patients, chemotherapy was stopped because of other reasons (three for infectious complications, three for protocol violation including one who underwent Allo-BMT, and one for a parent's refusal).

Among the intermediate-risk children, 22 had a matched related donor and 70 had no donor. Of 22 patients with a donor, 21 received MRD HSCT and one did not because of a fungal infection. After HSCT, two died in CR (one of respiratory distress and one of acute graft-versus-host disease). Among the 70 patients without a donor, 62 received chemotherapy only, three received Allo-HSCT, and five received auto HSCT. Of the 62 patients who received chemotherapy, seven relapsed, one died of infection during chemotherapy, and chemotherapy was stopped in two patients because of infectious complications. The 5-year DFS in the matched donor group and the no donor group were 81.8% (95% CI, 67.2% to 99.6%) versus 52.9% (95%CI, 42.4% to 65.9%; $P = .029$), respectively. However, there was no statistical difference in terms of OS in the matched donor group versus the no donor group (81.8%, 95% CI, 67.2% to 99.6% *v* 69.2%, 95% CI, 58.3% to 82.1%; $P = .380$).

Sixteen of the 23 children in the high-risk group received HSCT in the first CR (six related BMT, six unrelated BMT, and four cord blood stem-cell transplantation). Two patients who received cord blood stem-cell transplantation died in CR (one of fungal infection

Table 2. Outcome Data of the Recent Studies for Pediatric AML From Major Groups (continued)

Study Group	Cumulative Doses				5-Year EFS		5-Year OS	
	Anthracyclines (mg/m^2)	Cytarabine (g/m^2)	High-Dose Cytarabine (dose [/m^2] × times/course × number of courses)	Etoposide (mg/m^2)	%	SE (%)	%	SE (%)
EORTC-CLG 58,921[11,12]	380	23.32-29.32	3 g × 6 × 1 or 3 g × 8 × 1 or 3 g × 10 × 1; 2 g × 6 × 1	1,350	48	4	62	4
LAME-91[13,14]	460 Amsacrine 450	9.8-13.4	1 g × 8 × 1	400	48	4	62	4
BFM-93[15-17]	300-400	23.1-41.1	3 g × 6 × 1 or 3 g × 6 × 2	950	51	3	58	2
BFM-98[18,19]	420	41-47	3 g × 6 × 2 or 3 g × 6 × 2, 1 g × 6 × 1	950	49	3	62	3
MRC-AML10[20,21]	550 Amsacrine 500	10.6	1 g × 6 × 1	500-1,500	49		58	
MRC-AML12[22,23]	300-610 Amsacrine 500	4.6-34.6	(−) or 1 g × 6 × 1 or 3 g × 8 × 1 or both	1,500	56		66	
NOPHO-AML93[24,25]	300-375	49.6-61.3	1 g × 6 × 1; 2 g × 6 × 2 or 3; 3 g × 6 × 1	1,600	50	3	66	3
POG-8821[26,27]	360	55.7	3 g × 6 × 3	2,250	32	2	42	2
CCG-2891[28,29]	350	28.3	3 g × 4 × 2	1,900	34	3	45	3
TCCSG AML M91-13 and M96-14[10]	495	69.4-99.4	3 g × 6 × 2; 3 g × 5 × 4 or 2	3,750-5,750	56		62	
AML99	300-375	59.4-78.4	3 g × 6 × 2; 2 g × 10 × 1 or 2	3,150-3,200	61	3	75	3

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; EFS, event-free survival; OS, overall survival; EORTC-CLG, European Organization of Research and Treatment of Cancer–Children Leukemia Group; Ara-C, cytarabine; cont, continuous; IV, intravenously; VP-16, etoposide; MIT, mitoxantrone; IDA, idarubicin; LAME, French Leucemie Aigue Myeloblastique Enfant; BFM, Berlin-Frankfurt-Munster; ND, no data; DNR, daunorubicin; MRC, Medical Research Council; PO, orally; DOX, doxorubicin; NOPHO, Nordic Society of Pediatric Hematology and Oncology; POG, Pediatric Oncology Group; CCG, Children's Cancer Group; TCCSG-AML, Tokyo Children's Cancer Study Group–Acute Myeloid Leukemia.

and one of acute graft-versus-host disease). The 5-year OS of these 16 patients was 68.8%. Of seven patients who did not received Allo-HSCT in the first CR, five patients relapsed and died despite receiving Allo-HSCT after the first relapse, and two patients were still alive in the first CR with chemotherapy only.

DISCUSSION

The 5-year EFS of 61.6% and 5-year OS of 75.6% achieved in the AML99 is better than those reported in the Tokyo Children's Cancer Study Group (TCCSG) study (from August 1991 to September 1998) conducted preceding to the AML99 (5-year EFS, 56%; 5-year OS, 67%).[10] The chemotherapy regimens in TCCSG AML M91-13 and M96-14 comprised a total nine and seven courses, respectively. In these two studies, the remission induction course was the same as that of induction A course in the AML99 protocol and six of eight consolidation courses included high-dose cytarabine in M91-13 and four of six in M96-14. Since the reduction on consolidation chemotherapy courses from eight to six did not compromise the treatment results in this TCCSG studies, the chemotherapy regimen in the AML99 protocol comprised five consolidation courses. In TCCSG studies, only two high-dose cytarabine courses administered at 12-hour intervals and in the AML99 protocol, three or four high-dose cytarabine courses administered at 12-hour intervals including one or two courses of 2g/m^2 cytarabine every 12 hours for 5 days. This dose dense use of cytarabine in the AML99 protocol may be one of the main explanations for the superior outcome.

Table 2[10-29] presents that the results achieved in the Japanese AML99 protocol is currently the best among the large-scale studies reported from other major childhood AML study groups.

The induction regimen of AML99 is quite unique regarding its 12-day long duration of treatment and the precedent setting administration of etoposide. When comparing the marrow response rate after one course of chemotherapy, AML99 has a rate of 86% and this result is better than those of other studies (Table 2). This good marrow response rate may explain one of the reasons for the superior outcome observed in AML99.

Table 2 presents cumulative doses of drugs, the number of chemotherapy courses, and the survival rates in the major study groups. In comparison to other studies, AML99 used much more cumulative doses of cytarabine including two or three courses of high-dose cytarabine, more doses of etoposide, and moderate doses of anthracyclines

during total six courses of chemotherapy. The good survival rates achieved by incorporating high cumulative doses of anthracyclines in the French Leucémie Aiguë Myéloblastique Enfant study[13,14] and in the Medical Research Council (MRC) study,[20-23] or the frequent use of high-dose cytarabine in the Nordic Society of Pediatric Hematology and Oncology (NOPHO) study[24,25] shows that these strategies may improve the outcome of children with AML. However, considering the long-term adverse effects of cardiotoxicity caused by anthracyclines, high-dose cytarabine plays a key role in postremission chemotherapy.[2,30] Cancer and Leukemia Group B showed that the higher postremission cytarabine dose was associated with a better 5-year continuous CR (3 g/m^2, 42%; 400 mg/m^2, 33%; 100 g/m^2, 17%; $P < .001$) especially in core binding factor (CBF) AML, such as AML with t(8;21) or inv(16) and AML with a normal karyotype.[31] Repetitive use of high-dose cytarabine based postremission chemotherapy in AML99 may be one of the main explanations for the superior outcome. The treatment of AML is usually very intensive and near-myeloablative and the hematologic toxicities and related complications, such as infections, are severe and sometimes fatal. In AML99, the early death rate was only 1.7% and the death rate in first CR was 3.5%. These rates were the lowest among the major group studies.[1]

In the AML99 protocol, 89 patients with CBF AML were included and the 37% incidence (89 of 239 patients) was higher than the 31% incidence observed in TCCSG studies,[10] 20% in MRC12,[22,23] or 22% in Berlin-Frankfurt-Munster 98.[18,19] The patients with CBF AML tend to show a relatively favorable outcome and appear to profit from the administration of high-dose cytarabine. This may be one of the reasons for the superior outcome in the AML99 protocol. In the AML99 trial, low-risk children were treated with chemotherapy alone and their 5-year EFS and OS was 71.3% and 86.2%, respectively. These results reveal that children with low-risk AML can therefore be cured with chemotherapy alone. In the low-risk group, six patients had severe adverse events in CR (three died of infection and three had cessation of the protocol due to infection). It may therefore be appropriate to reduce the course of treatment for low-risk children, because there was no difference in the survival or relapse rate between four and five courses of treatment by the randomized control trial in the MRC AML12 study.[22,23]

In AML99, the intermediate-risk children were genetically randomly assigned to receive MRD HSCT during the first CR. Patients with MRD had a significantly better DFS, but the OS between the donor group and no-donor group did not differ significantly. These results suggest that matched related BMT should be reserved for the second CR in intermediate-risk children. MRC AML10 revealed that in patients treated with Allo-HSCT, there was a decrease in the relapse rate (donor 26% *v* no donor 42% at 7 years; $P = .02$), but no significant OS advantage (donor 70% *v* no donor 60% at 7 years; $P = .1$).[21,23] In the NOPHO-AML93, the 7-year DFS was higher in children treated with Allo-BMT in comparison to those treated with chemotherapy (64% *v* 51%; $P = .04$), but an analysis of the OS showed no difference (71% *v* 69%).[24,25] This good result in the chemotherapy group can be explained by the good results in the relapsed patients treated with HSCT in the second CR.[32] Since the outcome of pediatric AML treated only with intensive chemotherapy has been improved and relapsed children are still alive at the first CR after a successful subsequent HSCT, the indications for HSCT during the first remission should therefore be limited to high-risk children.

Based on these considerations, the following AML-05 study conducted by the Japanese Leukemia/Lymphoma Study Group, which covers almost all Japanese children with leukemia or lymphoma, is presently in progress to assess the validity of the reduced number of consolidation courses with more restrictive indications for HSCT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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