methotrexate was administered at a dose of 3 g/m^2 in a 3-hour infusion, with no IT in the French protocol.

Because IT injections impair the quality of life of patients during treatment[11] and may be associated with rare but major complications such as myelopathy, arachnoiditis, or leukoencephalopathy,[12,13] it was decided to ascertain whether the results of the NHL-BFM90 protocol would be maintained by substituting the standard treatment with IT for a higher dose of methotrexate in a shorter infusion without IT. This was the aim of this trial, which compares the efficacy and safety of two methotrexate doses and administration schedules in children with ALCL.

Study Design

This study was an international randomized trial comparing six courses of methotrexate 1 g/m^2 over 24 hours and IT chemotherapy (MTX1 arm) with six courses of methotrexate 3 g/m^2 over 3 hours without IT (MTX3 arm). The main objective of this trial was to estimate the differences in EFS between the MTX3 and the MTX1 arms. Additionally, high-risk patients (defined as patients with mediastinal and/or skin and/or visceral involvement) could enter a second random assignment before the second course that tested the impact on EFS of adding vinblastine during the five latter courses and then weekly for a total duration of treatment of 1 year (vinblastine trial using a factorial design). Only the results of the first random assignment (methotrexate trial) are reported here. Results of the second random assignment (vinblastine trial) will be the subject of a subsequent report.

Eligibility Criteria and Pretreatment Evaluation

This trial was conducted in 12 countries by 10 national or cooperative groups including most European pediatric/lymphoma study groups and a Japanese group. Eligible candidates were patients with biopsy-proven ALCL who were less than 22 years of age. Slides had to be available for a national pathology review. Patients with isolated skin disease, completely resected stage I disease, or CNS involvement were not eligible for the trial. Additional exclusion criteria were previous treatment, congenital immunodeficiency, AIDS, previous organ transplantation, or previous malignancy. Written informed consent had to be obtained. The local ethics committees approved the protocol according to current legislation in each country.

The diagnosis of ALCL was based on morphologic and immunophenotypic criteria and, if possible, on molecular criteria. Mandatory antibodies were CD30, CD15, EMA, ALK1, CD79a, CD20, CD3, CD43, and CD45RO. Slides were reviewed nationally and by an international panel of pathologists blinded to treatment allocation.

Pretreatment Evaluation

Patients underwent a physical examination, a full blood count and biochemical profile, chest/abdominal computed tomography and skeletal scintigraphy, bone marrow aspirate smears and bone marrow biopsies, cerebrospinal fluid cytospin examination, and biopsy of all skin lesions. Patients were staged according to the St Jude and Ann Arbor staging systems. Patients were classified as high risk if they had at least one risk factor, defined as the presence of skin and/or mediastinal and/or visceral involvement (defined as lung, liver, or spleen involvement), and as standard risk if they had no risk factors.

Treatment

Chemotherapy was based on the NHL-BFM90 protocol.[4] All patients received a 5-day prephase followed by six alternating courses (A and B) administered every 21 days (Table 1). The methotrexate dose and administration schedule in courses A and B were randomly allocated before the first course (course A). The duration of chemotherapy between the prephase and the sixth course was 4 months.

Table 1. Chemotherapy Doses and Schedule in Each Course

Course and Drug	Dose and Schedule
Prephase	
Dexamethasone	5 mg/m^2 on days 1 and 2; 10 mg/m^2 on days 3 to 5
Cyclophosphamide	200 mg/m^2 on days 1 and 2
Triple intrathecal injection	Day 1
Course A	
Dexamethasone	10 mg/m^2 on days 1 to 5
Methotrexate	Random assignment* on day 1
Ifosfamide	800 mg/m^2 on days 1 to 5
Cytarabine	150 mg/m^2 × 2 on days 4 and 5
Etoposide	100 mg/m^2 on days 4 and 5
Course B	
Dexamethasone	10 mg/m^2 on days 1 to 5
Methotrexate	Random assignment* on day 1
Cyclophosphamide	200 mg/m^2 on days 1 to 5
Doxorubicin	25 mg/m^2 on days 4 and 5

*Arm MTX1 included methotrexate 1 g/m^2 in 24-hour infusion with triple intrathecal injection at day 1 and leucovorin rescue (15 mg/m^2) at 42, 48, and 54 hours. Arm MTX3 included methotrexate 3 g/m^2 in 3-hour infusion with no intrathecal injection and leucovorin rescue (15 mg/m^2 every 6 hours) starting at 24 hours and ending when the methotrexate level was < 0.15 μm/L. Additionally, high-risk patients could enter the second randomized trial before the first course B (vinblastine trial), which randomly assigned patients to receive or not receive a vinblastine injection (6 mg/m^2) during the five latter courses and then weekly for a total duration of treatment of 1 year.

Response Criteria

Tumor response was evaluated after each course. A comprehensive evaluation had to be performed once all signs of disease had disappeared or no later than after the sixth course. A complete remission was defined as the disappearance of the disease for at least 4 weeks. A residual lesion at the end of treatment was not considered a treatment failure if the residual tumor volume was less than 30% of the initial tumor mass. Follow-up was performed every 2 to 4 months for the first 3 years, every 6 months during years 4 and 5, and then yearly. Relapses were to be confirmed by a biopsy.

Random Assignment

Overall, 175 centers participated in the trial. Random assignment was balanced and stratified according to country and risk group (standard- v high-risk group). Five different data centers managed the random assignment. A centralized randomization software was used in all five data centers except in Italy, with a minimization program (France) or stratified random assignment with permuted blocks of size four (Japan, Germany, and Sweden). In the Italian data center, predefined stratified balanced random assignment lists were used to allocate treatments.

Additionally, high-risk patients could enter a second random assignment before the first course B to receive or not receive vinblastine. This second random assignment was stratified according to country and to treatment allocated by the first random assignment (factorial design).

Statistical Considerations

The primary end point was EFS, which was defined as the time from random assignment to first failure (progression, relapse, second malignancy, or death) or to the last follow-up visit for patients in first complete remission. Secondary end points were overall survival (OS), complete remission, CNS relapse, and acute toxicity.

OS rates were estimated from the date of random assignment to the date of death, whatever the cause, or the date of the last follow-up visit for patients last seen alive. Survival rates (EFS and OS) were estimated using the Kaplan-Meier method with Rothman's 95% CIs.[14] Median follow-up time was estimated using Schemper's method.[15]

Acute toxicity was assessed using the National Cancer Institute Common Toxicity Criteria, version 2.0.[16] Grade 4 hematologic toxicity and grade 3 or 4 nonhematologic toxicity were classified as severe toxicity.

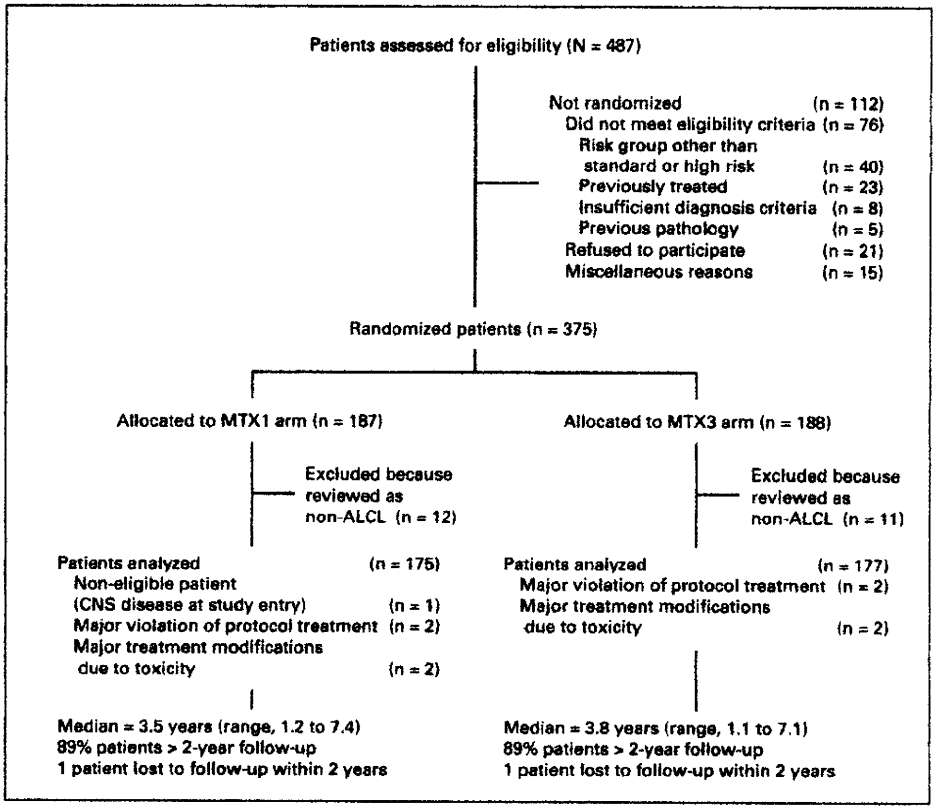

Fig 1. Participant flow CONSORT diagram. ALCL, anaplastic large-cell lymphoma.

The issue raised in this trial was formulated as a noninferiority question in terms of EFS. Considering the factorial design of the trial, the sample size was determined for the vinblastine trial to demonstrate a reduction of the risk of events by adding vinblastine in high-risk patients. A total of 204 high-risk patients were required for the vinblastine trial. Assuming that the high-risk patients eligible for the vinblastine random assignment accounted for 64% of those eligible for the methotrexate random assignment, we expected to accrue 320 patients (204/0.64) onto the methotrexate trial during accrual onto the vinblastine trial. Given the expected sample size, it was recognized that a noninferiority conclusion could never be proven. Therefore, we planned to only provide CIs for differences in EFS in the two arms.

Planned Analysis

Three planned interim analyses were performed using Fleming's plan[17] and discussed with the independent data monitoring committee (IDMC). The present analysis, which is the final analysis, was performed with a one-sided $P = .0412$. The cutoff date of the present analysis was July 1, 2007.

The main analysis of EFS was to be performed on a modified intent-to-treat population, excluding only the patients for whom the diagnosis of ALCL had been rejected after review. Two secondary analyses were performed, one with no exclusions and the second on a per-protocol population that excluded patients who were not eligible for random assignment, patients for whom the diagnosis of ALCL had been rejected, and patients with a major modification of the allocated treatment.

The hazard ratios (HRs) for events (EFS) and death (OS) and their CIs were estimated using Cox models adjusted by the risk group (standard- *v* high-risk group) and country and stratified by the treatment allocated by the second random assignment (not randomly assigned, no vinblastine, or vinblastine).

Prespecified secondary analyses, using Cox models, were performed to study variations in the treatment effect according to the risk group, treatment allocated by the second random assignment, and country. Heterogeneity in treatment effects according to country was assessed considering patients from Poland, Belgium, the Netherlands, and Sweden in a unique stratum because of a limited sample size in each of these countries. All reported *P* values for heterogeneity are two sided.

Toxicity rates between the MTX1 and MTX3 arms were compared using mixed models controlling for the number of the course (course 1 to 6) and the adjunction or not of vinblastine and considering the patient effect as a random effect (repetitive courses per patient). Data were entered and checked with the PIGAS software[18] and analyzed with SAS software (version 8.2; SAS Institute, Cary, NC).

Recruitment and Follow-Up

Between November 1999 and December 2005, 487 patients were screened for study entry. A total of 112 patients were not included in the trial (Fig 1). Thus, 375 patients (91% of the 411 potentially eligible patients) were included.

A central review of the slides was performed for 358 (95%) of 375 patients. The diagnosis of ALCL was rejected in 23 patients. Consequently, 352 patients were included in the main analysis; 175 were assigned to the MTX1 arm, and 177 were assigned to the MTX3 arm.

Baseline Data

The median age at diagnosis was 11.0 years (range, 4 months to 19.5 years). Baseline patient characteristics, overall and by treatment group, are listed in Table 2.

Table 2. Patient Characteristics by Treatment Arm

Characteristic	No. of Patients in MTX1 Arm (n = 175)	No. of Patients in MTX3 Arm (n = 177)	All Patients (N = 352)	
			No	%
Male	103	108	211	60
Age, years				
< 3	10	9	19	5
3-16	151	157	308	88
> 16	14	11	25	7
Risk group				
Standard risk	65	68	133	38
High risk	109	109	218	62
CNS disease	1	0	1	0.3
"B" symptoms (MD, n = 2)	104	93	197	56
Site of disease				
Peripheral lymph node	150	158	308	88
Mediastinal involvement*	85	82	167	47
Lung lesion*	35	40	75	21
Liver involvement†	30	19	49	14
Spleen involvement†	39	25	64	18
Skin lesion‡	33	35	68	19
Soft tissue mass (MD, n = 1)	32	23	55	16
Bone lesion (MD, n = 43)	21/154	37/155	58/309	19
Bone marrow involvement§	28	14	42	12
St Jude stage				
1	14	10	24	7
2	29	37	66	19
3	106	116	222	63
4	26	14	40	11
Ann Arbor stage				
1	18	11	29	8
2	53	57	110	31
3	50	53	103	29
4	54	56	110	31
International Prognostic Index (MD, n = 73)				
0	22	30	52	19
1	39	40	79	28
2	45	45	90	32
3	34	24	58	21
Allocated treatment by the second random assignment				
No vinblastine	49	51	100	28
Vinblastine	49	47	96	27
Not randomly assigned in the R2 trial	77	79	156	44

Abbreviations: MTX, methotrexate; MD, missing data.
*Radiologic diagnosis by x-ray and/or computed tomography.
†Liver and spleen were considered involved if palpable clinically or enlarged on imaging > 5 cm below the costal margin or nodular on imaging.
‡Skin involvement included biopsy-proven anaplastic large-cell lymphoma cutaneous involvement and clinically diagnosed skin lesions undoubtedly related to anaplastic large-cell lymphoma, with the exclusion of lesions limited to the skin overlying an involved node or a soft tissue mass.
§Bone marrow involvement was defined by the analysis of the bone marrow smears and trephine, using morphologic criteria.

All 352 patients were positive for CD30, 337 (96%) were positive for ALK, and 305 (87%) expressed at least one T-cell marker. According to the WHO classification,[19] which was available for 328 patients, the distribution of the subtypes was as follows: common type (n = 210, 64%), lymphohistiocytic (n = 10, 3%), small cell (n = 21, 6%), giant cell (n = 5, 1.5%), mixed (n = 76, 23%), and Hodgkin's-like (n = 6, 1.8%).

Treatment

Overall, 92% of the patients (162 patients in the MTX1 arm and 163 patients in the MTX3 arm) received protocol treatment of six courses with the planned methotrexate dose according to random assignment. A major protocol violation was observed in four patients (two patients in both arms); the treatment was significantly modified as a result of toxicity in four additional patients (two patients in both arms). These eight patients are included in the main analysis but were excluded from the per-protocol analysis. A modification of the methotrexate dose or of the IT injection in less than three courses was also observed in nine and 10 patients in the MTX1 and MTX3 arms, respectively.

Outcome and Follow-Up

Median follow-up time was 3.8 years from random assignment. Only two patients were lost to follow-up. Disease disappeared completely from all initially involved sites in 309 (88%) of 352 patients.

Among the 43 remaining patients, 14 experienced early progression on treatment, one was not assessable because of an early change of treatment, two died of treatment-related toxicity before achieving a complete remission, and 26 presented with a residual abnormality after the sixth course. Overall, 102 events were reported (treatment-related death, n = 4; early progression, n = 14; and relapse, n = 84). Seventy-three of the 84 relapses occurred during the first 2 years after random assignment. Progression and relapses occurred most frequently at the site of the primary tumor (69%) and were associated or not with new tumor site(s). Only two patients had a CNS relapse as the first event. The 2-year EFS rate of the 352 patients was 74.1% (95% CI, 69.2% to 78.4%).

Overall, 32 deaths were reported (21 as a result of disease progression and 11 as a result of toxicity), including seven deaths after progression or relapse. The 2-year OS rate of the 352 patients was 92.5% (95% CI, 89.3% to 94.8%).

Comparison of Outcome Between Treatment Arms

The outcome results by treatment arm are listed in Table 3. There was no significant difference between the two randomized groups for any of the main and secondary efficacy end points.

The complete remission rates were 89% and 87% in the MTX1 and MTX3 arms, respectively (difference = −2%; 91.76% CI, −8% to 4%). As shown in Figure 2B, the EFS curves were superimposed, with 2-year EFS rates of 73.7% and 74.5% in the MTX1 and MTX3 arms, respectively. The 2-year EFS difference was +0.8% (91.76% CI, −7.3% to 9.0%). The HR for events in the MTX3 arm compared with the MTX1 arm was 0.98 (91.76% CI, 0.69 to 1.38). This result was similar when the strict intent-to-treat population (HR = 1.02; 91.76% CI, 0.74 to 1.42) or the per-protocol population (HR = 1.02; 91.76% CI, 0.72 to 1.45) was considered.

There was no significant heterogeneity in treatment effects in terms of EFS according to country ($P = .86$), risk group ($P = .15$), or the treatment allocated by the second random assignment ($P = .41$). The 2-year OS rates were 90.1% and 94.9% in the MTX1 and MTX3 arms, respectively (Fig 2C). The HR for death in the MTX3 arm compared with the MTX1 arm was 0.67 (91.76% CI, 0.36 to 1.25).

Table 3. Outcome by Treatment Arm

Outcome	No. of Patients	
	MTX1 Arm (n = 175)	MTX3 Arm (n = 177)
Response to chemotherapy		
Complete remission*	155	154
Residual abnormality	10	16
Progressive disease	8†	6†
Not assessed	2	1
Event	51	51
Progression on treatment	8†	6†
Relapse	42	42
Toxic death as first event	1	3
CNS relapse	2	0
Deaths	19	13

Abbreviation: MTX, methotrexate.
*Complete remission was defined as the disappearance of disease from all initially involved sites lasting for at least 4 weeks.
†The eight and six patients with progression on treatment are the same as those listed as having progressive disease under the Response to chemotherapy heading.

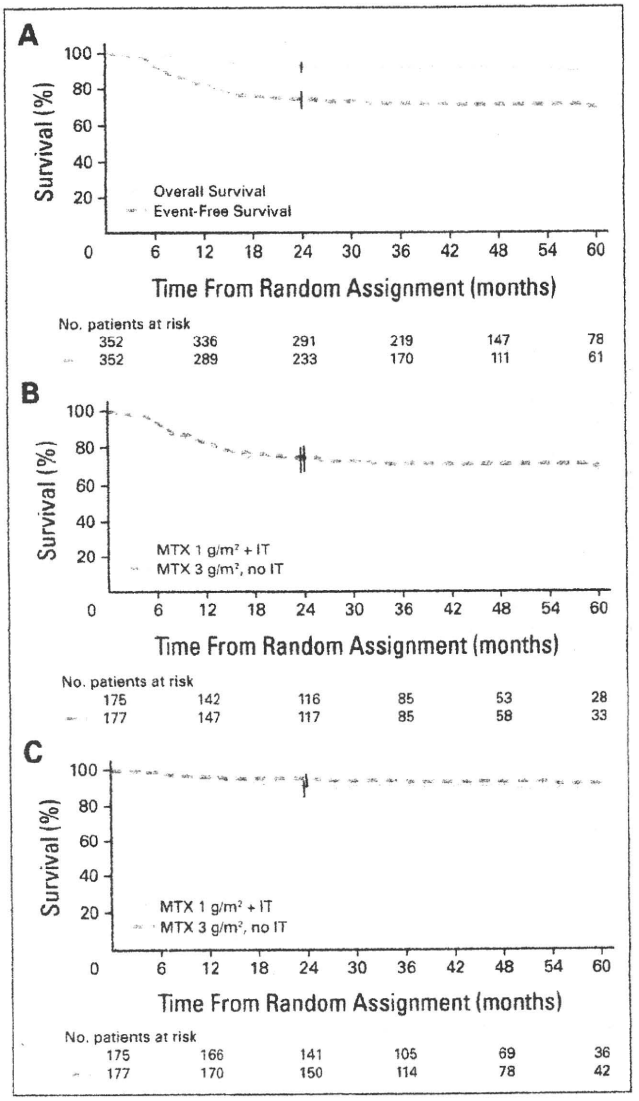

Fig 2. (A) Event-free survival (EFS) and overall survival (OS) of the whole study population. (B) EFS by treatment. (C) OS by treatment. MTX, methotrexate.

Toxicity

Toxicity results are listed in Table 4. Severe toxicity was reported after 75% of courses and consisted mostly of grade 4 hematologic toxicity (72% courses) and grade 3 to 4 mucositis (13%). These toxicities were significantly more frequent after MTX1 courses than after MTX3 courses. The incidence of grade 3 to 4 infection was low (5%) and comparable for both types of courses. However, if all grades of infection are considered, the incidence was significantly higher after MTX1 courses (50%) compared with MTX3 courses (32%; $P < .0001$). No severe complications related to the IT injections were reported.

In this trial, to our knowledge the largest ever conducted in ALCL, we observed that the EFS curve for patients treated with chemotherapy

Table 4. Acute Toxicity According to Treatment Arm

Reported Toxicity	Courses in MTX1 Arm (n = 1,025)			Courses in MTX3 Arm (n = 1,025)*			P†
	No. of Courses With Toxicity	No. of Courses Evaluated	% of Courses With Toxicity	No. of Courses With Toxicity	No. of Courses Evaluated	% of Courses With Toxicity	
All types, all grades	997	1,025	97	941	1,025	92	.002
Severe toxicity	846	1,025	83	701	1,025	68	< .0001
Hematologic grade 4 toxicity	812	1,024	79	655	1,022	64	< .0001
Neutropenia	794	1,024	78	639	1,023	62	< .0001
Anemia	83	1,024	8	50	1,023	5	.06
Thrombocytopenia	215	1,024	21	123	1,021	12	< .0001
Infection							
Grade 3-4	60	1,019	6	50	1,021	5	.32
All grades	508	1,019	50	331	1,021	32	< .0001
Other grade 3-4 toxicity	326	1,025	32	168	1,025	16	< .0001
Stomatitis	210	1,021	21	59	1,023	6	< .0001
Liver toxicity	128	955	13	97	977	10	.06
Miscellaneous	73	1,025	7	56	1,025	5	.13

Abbreviation: MTX, methotrexate.
*Detailed information on all courses (A and B) and toxicity observed after the courses was available for all patients except for one patient on the MTX3 arm.
†*P* value of the test comparing the toxicity rate between the two treatment groups by the means of mixed models controlling for the number of the course (course 1 to 6), the adjunction or not of vinblastine (treatment allocated by the second random assignment), the type of course (A *v* B), and the country, considering the patient effect as a random effect (repetitive courses per patient).

based on the NHL-BFM90 protocol with methotrexate at 3 g/m^2 in a 3-hour infusion without IT was superimposable on the EFS curve for patients treated with the same regimen but with methotrexate at 1 g/m^2 in a 24-hour infusion with IT. However, toxicity was significantly reduced in the MTX3 arm.

Conducting such a trial in this rare disease was only possible through the collaboration of European cooperative groups and a Japanese group. The external validity of this study is quite robust because, in all participating groups, most patients with childhood ALCL diagnosed between 1999 and 2006 were screened for trial entry with a random assignment rate of 91% among patients eligible for this trial. Furthermore, initial patient characteristics are those of the target population, as expected from previous reports.[20] The slides of the majority of patients were centrally reviewed, and the diagnosis of ALCL was rejected in only a small number of patients (23 of 358 patients).

The results of the NHL-BFM90 study[4] were reproduced in this international study. The 2-year EFS rate of 74% obtained for the whole trial population compares favorably with the results of previous reports on childhood ALCL.[2-6,9,10]

Although the EFS curves were superimposed, equivalence of the two arms in terms of EFS could not be statistically proven because of the limited number of patients. A total of 2,200 patients would have been required to prove noninferiority of MTX3 compared with MTX1, considering a 5% decrease in the 2-year EFS rate as the maximum allowable difference (limit HR = 1.23). Nevertheless, we were able to exclude the possibility that 2-year EFS of patients treated with MTX3 might be decreased by more than 7.3% compared with the EFS of patients treated with MTX1 with 95% confidence.

We demonstrated that the treatment in the MTX3 arm caused less hematologic and gut toxicity than the treatment in the MTX1 arm despite a higher dose of methotrexate. Decreased toxicity related to a shortened infusion of methotrexate has already been observed by the BFM group in the NHL-BFM95 study comparing methotrexate in a 4-hour infusion with methotrexate in a 24-hour infusion in childhood B-cell non-Hodgkin's lymphoma.[21] In the present study, the interval between the end of the MTX infusion and folinic acid rescue was reduced in the short infusion arm. Therefore, the higher toxicity rate observed in the MTX1 arm may be a result of longer exposure to methotrexate as well as the delayed rescue.

In this study, only two patients had a CNS relapse as a first event. The low incidence of CNS relapses in ALCL has been evidenced in a number of previous reports in children[2,3,5,6,9,10,22-24] and adults.[25,26] However, most pediatric groups still recommend minimal CNS prophylaxis based either on high-dose methotrexate or on IT injections. In previous studies, the 3 g/m^2 dose of methotrexate in a 3-hour infusion was shown to provide potentially cytotoxic concentrations of the drug in CSF for several hours after the infusion.[27] The present study confirms that replacing methotrexate 1 g/m^2 in a 24-hour infusion plus an IT injection with methotrexate 3 g/m^2 in a 3-hour infusion is not associated with any excess CNS relapses in ALCL. Furthermore, the omission of triple IT therapy and the reduction in toxicity in the MTX3 arm should contribute to an improvement in the quality of life of the patients during treatment. Although toxicity was reduced in the MTX3 arm, this regimen still induces substantial acute toxicity. However, the low total doses of anthracyclines (150 mg/m^2 of doxorubicin) and alkylating agents (3.4 g/m^2 of cyclophosphamide and 12 g/m^2 of ifosfamide) in this regimen should avoid long-term complications.

Nevertheless, it is difficult to assess the exact role of high-dose methotrexate in the treatment of childhood ALCL. The results obtained in pediatric ALCL by the Pediatric Oncology Group,[6] with protocols based on doxorubicin, prednisone, and vincristine chemotherapy plus triple IT injections but without high-dose methotrexate, or in adults by several cooperative groups with the cyclophosphamide, doxorubicin, vincristine, and prednisone regimen are similar to those of our study.[28] These protocols are associated with less acute toxicity than the ones described in this study. However, the cumulative doses of anthracyclines and/or alkylating agents are significantly higher than those in the ALCL99 protocol and, therefore, may lead to long-term

adverse effects. Further trials are needed to assess whether methotrexate can be safely omitted from a short intensive treatment similar to the ALCL99 regimen for some subgroups of patients.

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

Conception and design: Laurence Brugières, Marie-Cécile Le Deley, Angelo Rosolen, Denise Williams, Grazyna Wrobel, Georg Mann, Joszef Zsiros, Anne Uyttebroeck, Ildiko Marky, Alfred Reiter

Administrative support: Marie-Cécile Le Deley

Provision of study materials or patients: Laurence Brugières, Angelo Rosolen, Denise Williams, Keizo Horibe, Grazyna Wrobel, Georg Mann, Joszef Zsiros, Anne Uyttebroeck, Ildiko Marky, Laurence Lamant, Alfred Reiter

Collection and assembly of data: Laurence Brugières, Marie-Cécile Le Deley, Denise Williams, Keizo Horibe, Grazyna Wrobel, Georg Mann, Joszef Zsiros, Anne Uyttebroeck, Ildiko Marky, Laurence Lamant, Alfred Reiter

Data analysis and interpretation: Laurence Brugières, Marie-Cécile Le Deley

Manuscript writing: Laurence Brugières, Marie-Cécile Le Deley

Final approval of manuscript: Laurence Brugières, Marie-Cécile Le Deley, Angelo Rosolen, Denise Williams, Keizo Horibe, Grazyna Wrobel, Georg Mann, Joszef Zsiros, Anne Uyttebroeck, Ildiko Marky, Laurence Lamant, Alfred Reiter

1. Wright D, McKeever P, Carter R: Childhood non-Hodgkin lymphomas in the United Kingdom: Findings from the UK Children's Cancer Study Group. J Clin Pathol 50:128-134, 1997

2. Brugières L, Deley MC, Pacquement H, et al: CD30(+) anaplastic large-cell lymphoma in children: Analysis of 82 patients enrolled in two consecutive studies of the French Society of Pediatric Oncology. Blood 92:3591-3598, 1998

3. Reiter A, Schrappe M, Tiemann M, et al: Successful treatment strategy for Ki-1 anaplastic large-cell lymphoma of childhood: A prospective analysis of 62 patients enrolled in three consecutive Berlin-Frankfurt-Munster group studies. J Clin Oncol 12:899-908, 1994

4. Seidemann K, Tiemann M, Schrappe M, et al: Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: A report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. Blood 97:3699-3706, 2001

5. Williams DM, Hobson R, Imeson J, et al: Anaplastic large cell lymphoma in childhood: Analysis of 72 patients treated on The United Kingdom Children's Cancer Study Group chemotherapy regimens. Br J Haematol 117:812-820, 2002

6. Laver JH, Kraveka JM, Hutchison RE, et al: Advanced-stage large-cell lymphoma in children and adolescents: Results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen—A Pediatric Oncology Group phase III trial. J Clin Oncol 23:541-547, 2005

7. Sandlund JT, Pui CH, Santana VM, et al: Clinical features and treatment outcome for children with CD30+ large-cell non-Hodgkin's lymphoma. J Clin Oncol 12:895-898, 1994

8. Massimino M, Gasparini M, Giardini R: Ki-1 (CD30) anaplastic large-cell lymphoma in children. Ann Oncol 6:915-920, 1995

9. Mori T, Kiyokawa N, Shimada H, et al: Anaplastic large cell lymphoma in Japanese children: Retrospective analysis of 34 patients diagnosed at the National Research Institute for Child Health and Development. Br J Haematol 121:94-96, 2003

10. Rosolen A, Pillon M, Garaventa A, et al: Anaplastic large cell lymphoma treated with a leukemia-like therapy: Report of the Italian Association of Pediatric Hematology and Oncology (AIEOP) LNH-92 protocol. Cancer 104:2133-2140, 2005

11. Keidan I, Bielorai B, Berkenstadt H, et al: Prospective evaluation of clinical and laboratory effects of intrathecal chemotherapy on children with acute leukemia. J Pediatr Hematol Oncol 27:307-310, 2005

12. Bay A, Oner AF, Etlik O, et al: Myelopathy due to intrathecal chemotherapy: Report of six cases. J Pediatr Hematol Oncol 27:270-272, 2005

13. von der Weid NX, de Crousaz H, Beck D, et al: Acute fatal myeloencephalopathy after combined intrathecal chemotherapy in a child with acute lymphoblastic leukemia. Med Pediatr Oncol 19:192-198, 1991

14. Rothman KJ: Estimation of confidence limits for the cumulative probability of survival in life table analysis. J Chronic Dis 31:557-560, 1978

15. Schemper M, Smith TL: A note on quantifying follow-up in studies of failure time. Control Clin Trials 17:343-346, 1996

16. National Cancer Institute: Common Toxicity Criteria, Version 2.0. http://ctep.cancer.gov/reporting/ctc.html

17. Fleming TR, Harrington DP, O'Brien PC: Designs for group sequential tests. Control Clin Trials 5:348-361, 1984

18. Wartelle M, Kramar A, Jan P, et al: PIGAS: An interactive statistical database management system. Proceeding of the Second International Workshop on Statistical Database Management, Los Altos, CA, September 27-29, 1983, pp 124-132

19. Jaffe ES: Anaplastic large cell lymphoma: The shifting sands of diagnostic hematopathology. Mod Pathol 14:219-228, 2001

20. Le Deley MC, Reiter A, Williams D, et al: Prognostic factors in childhood anaplastic large cell lymphoma: Results of a large European Intergroup Study. Blood 111:1560-1566, 2008

21. Woessmann W, Seidemann K, Mann G, et al: The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: A report of the BFM Group Study NHL-BFM95. Blood 105:948-958, 2005

22. Brugieres L, Quartier P, Le Deley MC, et al: Relapses of childhood anaplastic large-cell lymphoma: Treatment results in a series of 41 children—A report from the French Society of Pediatric Oncology. Ann Oncol 11:53-58, 2000

23. Mori T, Sugita K, Kimura K, et al: Isolated central nervous system (CNS) relapse in a case of childhood systemic anaplastic large cell lymphoma without initial CNS involvement. J Pediatr Hematol Oncol 25:975-977, 2003

24. Mori T, Takimoto T, Katano N, et al: Recurrent childhood anaplastic large cell lymphoma: A retrospective analysis of registered cases in Japan. Br J Haematol 132:594-597, 2006

25. Boehme V, Zeynalova S, Kloess M, et al: Incidence and risk factors of central nervous system recurrence in aggressive lymphoma: A survey of 1693 patients treated in protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Ann Oncol 18:149-157, 2007

26. Haioun C, Besson C, Lepage E, et al: Incidence and risk factors of central nervous system relapse in histologically aggressive non-Hodgkin's lymphoma uniformly treated and receiving intrathecal central nervous system prophylaxis: A GELA study on 974 patients—Groupe d'Etudes des Lymphomes de l'Adulte. Ann Oncol 11:685-690, 2000

27. Vassal G, Valteau D, Bonnay M, et al: Cerebrospinal fluid and plasma methotrexate levels following high-dose regimen given as a 3-hour intravenous infusion in children with nonHodgkin's lymphoma. Pediatr Hematol Oncol 7:71-77, 1990

28. Greer JP: Therapy of peripheral T/NK neoplasms. Hematology Am Soc Hematol Educ Program 331-337, 2006

Appendix

The following groups participated in this study: European Intergroup for Childhood Non-Hodgkin Lymphoma; Société Française de Lutte Contre les Cancers et Leucémies de l'Enfant; Associazione Italiana di Ematologia ed Oncologia Pediatrica; United Kingdom Children's Cancer and Leukaemia Group; Japanese Pediatric Leukemia/Lymphoma Study Group; Polish Pediatric Leukemia/Lymphoma Study Group; Austria–Berlin-Frankfurt-Muenster Group; Dutch Childhood Oncology Group; Belgian Society of Paediatric Haematology and Oncology; Nordic Society for Pediatric Hematology and Oncology; and Berlin-Frankfurt-Muenster Group.

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

Ichiro Tsukimoto, Akio Tawa, Keizo Horibe, Ken Tabuchi, Hisato Kigasawa, Masahiro Tsuchida, Hiromasa Yabe, Hideki Nakayama, Kazuko Kudo, Ryoji Kobayashi, Kazuko Hamamoto, Masue Imaizumi, Akira Morimoto, Shigeru Tsuchiya, and Ryoji Hanada

From the Department of Pediatrics, Toho University School of Medicine, Tokyo; Department of Pediatrics, Osaka National Hospital, Osaka; Clinical Research Center, Nagoya Hospital Organization Nagoya Medical Center; Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya; Division of Hematology, Kanagawa Children's Medical Center, Yokohama; Department of Pediatrics, Ibaraki Children's Hospital, Mito; Specialized Clinical Science, Pediatrics, Tokai University School of Medicine, Kanagawa; Department of Pediatrics, Hamanomachi Hospital, Fukuoka; Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo; Department of Pediatrics, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Hiroshima; Department of Hematology and Oncology, Miyagi Children's Hospital, Sendai; Department of Pediatrics, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto; Department of Pediatric Oncology, Institute of Development, Aging and Cancer, Tohoku University, Miyagi; Department of Hematology/Oncology, Saitama Children's Medical Center, Saitama, Japan.

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.

Corresponding author: Akio Tawa, MD, PhD, Department of Pediatrics, National Hospital Organization Osaka National Hospital, 2-1-14 Hoenzaka, Chuo-ku, Osaka 540-0006, Japan; e-mail: tawa@onh.go.jp.

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

The use of intensive chemotherapy and hematopoietic 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

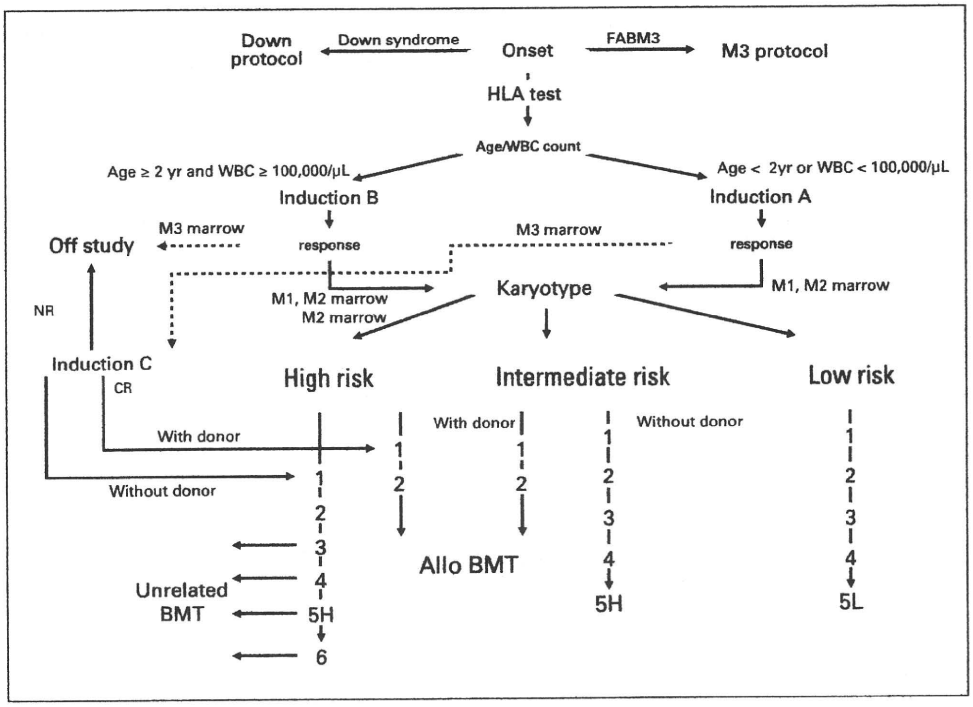

Fig 1. Scheme and details of the Japanese cooperative study AML99. Refer to the Appendix (online only) for further explanation. Abbreviations: FABM3, French-American-British classification M3; Allo, allogenic; NR, no response; CR, complete remission; BMT, bone marrow transplant; HLA, human leukocyte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

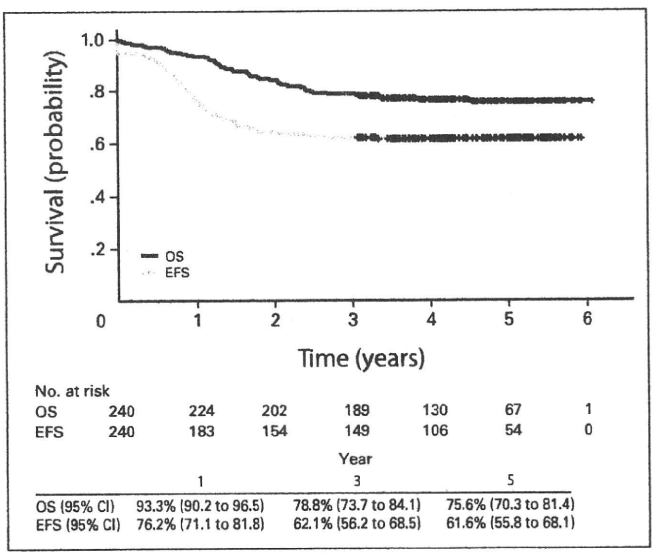

Fig 2. Probability of overall survival (OS) and event-free survival (EFS) in the Japanese cooperative study AML99.

Table 1. Patient and Disease Characteristics

Characteristic	Patients	
	No.	%
Patients 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.

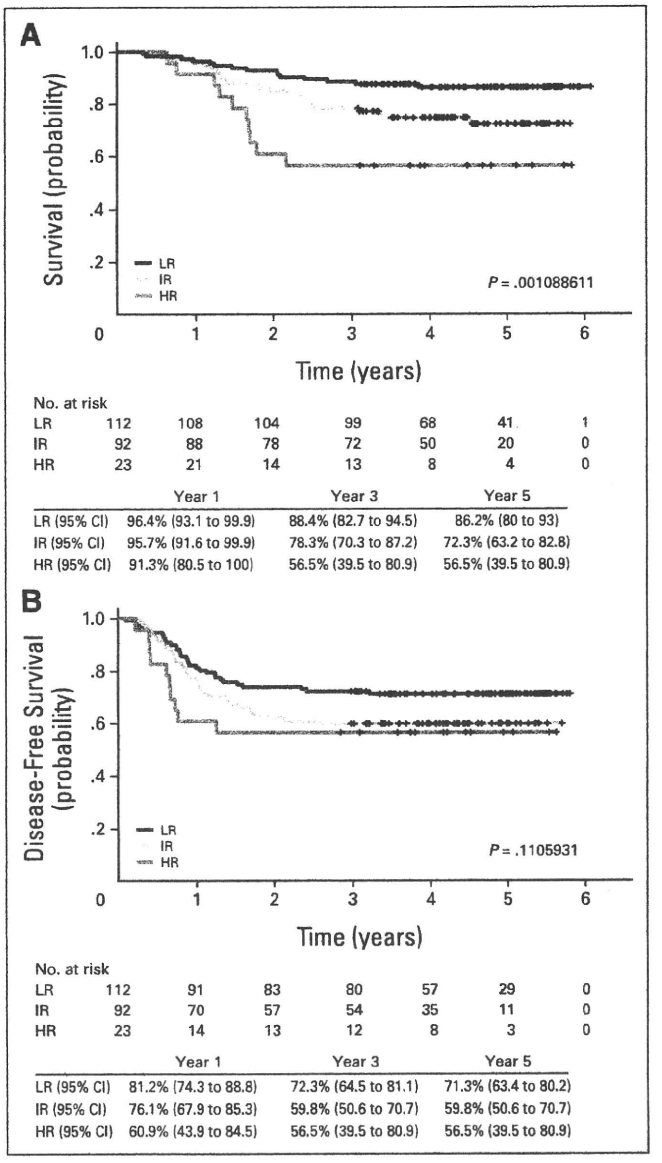

Fig 3. Probability of survival by risk group in the Japanese cooperative study AML99: (A) overall survival and (B) disease free survival. LR, low risk; IR, interediate risk; HR, high risk.

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 (/m²)	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.

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.

AUTHOR CONTRIBUTIONS

Conception and design: Ichiro Tsukimoto, Akio Tawa, Keizo Horibe, Ryoji Hanada
Financial support: Ichiro Tsukimoto, Keizo Horibe
Administrative support: Ichiro Tsukimoto
Provision of study materials or patients: Ichiro Tsukimoto, Akio Tawa, Keizo Horibe, Ken Tabuchi, Hisato Kigasawa, Masahiro Tsuchida, Hiromasa Yabe, Hideki Nakayama, Kazuko Kudo, Ryoji Kobayashi, Kazuko Hamamoto, Masue Imaizumi, Akira Morimoto, Shigeru Tsuchiya, Ryoji Hanada
Collection and assembly of data: Ichiro Tsukimoto, Keizo Horibe, Ken Tabuchi
Data analysis and interpretation: Ichiro Tsukimoto, Akio Tawa, Ken Tabuchi, Hiromasa Yabe, Hideki Nakayama, Ryoji Kobayashi, Kazuko Hamamoto, Akira Morimoto, Ryoji Hanada
Manuscript writing: Ichiro Tsukimoto, Akio Tawa, Keizo Horibe
Final approval of manuscript: Ichiro Tsukimoto, Akio Tawa, Keizo Horibe, Ken Tabuchi, Hisato Kigasawa, Masahiro Tsuchida, Hiromasa Yabe, Hideki Nakayama, Kazuko Kudo, Ryoji Kobayashi, Kazuko Hamamoto, Masue Imaizumi, Akira Morimoto, Shigeru Tsuchiya, Ryoji Hanada

REFERENCES

1. Kaspers GJL, Creutzig U: Pediatric acute myeloid leukemia: International progress and future directions. Leukemia 19:2025-2029, 2005
2. Woods WG: Curing childhood acute myeloid leukemia (AML) at the half-way point: Promises to keep and miles to go before we sleep. Pediatr Blood Cancer 46:565-569, 2006
3. Bleakley M, Lau L, Shaw PJ, et al: Acute myeloid leukaemia: Bone marrow transplantation for paediatric AML in first remission—A systematic review and meta-analysis. Bone Marrow Transplant 29:843-852, 2002
4. Oliansky DM, Rizzo JD, Aplan PD, et al: The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia in children: An evidence-based review. Biology Blood Marrow Transplant 13:1-25, 2007
5. Creutzig U, Reinhardt D: Current controversies: Which patients with acute myeloid leukaemia should receive a bone marrow transplantation? A European view. Br J Haematol 118:365-377, 2002
6. Watson M, Buck G, Wheatley K, et al: Adverse impact of bone marrow transplantation on quality of life in acute myeloid leukaemia patients: Analysis of the UK Medical Research Council AML 10 trial. Eur J Cancer 40:971-978, 2004
7. Grimwade D, Walker H, Oliver F, et al: The importance of diagnostic cytogenetics on outcome in AML: Analysis of 1,612 patients entered into the MRC AML 10 trial. Blood 92:2322-2333, 1998
8. Kong X-T, Ida K, Ichikawa H, et al: Consistent detection of *TLS/FUS-ERG* chimeric transcripts in acute myeloid leukemia with t(16;21)(p11;q22) and identification of a novel transcript. Blood 90:1192-1199, 1997
9. Cuneo A, Ferrant A, Michaux JL, et al: Philadelphia chromosome-positive acute myeloid leukemia: Cytoimmunologic and cytogenetic features. Haematologica 81:423-427, 1996
10. Tomizawa D, Tabuchi K, Kinoshita A, et al: Repetitive cycles of high-dose cytarabine are effective

for childhood acute myeloid leukemia: Long-term outcome of the children with AML treated on two consecutive trials of Tokyo Children's Cancer Study Group. Pediatr Blood Cancer 49:127-132, 2007

11. Béhar C, Suciu S, Benoit Y, et al: Mitoxantrone-containing regimen for treatment of childhood acute leukemia (AML) and analysis of prognostic factors: Results of the EORTC Children Leukemia Cooperative Study 58872. Med Pediatr Oncol 26:173-179, 1996

12. Entz-Werle N, Suciu S, van der Werff ten Bosch J, et al: Results of 58872 and 58921 trials in acute myeloblastic leukemia and relative value of chemotherapy vs allogeneic bone marrow transplantation in first complete remission: The EORTC Children Leukemia Group report. Leukemia 19: 2072-2081, 2005

13. Perel Y, Auvrignon A, Leblanc T, et al: Impact of addition of maintenance therapy to intensive induction and consolidation chemotherapy for childhood acute myeloblastic leukemia: Results of a prospective randomized trial, LAME 89/91. J Clin Oncol 20:2774-2782, 2002

14. Perel Y, Auvrignon A, Leblanc T, et al: Treatment of childhood acute myeloblastic leukemia: Dose intensification improves outcome and maintenance therapy is of no benefit—Multicenter studies of the French LAME (Leucémie Aiguë Myéloblastique Enfant) Cooperative Group. Leukemia 19:2082-2089, 2005

15. Creutzig U, Ritter J, Zimmermann M, et al: Improved treatment results in high-risk pediatric acute myeloid leukemia patients after intensification with high-dose cytarabine and mitoxantrone: Results of study acute myeloid leukemia—Berlin-Frankfurt-Münster 93. J Clin Oncol 19:2705-2713, 2001

16. Creutzig U, Ritter J, Zimmermann M, et al: Idarubicin improves blast cell clearance during induction therapy in children with AML: Results of study AML-BFM 93. Leukemia 15:348-354, 2001

17. Creutzig U, Zimmermann M, Ritter J, et al: Treatment strategies and long-term results in paediatric patients treated in four consecutive AML-BFM trials. Leukemia 19:2030-2042, 2005

18. Creutzig U, Reinhardt D, Zimmermann M: Prognostic relevance of risk groups in the pediatric AML-BFM trials 93 and 98. Ann Hematol 83:S112-S116, 2004 (suppl 1)

19. Creutzig U, Zimmermann M, Lehrnbecher T, et al: Less toxicity by optimizing chemotherapy, but not by addition of granulocyte colony-stimulating factor in children and adolescents with acute myeloid leukemia: Results of AML-BFM 98. J Clin Oncol 24:4499-4506, 2006

20. Hann IM, Stevens RF, Goldstone AH, et al: Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukemia: Results of the Medical Research Council's 10th AML trial (MRC AML 10). Blood 89:2311-2318, 1997

21. Stevens RF, Hann IM, Wheatley K, et al: Marked improvements in outcome with chemotherapy alone in paediatric acute myeloid leukemia: Results of the United Kingdom Medical Research Council's 10 th AML trial. Br J Haematol 101:130-140, 1998

22. Hann IM, Webb DKW, Gibson BES, et al: MRC trials in childhood acute myeloid leukemia. Ann Hematol 83:S108-S112, 2004 (suppl 1)

23. Gibson BES, Wheatley K, Hann IM, et al: Treatment strategy and long-term results in paediatric patients treated in consecutive UK AML trials. Leukemia 19:2130-2138, 2005

24. Lie SO, Abrahamsson J, Clausen N, et al: Treatment stratification based on initial in vivo response in acute myeloid leukaemia in children without Down's syndrome: Results of NOPHO-AML trials. Br J Haematol 122:217-225, 2003

25. Lie SO, Abrahamsson J, Clausen N, et al: Long-term results in children with AML: NOPHO-AML Study Group—Report of three consecutive trials. Leukemia 19:2090-2100, 2005

26. Ravindranath Y, Yeager AM, Chang MN, et al: Autologous bone marrow transplantation versus intensive consolidation chemotherapy for acute myeloid leukemia in childhood. N Engl J Med 334:1428-1434, 1996

27. Ravindranath Y, Chang M, Steuber CP, et al: Pediatric Oncology Group (POG) studies of acute myeloid leukemia (AML): A review of four consecutive childhood AML trials conducted between 1981 and 2000. Leukemia 19:2101-2116, 2005

28. Woods WG, Kobrinsky N, Buckley JD, et al: Timed-sequential induction therapy improves post-remission outcome in acute myeloid leukemia: A report from the Children's Cancer Group. Blood 87:4979-4989, 1996

29. Smith FO, Alonzo TA, Gerbing RB, et al: Long-term results of children with acute myeloid leukemia: A report of three consecutive phase III trials by the Children's Cancer Group—CCG 251, CCG213 and CCG 2891. Leukemia 19:2054-2062, 2005

30. Estey E, Döhner H: Acute myeloid leukemia. Lancet 368:1894-1907, 2006

31. Bloomfield CD, Lawrence D, Byrd JC, et al: Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogetetic subtype. Cancer Res 58:4173-4179, 1998

32. Abrahamsson J, Clausen N, Gustafsson G, et al: Improved outcome after relapse in children with acute myeloid leukaemia. Br J Haematol 136:229-236, 2006

VOLUME 28 · NUMBER 25 · SEPTEMBER 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Vinblastine in Children and Adolescents With High-Risk Anaplastic Large-Cell Lymphoma: Results of the Randomized ALCL99-Vinblastine Trial

Marie-Cécile Le Deley, Angelo Rosolen, Denise M. Williams, Keizo Horibe, Grazyna Wrobel, Andishe Attarbaschi, Jozsef Zsiros, Anne Uyttebroeck, Ildiko M. Marky, Laurence Lamant, Wilhelm Woessmann, Marta Pillon, Rachel Hobson, Audrey Mauguen, Alfred Reiter, and Laurence Brugières

From the Institut Gustave-Roussy, Villejuif; Université Paris-Sud, Le Kremlin-Bicêtre; Centre Hospitalier Universitaire Toulouse, Hôpital Purpan; L'Institut National de la Santé et de la Recherche Médicale U563, Centre de Physiopathologie de Toulouse Purpan, Toulouse, France; University Hospital, Padova, Italy; Cambridge University Hospital National Health Service Trust, Cambridge; Children's Cancer and Leukaemia Group Data Centre, Leicester, United Kingdom; Clinical Research Center, National Hospital Organization Nagoya Medical Center, Aichi, Japan; Children Oncology and Hematology, Medical University, Wroclaw, Poland; St Anna Children's Hospital, Vienna, Austria; Emma Kinderziekenhuis, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; University Hospital, Leuven, Belgium; Göteborg University, Göteborg, Sweden; and Non-Hodgkin's Lymphoma–Berlin-Frankfurt-Muenster Study Centre, Justus-Liebig-University, Giessen, Germany.

Submitted February 26, 2010; accepted May 17, 2010; published online ahead of print at www.jco.org on August 2, 2010.

Information regarding grant support for this study can be found in the online version of this article, at JCO.org.

A.Re. and L.B. contributed equally to this work.

Presented in part at the 50th Annual Meeting of the American Society of Hematology, December 6-9, 2008, San Francisco, CA, and the Third International Symposium on Childhood, Adolescent and Young Adult Non-Hodgkin's Lymphoma, June 11-13, 2009, Frankfurt, Germany.

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

Clinical Trials repository link available on JCO.org.

Corresponding author: Marie-Cécile Le Deley, MD, PhD, Biostatistics and Epidemiology Unit, Institut Gustave-Roussy, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France; e-mail: marie-cecile.ledeley@igr.fr.

0732-183X/10/2825-3987/$20.00

DOI: 10.1200/JCO.2010.28.5999

ABSTRACT

Purpose
The impact of adding vinblastine to a 4-month chemotherapy regimen, based on the Non-Hodgkin's Lymphoma Berlin-Frankfurt-Münster 90 protocol, in childhood high-risk anaplastic large-cell lymphoma (ALCL) was assessed.

Patients and Methods
Children and adolescents with high-risk ALCL, defined by mediastinal, lung, liver, spleen, or skin involvement, were eligible for the trial. After a prephase and one chemotherapy course, patients were randomly assigned to receive either five further chemotherapy courses without vinblastine or the same regimen with one vinblastine injection (6 mg/m^2) during each course followed by weekly vinblastine to complete a total of 1 year of treatment. The primary end point was event-free survival (EFS), analyzed on the intent-to-treat population.

Results
Between November 1999 and June 2006, 110 patients were randomly assigned to receive vinblastine, and 107 were randomly assigned not to receive vinblastine. Median follow-up was 4.8 years. Patients in the vinblastine arm had a significantly reduced risk of events during the first year (hazard ratio [HR] = 0.31; 95% CI, 0.15 to 0.67; P = .002) followed by an increased risk thereafter (HR = 4.98; 95% CI, 1.65 to 15.0; P = .003). Consequently, EFS at 1 year differed significantly (91% in the vinblastine group *v* 74% in the no-vinblastine group), with no difference at 2 years (73% and 70%, respectively). Overall EFS curves did not differ significantly (HR = 0.91; 95% CI, 0.55 to 1.5; P = .71). Thirty-one percent of weekly doses of vinblastine were reduced as a result of hematologic toxicity, although vinblastine was discontinued for toxicity in only three patients.

Conclusion
Adding vinblastine during induction and as maintenance for a total treatment duration of 1 year significantly delayed the occurrence of relapses but did not reduce the risk of failure.

J Clin Oncol 28:3987-3993. © 2010 by American Society of Clinical Oncology

INTRODUCTION

There is still no consensus regarding the standard treatment for anaplastic large-cell lymphoma (ALCL). Most European pediatric oncology groups have used short-pulse chemotherapy regimens based on mature B-cell non-Hodgkin's lymphoma (NHL) strategies, including high-dose methotrexate (MTX), cyclophosphamide, vincristine, doxorubicin, and corticosteroids with a duration of 4 to 6 months.[1-4] In North America, patients with ALCL receive prolonged repeated-pulse chemotherapy.[5,6] The failure rate at 2 years remains at 30% for most of these regimens.[1-10]

In a retrospective multivariate analysis of European ALCL studies including 225 patients treated between 1986 and 1995, the following three factors were found to be significantly associated with a high risk of disease failure: mediastinal involvement, visceral involvement (defined as lung, liver, or spleen involvement), and skin lesions. Patients with at least one risk factor, accounting for 64% of the population, had a 5-year progression-free survival rate of 61%, compared with a rate of 89% in standard-risk patients.[11]

Vinblastine seemed to be a promising candidate to reduce the risk of failure because, when given as a single agent, it has been shown to induce

complete remission in patients with relapsed ALCL even after high-dose chemotherapy or multiple relapses.[12,13] Surprisingly, in a small series of heavily pretreated patients with relapsed ALCL who then received vinblastine alone for a median duration of 14 months, 30% of patients were alive without subsequent relapse 5 years later.[13] The good safety profile of vinblastine is known from the experience in Langerhans cell histiocytosis.[14] The aim of the ALCL99-vinblastine trial was to evaluate the role of vinblastine in reducing the risk of failure in patients with high-risk ALCL defined by the involvement of mediastinum, visceral organs, or skin.

Study Design

The ALCL99-vinblastine trial was a large international randomized trial based on the NHL Berlin-Frankfurt-Münster (NHL-BFM) 90 protocol,[3] which compared six induction courses of chemotherapy (no-vinblastine arm) with the same treatment plus a vinblastine injection (6 mg/m^2) during the five latter induction courses and then weekly for a total treatment duration of 1 year (vinblastine arm).

The ALCL99-vinblastine study was part of a factorial design trial including another trial comparing the efficacy and safety of two MTX doses and administration schedules during the six induction courses of chemotherapy (MTX trial).[15]

Eligibility Criteria

This trial was conducted in 12 countries, via 10 national or cooperative groups including most European pediatric lymphoma study groups and a Japanese group. Eligible candidates were younger than 22 years old with biopsy-proven ALCL classified as high-risk disease (mediastinal, lung, liver, or spleen involvement or biopsy-proven skin lesion). Patients with isolated skin disease or involvement of the CNS were not eligible for the trial. Additional exclusion criteria were progressive disease after the first chemotherapy course, previous treatment, evidence of congenital immunodeficiency, AIDS, previous organ transplantation, or previous malignancy. Written informed consent was mandatory. The local ethics committees approved the protocol in line with the legislation in each country.

The diagnosis of ALCL was based on morphologic and immunophenotypic criteria[16] and, whenever possible, on molecular definition (evidence of anaplastic lymphoma kinase fusion genes). A review by the national pathologist was requested before random assignment for all patients negative for anaplastic lymphoma kinase 1 (ALK1) immunostaining or patients expressing B-cell markers. Additionally, all patients were to be reviewed by an international panel of pathologists blinded to treatment allocation.

Pretreatment Evaluation

Patients underwent a physical examination, chest-abdominal computed tomography and skeletal scintigraphy, bone marrow aspiration and biopsies, CSF cytospin examination, and biopsy of skin lesions. Patients were staged according to the St Jude and Ann Arbor staging systems.[17,18]

Treatment

Chemotherapy was based on the NHL-BFM90 protocol.[3] All patients received a 5-day prephase followed by six alternating induction courses (courses A and B), given every 21 days (Table 1). The MTX dose and administration schedule were randomly allocated before the first course (MTX trial).[15]

Before the second course, high-risk patients were randomly assigned to receive (or not) one vinblastine injection (6 mg/m^2; maximum, 10 mg per injection) during courses 2 to 6 and then weekly as maintenance treatment, for a total treatment duration of 1 year (vinblastine arm) compared with a 4-month treatment duration in the no-vinblastine arm. During maintenance, vinblastine was withheld for grade 4 neutropenia or grade 3 or 4 thrombocytopenia, and the dose was reduced to 4 mg/m^2 in case of two episodes of grade 4 neutropenia or grade 3 or 4 thrombocytopenia. The dose was reduced to 3 mg/m^2 if symptomatic peripheral neuropathy occurred.

Table 1. Chemotherapy Doses and Schedule in Each Induction Course

Course and Drug	Dose per Day	Schedule
Prephase		
Dexamethasone	5 mg/m^2	Days 1 and 2
	10 mg/m^2	Days 3 to 5
Cyclophosphamide	200 mg/m^2	Days 1 and 2
Intrathecal therapy*		Day 1
Course A		
Dexamethasone	10 mg/m^2	Days 1 to 5
Methotrexate	Randomized†	Day 1
Ifosfamide	800 mg/m^2	Days 1 to 5
Cytarabine	150 mg/m^2×2	Days 4 and 5
Etoposide	100 mg/m^2	Days 4 and 5
Vinblastine	Randomized‡	Day 1
Course B		
Dexamethasone	10 mg/m^2	Days 1 to 5
Methotrexate	Randomized†	Day 1
Cyclophosphamide	200 mg/m^2	Days 1 to 5
Doxorubicin	25 mg/m^2	Days 4 and 5
Vinblastine	Randomized‡	Day 1

*Intrathecal therapy consisted of intrathecal injection of methotrexate, cytarabine, and hydrocortisone.

†MTX1 arm: methotrexate 1 g/m^2 as a 24-hour infusion with intrathecal therapy at day 1 and leucovorin rescue (15 mg/m^2) at hours 42, 48, and 54; MTX3 arm: methotrexate 3 g/m^2 as a 3-hour infusion with no intrathecal therapy and leucovorin rescue (15 mg/m^2 every 6 hours) starting at hour 24 and ending when the methotrexate level was < 0.15 μmol/L.

‡According to random assignment, patients did or did not receive one injection of vinblastine (6 mg/m^2) during courses 2 to 5.

Response Criteria

Tumor response was evaluated after each course. A complete remission was defined as the disappearance of the disease for at least 4 weeks, and an unconfirmed complete remission was defined as a reduction in tumor size exceeding 70%.[19] Follow-up was performed every 2 to 4 months for the first 3 years, every 6 months during years 4 and 5, and then yearly. Relapses required confirmation by biopsy.

Random Assignment

Overall, 175 centers participated in the trial. The random assignment was performed after the first induction course to allow for a pathology review for patients not fulfilling the classical criteria for diagnosis. Random assignment was balanced and stratified according to country and to the treatment allocated by the first random assignment for the MTX trial (factorial design).[15] Five different data centers managed the random assignment. A centralized randomization software was used in all five data centers except in Italy, with a minimization program (France) or stratified random assignment with permuted blocks of size four (Japan, BFM, and Sweden). In the Italian data center, predefined stratified balanced random assignment lists were used to allocate treatments.

Blinding to therapy could not be achieved because of the obvious differences in the treatments, but a central review of all events was performed at the end of the study by the principal investigator blinded to the allocated treatment. Questionable events were reviewed by the whole study committee.

Statistical Considerations

The primary end point was event-free survival (EFS), which was defined as the time from random assignment to the time of the first failure (progression, relapse, second malignancy, or death) or to the last follow-up visit for patients in first complete remission. Secondary end points were overall survival (OS), complete remission, and acute toxicity. OS rates were estimated from the date of random assignment to death, whatever the cause, or the date

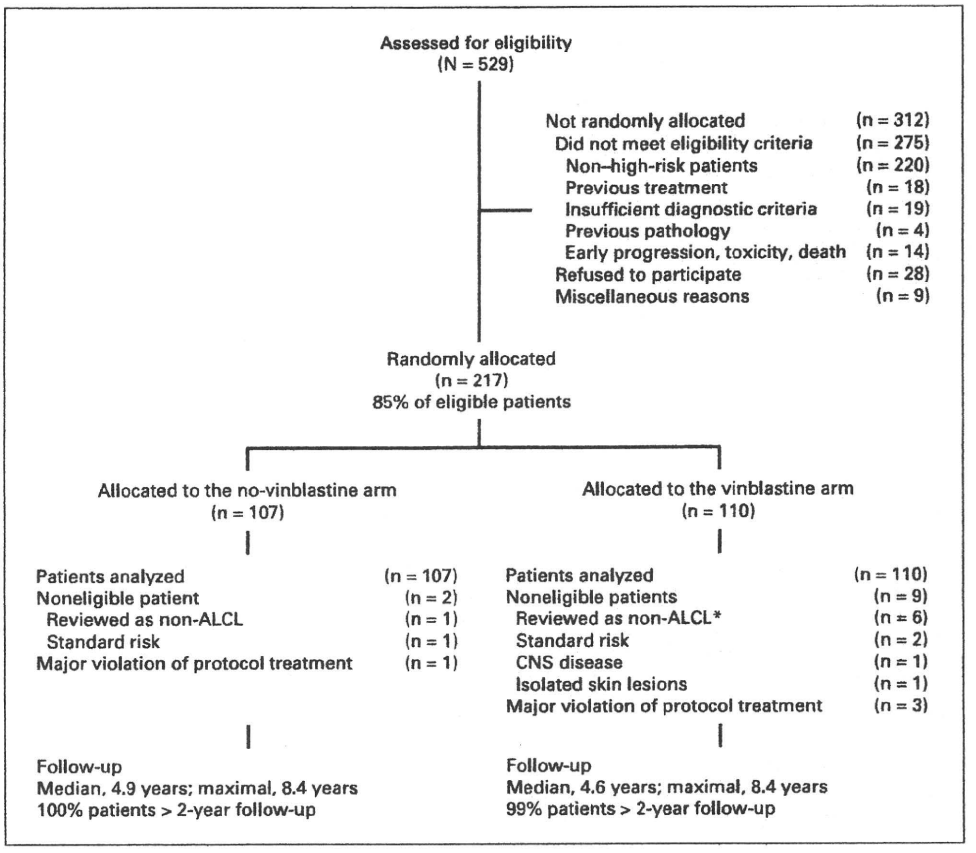

Fig 1. Participant flow. (*) One of the six patients for whom the diagnosis of anaplastic large-cell lymphoma (ALCL) was rejected is also included among the four non–high-risk patients (isolated skin lesions, diagnosis reviewed as CD30-positive cutaneous lymphoproliferation).

of the last follow-up visit for patients last seen alive. Toxicity, including neurologic toxicity, was assessed after each course during induction therapy and weekly during maintenance treatment using the National Cancer Institute Common Toxicity Criteria (version 2.0).

Survival rates (EFS and OS) were estimated using the Kaplan-Meier method with Rothman's 95% CIs. Median follow-up was estimated using Schemper's method. The hazard ratios (HRs) for events (EFS) and deaths (OS) were estimated using Cox models adjusted on country and on treatment allocated by the first random assignment (MTX1/MTX3).

The trial was designed to demonstrate an improvement from 62%[11] to 80% in the 2-year EFS probability (HR = 0.47). A total of 59 events and 204 patients were required to reach a power of 80% with a type I error of 5% (two-sided log-rank test).

Three planned interim analyses were performed after observing 25%, 50%, and 75% of events, using Fleming's plan and discussed with the independent data monitoring committee. The present analysis is the final analysis, performed with a two-sided $P = .0412$.

The main analysis of EFS was performed on the intent-to-treat population. A prespecified secondary analysis was performed after exclusion of patients for whom the diagnosis of ALCL had been rejected after review. Prespecified analyses were performed to study variations in the treatment effect according to the treatment allocated by the first random assignment and according to country. Exploratory analyses were performed on patients receiving vinblastine maintenance treatment to investigate the effect of actual dose-intensity and overall treatment duration on the risk of failure. This former analysis was performed on patients who had received at least 50 weeks of treatment. All reported P values for heterogeneity are two-sided.

Vinblastine dose-intensity was computed taking into account the injections given from the start to the end of maintenance treatment, truncated at 52 weeks. Data were entered and checked with the PIGAS software[19a] and analyzed with the SAS software version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patients

Between November 1999 and May 2006, 529 patients were screened for study entry (Fig 1). Overall, 217 (85%) of 254 potentially eligible patients were included (107 in the no vinblastine arm and 110 in the vinblastine arm). All patients, except one, were observed for at least 2 years from random assignment (median, 4.8 years; maximum, 8.4 years). Patient characteristics are listed in Table 2.

A central histopathology review was performed for 207 of 217 patients. The diagnosis of ALCL was rejected in seven patients (Hodgkin's lymphoma, n = 1; ALK-negative peripheral T-cell NHL not otherwise specified, n = 3; ALK-negative B-cell NHL, n = 1; ALK-positive immunoblastic B-cell NHL, n = 1; CD30-positive cutaneous lymphoproliferation, n = 1). All 210 other patients were CD30-positive, 200 (95%) were positive for ALK1, and 187 (89%) expressed at least one T-cell marker. The distribution of subtypes according to the WHO classification, available for 195 patients (93%), was as follows: common type (n = 107), mixed (n = 58), small cell (n = 14), lymphohistiocytic (n = 7), Hodgkin's like (n = 6), and giant cell (n = 3).

Treatment

A major protocol violation was observed in four patients. Three patients in the vinblastine arm did not receive any of the planned vinblastine injections, and one patient in the no-vinblastine arm received the whole maintenance treatment.

Table 2. Patient Demographic and Clinical Characteristics by Treatment Arm

Characteristic	No. of Patients (N = 217)	
	No-Vinblastine Arm (n = 107)	Vinblastine Arm (n = 110)
Male	69	62
Age, years		
< 3	13	6
3-16	88	97
> 16	6	7
Risk group		
Isolated skin lesions	0	1
Standard risk	1	2
High risk	106	106
CNS disease	0	1
MTX randomized group		
Not randomized	1	2
MTX1 arm	52	56
MTX3 arm	54	52
"B" symptoms*	72	75
Site of disease		
Peripheral lymph node	100	96
Mediastinal involvement†	72	86
Lung lesion†	28	36
Liver involvement‡	21	18
Spleen involvement‡	30	27
Skin lesion§	31	34
Soft tissue mass	15	16
Bone lesion‖	15	18
Bone marrow involvement	15	17
St Jude stage		
1	0	1
2	7	4
3	86	88
4	14	17
Ann Arbor stage		
1	1	1
2	26	26
3	39	38
4	41	45
International Prognostic Index¶		
0	10	11
1	22	20
2	36	34
3	20	27

Abbreviation: MTX, methotrexate.
* Information on "B" symptoms was missing for two patients.
†Radiologic diagnosis was made by x-ray and/or computed tomography.
‡Liver and spleen were considered involved if palpable clinically or enlarged on imaging more than 5 cm below the costal margin or by nodular involvement on imaging.
§Skin involvement included biopsy-proven anaplastic large-cell lymphoma cutaneous involvement and clinically diagnosed skin lesions undoubtedly related to anaplastic large-cell lymphoma, with the exclusion of lesions limited to the skin overlying an involved node or a soft tissue mass.
‖Information on bone lesion was missing for 29 patients.
¶International Prognostic Index information was missing for 37 patients.

Ten of the 110 patients in the vinblastine arm did not receive any maintenance treatment as a result of progression or death (n = 5), protocol violation (n = 3), or other reasons (n = 2). The median duration of treatment was 53 weeks (range, 21 to 86 weeks). Treatment duration was less than 50 weeks for 10 patients as a result of progression (n = 3), toxicity (n = 3), protocol violation (n = 1), and miscellaneous reasons (n = 3); duration was between 50 and 54 weeks as planned in the protocol for 53 patients, between 54 and 70 weeks for 20 patients, and greater than 70 weeks for 17 patients. Prolonged treatment durations were a result of misinterpretation of the term total duration of treatment versus the duration of maintenance. The average vinblastine dose was 4.7 mg/m^2/wk during maintenance treatment. Overall, 33 of 100 patients received at least 90% of the planned weekly dose of vinblastine (5.4 mg/m^2/wk). As detailed later, dose reductions were mainly a result of hematologic toxicity.

Outcome

Overall, 205 evaluable patients achieved complete remission or unconfirmed complete remission before the end of induction treatment. An event was reported in 66 of 217 patients (10 progressions during treatment, 55 relapses, and one death as a result of toxicity of induction treatment). Seventeen patients died after progression or relapse, including six deaths related to the toxicity of second-line treatment. Two-year EFS and OS rates were 71% (95% CI, 75% to 77%) and 94% (95% CI, 89% to 96%), respectively, for the whole trial population. The outcome results by treatment arm are listed in Table 3.

The overall number of events was well balanced, but the median interval from random assignment to progression/relapse differed greatly between the two arms (13.1 months in the vinblastine arm *v* 6.5 months in the no-vinblastine arm; Wilcoxon test, $P < .001$). Time to relapse from the last chemotherapy injection did not differ significantly between the vinblastine and no-vinblastine arms (median, 1.6 *v* 2.7 months, respectively; $P = .07$). During the first year, we observed a significantly lower risk of events in the vinblastine arm compared with the no-vinblastine arm (HR = 0.31; 95% CI, 0.15 to 0.67; $P = .002$), whereas the risk was significantly increased after the first year (HR =

Table 3. Outcome by Treatment Arm

Outcome	No-Vinblastine Arm (n = 107)	Vinblastine Arm (n = 110)
Response to induction chemotherapy, No. of patients		
Complete remission	91	93
Complete remission unconfirmed	10	11
Progressive disease	6	4
Not evaluable	0	2*
No. of events	32	34
Type of first event, No.		
Progression/relapse	32	33
Toxic death	0	1
Time of progression/relapse, No.		
Progression during therapy (or ≤ 31 days after end of therapy)	6	4
Relapse after completion of induction treatment but within 1 year from random assignment	20	3
Relapse occurring > 1 year after random assignment	6	26
No. of deaths	8	10

*Two patients were not evaluable for response to induction chemotherapy because the treatment was stopped prematurely (one patient with isolated skin lesions reviewed as CD30-positive cutaneous lymphoproliferation and one patient with protocol violation).

4.98; 95% CI, 1.65 to 15.0; $P = .003$). This led to a 17% difference in 1-year EFS (90.9% in vinblastine arm *v* 73.8% in no-vinblastine arm), whereas there was no significant difference at 2 years (72.5% *v* 70.1%, respectively; difference = +2.4%; 95% CI, −10% to 15%; Fig 2A). Throughout the whole follow-up period, there was no significant difference in EFS between the randomized groups (HR = 0.91; 95% CI, 0.55 to 1.5; $P = .71$). The effect of vinblastine on EFS did not differ according to the country ($P = .28$). No significant interaction was detected between the effect of vinblastine and the dose of MTX (factorial design, interaction test, $P = .83$). Considering the 100 patients who started vinblastine maintenance treatment, there was a nonsignificant reduction in the risk of failure in the 33 patients who received at least 90% of the planned weekly dose of vinblastine compared with the patients with lower dose-intensity (HR = 0.60; 95% CI, 0.25 to 1.41; $P = .24$). With a similar follow-up after the end of treatment in both groups, patients with a treatment duration greater than 70 weeks had a nonsignificant reduction in the number of treatment failures compared with patients with a shorter duration of treatment (three [18%] of 17 patients *v* 23 [32%] 73 patients, respectively; Fisher's exact test, $P = .38$). There was no significant effect of vinblastine on OS (HR = 1.28; 95% CI, 0.49 to 3.38; $P = .60$; Fig 2B). Results were similar after exclusion of the seven patients for whom the diagnosis of ALCL was rejected after central pathology review.

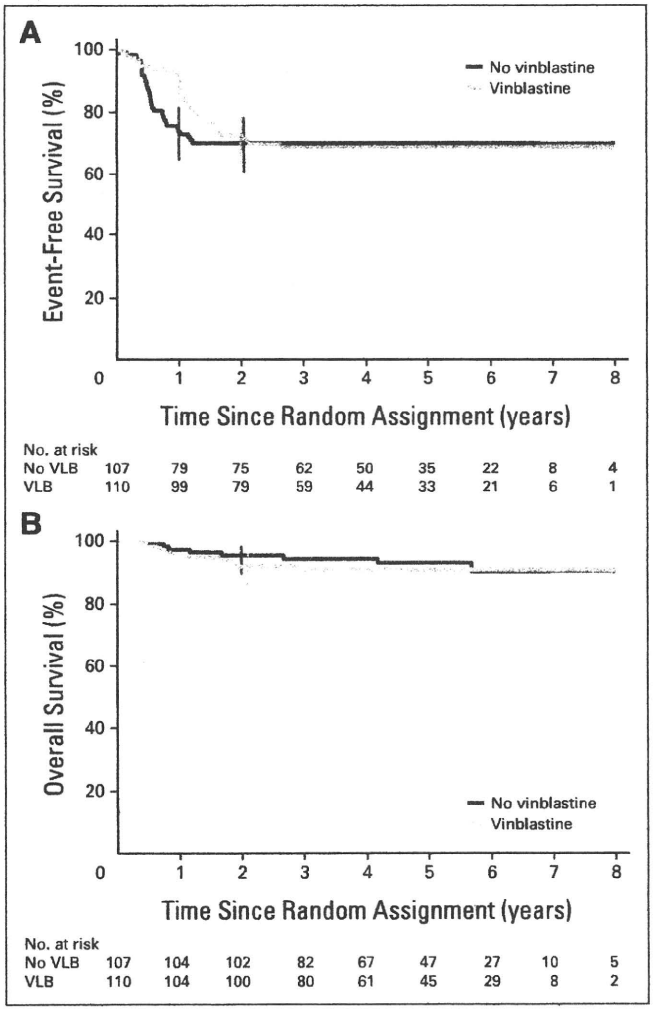

Fig 2. (A) Event-free survival (EFS) by treatment group. (B) Overall survival (OS) by treatment group. VLB, vinblastine.

Toxicity

During the induction courses, there was no significant difference in the incidence of toxicity between the vinblastine and no-vinblastine arms except for grade 4 anemia (8% of the vinblastine arm *v* 5% of the no-vinblastine arm; $P = .05$) and grade 3 or 4 stomatitis (13% *v* 9%, respectively; $P = .05$). One patient in the vinblastine arm experienced grade 3 peripheral neuropathy during induction treatment.

Only three patients stopped vinblastine maintenance as a result of toxicity, but the dose of vinblastine was reduced in 793 (31%) of 2,563 courses. Hematologic toxicity was the main reason for dose reduction. Of the 2,164 evaluated maintenance courses, grade 3 and grade 4 neutropenia were reported after 634 courses (29%) and 253 courses (12%), respectively. All but 11 patients experienced at least one episode of grade 3 or 4 neutropenia. Sixteen patients received at least one RBC transfusion during maintenance. No platelet transfusion was required. During maintenance treatment, four patients experienced grade 3 peripheral neuropathy, which was transient in two patients but led to the premature stopping of treatment in one patient and to a significant dose reduction in the other.

Discussion

This trial demonstrated that adding vinblastine to standard chemotherapy for a total treatment duration of 1 year in children with high-risk ALCL significantly delayed the occurrence of relapse but did not reduce the risk of failure, resulting in no benefit in the 2-year EFS or overall EFS curves.

We were able to reproduce the results of the NHL-BFM90 study[3] in this large study involving 12 different countries, with a 2-year EFS probability of 71% in the whole trial population. This result was better than expected in the control arm. In addition, despite the rarity of the disease, the number of patients recruited in the study allowed comparison of the two treatment groups in a randomized trial with an acceptable power.

The external validity of this study is robust; in all participating groups, patients with childhood ALCL diagnosed between 1999 and 2006 were screened for trial entry eligibility, and there was a subsequent 85% random assignment rate. Furthermore, the slides of 95% of patients were centrally reviewed, and the diagnosis of ALCL was rejected in only seven patients.

Maintenance treatment with weekly vinblastine proved feasible. Although hematologic toxicity occurred frequently, few patients stopped maintenance treatment as a result of toxicity, and the mean dose-intensity was 78% of the planned weekly dose.

The trial demonstrated a significant reduction in the risk of relapse during vinblastine maintenance treatment, leading to a 6-month postponement of the median time to relapse. This confirmed that weekly vinblastine is an important agent in this disease as suggested by data on patients experiencing relapse[12,13,20] and by in vitro data.[21] However, we cannot exclude the possibility that comparable results might be obtained by different maintenance treatments because several patients reported in the literature have achieved remission with prolonged treatment with other drugs such as oral MTX or

etoposide.[12,22] However, in a mouse model, vinblastine has recently been shown to have a dual therapeutic effect, combining direct induction of tumor cell death and maturation of dendritic cells, thereby leading to an increased host immunity against tumor antigens.[22-24] This latter effect might be important in ALCL in which increasing evidence supports an important role of the immune system.[25-31] The design of the present study was probably not optimal to test the clinical impact of immunologic properties of vinblastine.

Several patients experienced relapse after the end of maintenance, so overall, the proportion of patients who experienced relapse was similar in both treatment arms, suggesting that weekly vinblastine maintenance after chemotherapy for up to 1 year was unable to eradicate minimal residual disease. Although we observed a reduction in the risk of failure in patients who were able to tolerate 90% of the planned weekly dose and in patients with duration of treatment longer than 70 weeks, these results were not statistically significant, and no firm conclusion can be drawn from these exploratory analyses.

The OS of the whole trial population is excellent, with a 5-year OS rate of 92%, with no significant difference between both randomized groups. These findings suggest that the residual tumor cells do not acquire resistance to chemotherapy. The chemotherapy sensitivity of ALCL after relapse is quite unique when compared with other malignancies, especially other aggressive lymphomas. Considering that prolonged treatment with single-drug vinblastine can induce long-term survival after relapse,[12,13,20] we cannot rule out the possibility that a longer treatment could be more effective in eradicating residual tumor cells than the 1-year therapy tested in this trial.

In conclusion, we have shown that the addition of vinblastine to standard chemotherapy for a total duration of 1 year significantly delayed the occurrence of relapse but did not reduce the risk of failure, resulting in no benefit in terms of 2-year EFS and overall EFS.

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

Conception and design: Marie-Cécile Le Deley, Angelo Rosolen, Denise M. Williams, Alfred Reiter, Laurence Brugières
Provision of study materials or patients: Angelo Rosolen, Denise M. Williams, Keizo Horibe, Grazyna Wrobel, Andishe Attarbaschi, Jozsef Zsiros, Anne Uyttebroeck, Ildiko M. Marky, Laurence Lamant, Wilhelm Woessmann, Marta Pillon, Alfred Reiter, Laurence Brugières
Collection and assembly of data: Marie-Cécile Le Deley, Marta Pillon, Rachel Hobson, Laurence Brugières
Data analysis and interpretation: Marie-Cécile Le Deley, Angelo Rosolen, Denise M. Williams, Keizo Horibe, Grazyna Wrobel, Andishe Attarbaschi, Jozsef Zsiros, Anne Uyttebroeck, Ildiko M. Marky, Laurence Lamant, Wilhelm Woessmann, Audrey Mauguen, Alfred Reiter, Laurence Brugières
Manuscript writing: Marie-Cécile Le Deley, Angelo Rosolen, Denise M. Williams, Keizo Horibe, Grazyna Wrobel, Andishe Attarbaschi, Jozsef Zsiros, Anne Uyttebroeck, Ildiko M. Marky, Laurence Lamant, Wilhelm Woessmann, Marta Pillon, Rachel Hobson, Audrey Mauguen, Alfred Reiter, Laurence Brugières
Final approval of manuscript: Marie-Cécile Le Deley, Angelo Rosolen, Denise M. Williams, Keizo Horibe, Grazyna Wrobel, Andishe Attarbaschi, Jozsef Zsiros, Anne Uyttebroeck, Ildiko M. Marky, Laurence Lamant, Wilhelm Woessmann, Marta Pillon, Rachel Hobson, Audrey Mauguen, Alfred Reiter, Laurence Brugières

1. Brugières L, Deley MC, Pacquement H, et al: CD30(+) anaplastic large-cell lymphoma in children: Analysis of 82 patients enrolled in two consecutive studies of the French Society of Pediatric Oncology. Blood 92:3591-3598, 1998

2. Reiter A, Schrappe M, Tiemann M, et al: Successful treatment strategy for Ki-1 anaplastic large-cell lymphoma of childhood: A prospective analysis of 62 patients enrolled in three consecutive Berlin-Frankfurt-Munster group studies. J Clin Oncol 12:899-908, 1994

3. Seidemann K, Tiemann M, Schrappe M, et al: Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: A report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. Blood 97:3699-3706, 2001

4. Williams DM, Hobson R, Imeson J, et al: Anaplastic large cell lymphoma in childhood: Analysis of 72 patients treated on the United Kingdom Children's Cancer Study Group chemotherapy regimens. Br J Haematol 117:812-820, 2002

5. Laver JH, Kraveka JM, Hutchison RE, et al: Advanced-stage large-cell lymphoma in children and adolescents: Results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen—A Pediatric Oncology Group phase III trial. J Clin Oncol 23:541-547, 2005

6. Lowe EJ, Sposto R, Perkins SL, et al: Intensive chemotherapy for systemic anaplastic large cell lymphoma in children and adolescents: Final results of Children's Cancer Group Study 5941. Pediatr Blood Cancer 52:335-339, 2009

7. Sandlund JT, Pui CH, Santana VM, et al: Clinical features and treatment outcome for children with CD30+ large-cell non-Hodgkin's lymphoma. J Clin Oncol 12:895-898, 1994

8. Massimino M, Gasparini M, Giardini R: Ki-1 (CD30) anaplastic large-cell lymphoma in children. Ann Oncol 6:915-920, 1995

9. Mori T, Kiyokawa N, Shimada H, et al: Anaplastic large cell lymphoma in Japanese children: Retrospective analysis of 34 patients diagnosed at the National Research Institute for Child Health and Development. Br J Haematol 121:94-96, 2003

10. Rosolen A, Pillon M, Garaventa A, et al: Anaplastic large cell lymphoma treated with a leukemia-like therapy: Report of the Italian Association of Pediatric Hematology and Oncology (AIEOP) LNH-92 protocol. Cancer 104:2133-2140, 2005

11. Le Deley MC, Reiter A, Williams D, et al: Prognostic factors in childhood anaplastic large cell lymphoma: Results of a large European intergroup study. Blood 111:1560-1566, 2008

12. Brugieres L, Quartier P, Le Deley MC, et al: Relapses of childhood anaplastic large-cell lymphoma: Treatment results in a series of 41 children—A report from the French Society of Pediatric Oncology. Ann Oncol 11:53-58, 2000

13. Brugières L, Pacquement H, Le Deley MC, et al: Single-drug vinblastine as salvage treatment for refractory or relapsed anaplastic large-cell lymphoma: A report from the French Society of Pediatric Oncology. J Clin Oncol 27:5056-5061, 2009

14. Gadner H, Grois N, Arico M, et al: A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J Pediatr 138:728-734, 2001

15. Brugières L, Le Deley MC, Rosolen A, et al: Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: Results of a randomized trial of the EICNHL Group. J Clin Oncol 27:897-903, 2009

16. Harris NL, Jaffe ES, Stein H, et al: A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 84:1361-1392, 1994

17. Murphy SB: Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: Dissimilarities from lymphomas in adults. Semin Oncol 7:332-339, 1980

18. Carbone PP, Kaplan HS, Musshoff K, et al: Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 31:1860-1861, 1971

19. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. J Clin Oncol 17:1244, 1999

19a. Wartelle M, Kramar A, Jan P, et al: PIGAS: An interactive statistical database management system, in Hammond R, MacCarty JL (eds), Proceedings of the Second National Workshop on Statistical Database Management. Los Altos, CA, Laurence Berkeley Laboratory-Statistics Canada, 1983, pp 124-132

20. Garner R, Li Y, Gray B, et al: Long-term disease control of refractory anaplastic large cell lymphoma with vinblastine. J Pediatr Hematol Oncol 31:145-147, 2009

21. Muto A, Nakagawa A, Shimomura Y, et al: Antineoplastic agents for pediatric anaplastic large cell lymphoma: Vinblastine is the most effective in vitro. Leuk Lymphoma 46:1489-1496, 2005

22. Stockklausner C, Behnisch W, Mechtersheimer G, et al: Long-term remission of children with relapsed and secondary anaplastic large cell non-Hodgkin lymphoma (ALCL) following treatment with pulsed dexamethasone and low dose etoposide. Pediatr Blood Cancer 50:126-129, 2008

23. Tanaka H, Matsushima H, Nishibu A, et al: Dual therapeutic efficacy of vinblastine as a unique chemotherapeutic agent capable of inducing dendritic cell maturation. Cancer Res 69:6987-6994, 2009

24. Tanaka H, Matsushima H, Mizumoto N, et al: Classification of chemotherapeutic agents based on their differential in vitro effects on dendritic cells. Cancer Res 69:6978-6986, 2009

25. Ait-Tahar K, Cerundolo V, Banham AH, et al: B and CTL responses to the ALK protein in patients with ALK-positive ALCL. Int J Cancer 118:688-695, 2006

26. Ait-Tahar K, Barnardo MC, Pulford K: CD4 T-helper responses to the anaplastic lymphoma kinase (ALK) protein in patients with ALK-positive anaplastic large-cell lymphoma. Cancer Res 67:1898-1901, 2007

27. Ait-Tahar K, Damm-Welk C, Burkhardt B, et al: Correlation of the autoantibody response to the ALK oncoantigen in pediatric anaplastic lymphoma kinase-positive anaplastic large cell lymphoma with tumor dissemination and relapse risk. Blood 115:3314-3319, 2010

28. Mussolin L, Bonvini P, Ait-Tahar K, et al: Kinetics of humoral response to ALK and its relationship with minimal residual disease in pediatric ALCL. Leukemia 23:400-402, 2009

29. Cesaro S, Pillon M, Visintin G, et al: Unrelated bone marrow transplantation for high-risk anaplastic large cell lymphoma in pediatric patients: A single center case series. Eur J Haematol 75:22-26, 2005

30. Woessmann W, Peters C, Lenhard M, et al: Allogeneic haematopoietic stem cell transplantation in relapsed or refractory anaplastic large cell lymphoma of children and adolescents: A Berlin-Frankfurt-Munster group report. Br J Haematol 133:176-182, 2006

31. Chiarle R, Martinengo C, Mastini C, et al: The anaplastic lymphoma kinase is an effective oncoantigen for lymphoma vaccination. Nat Med 14:676-680, 2008

