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VI. 代表的論文

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ORIGINAL REPORT

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

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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.

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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.

PATIENTS AND METHODS

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

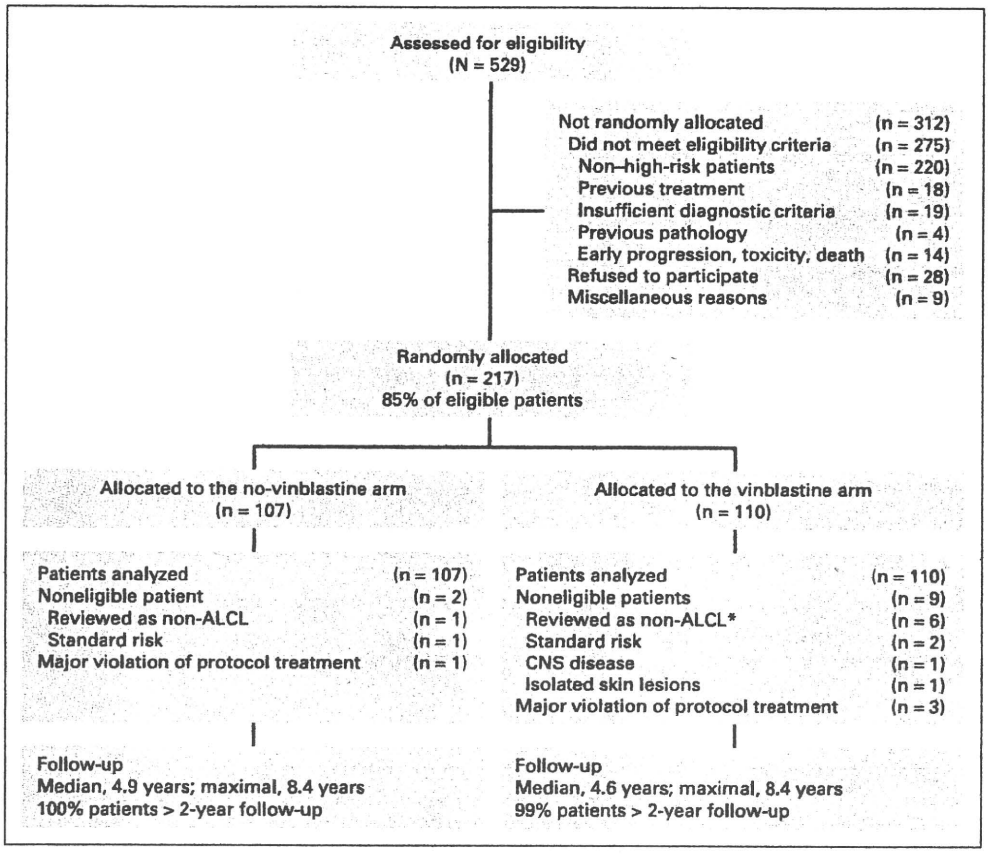

Fig 1. Participant flow. (*) One of the six patients for whom the diagnosis of anaplastic large-cell lymphoma (ALCL) was rejected is also included among the four non–high-risk patients (isolated skin lesions, diagnosis reviewed as CD30-positive cutaneous lymphoproliferation).

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.

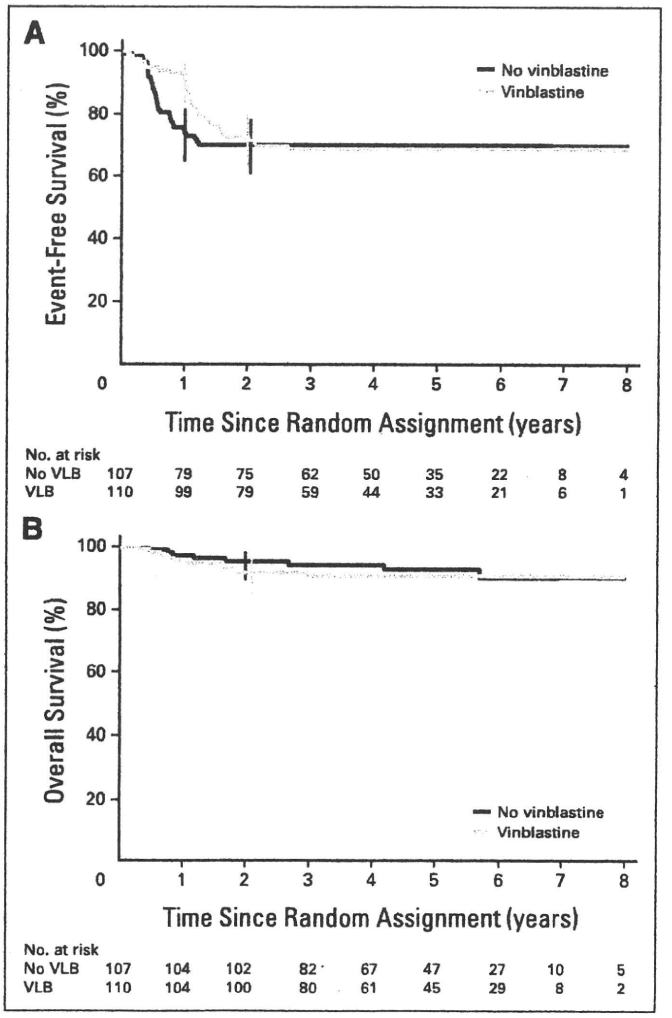

Fig 2. (A) Event-free survival (EFS) by treatment group. (B) Overall survival (OS) by treatment group. VLB, vinblastine.

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.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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ORIGINAL REPORT

Clinical Outcome of Children With Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia Treated Between 1995 and 2005

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ABSTRACT

Purpose
In a previous analysis of 326 children with Philadelphia chromosome (Ph) –positive acute lymphoblastic leukemia (ALL) treated between 1986 and 1996, hematopoietic stem-cell transplantation from HLA-matched related donors, but not from unrelated donors, offered a superior outcome than chemotherapy alone. To evaluate the impact of recent improvements in chemotherapy and transplantation, we performed a similar analysis on patients treated in the following decade.

Patients and Methods
We analyzed 610 patients with Ph-positive ALL treated between 1995 and 2005 without tyrosine kinase inhibitor therapy. The median follow-up duration was 6.3 years.

Results
Complete remission was achieved in 89% of patients. The 7-year event-free survival and overall survival rates were superior in the present cohort compared with the previous cohort (32.0% ± 2.0% *v* 25.0% ± 3.0, respectively, $P = .007$; and 44.9% ± 2.2% *v* 36.0% ± 3.0%, respectively, $P = .017$). Compared with chemotherapy alone, transplantation with matched related donors or unrelated donors in first remission (325 patients) showed an advantage with increasing follow-up, suggesting greater protection against late relapses (hazard ratio at 5 years, 0.37; $P < .001$). In the multivariate Cox regression analysis accounting for treatment (transplantation *v* no transplantation), age, leukocyte count, and early response had independent impact on treatment outcome.

Conclusion
Clinical outcome of children and adolescents with Ph-positive ALL has improved with advances in transplantation and chemotherapy. Transplantations with matched related donors and unrelated donors were equivalent and offered better disease control compared with chemotherapy alone. Age, leukocyte count, and early treatment response were independent prognostic indicators. The results of this study will serve as a historical reference to evaluate the therapeutic impact of tyrosine kinase inhibitors on the outcome of Ph-positive ALL.

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INTRODUCTION

With current cure rates of 85% or greater in childhood acute lymphoblastic leukemia (ALL),[1] precise risk assessment is important to direct treatment. Patients with low-risk leukemia can be assigned to receive less intensive treatment to minimize late sequelae. Conversely, the subset of patients with high risk of relapse should be allocated to receive intensive treatment or novel therapies. With continuing improvement in therapy, the impact of many prognostic factors has been diminished or abolished altogether. Until recently, the Philadelphia chromosome (Ph) resulting from chromosomal translocation t(9;22), which occurs in 3% to 5% of children and 25% of adults with ALL, has consistently been associated with dismal treatment outcome. The translocation results in a fusion protein of 210 kDa (p210) when the *ABL1* proto-oncogene moves from chromosome 9 to the major breakpoint cluster region on chromosome 22, as usually observed in chronic myelogenous leukemia. The *ABL1* gene can also translocate to the minor breakpoint cluster region on chromosome 22, resulting in a 190-kDa fusion protein (p190) that occurs exclusively in ALL. More than 90% of children

with Ph-positive ALL have this subtype of t(9;22). Both the p210 and p190 proteins can be readily detected with techniques based on the polymerase chain reaction. [2-5] In a recent genome-wide analysis of diagnostic leukemia samples from 304 individuals with ALL, *IKZF1* (encoding the transcription factor Ikaros) was deleted in 83.7% of *BCR-ABL1* ALL.[6]

With conventional treatment including hematopoietic stem-cell transplantation (HSCT), only one third of children and adolescents with Ph-positive ALL have been long-term survivors.[7-19] A recent study showed that intensive chemotherapy in combination with continuous exposure to a tyrosine kinase inhibitor (imatinib) markedly improved early treatment outcome in a small group of children with Ph-positive ALL,[20] raising the question of whether HSCT remains the treatment of choice for children or young adults with Ph-positive ALL. In our previous study of 326 children and adolescents treated by 10 cooperative study groups or single institutions between 1986 and 1996, we demonstrated that HSCT with matched related donors, but not unrelated donors, was superior to chemotherapy alone.[21] With recent improvement in both chemotherapy and HSCT, we performed a similar analysis of patients treated between 1995 and 2005 without tyrosine kinase inhibitors, so that the results can serve as baseline data to guide future development of treatment for patients with Ph-positive ALL.

PATIENTS AND METHODS

Review of Data

Each study group reviewed its records to identify patients age less than 18 years with Ph-positive ALL registered in clinical trials between 1995 and 2005. Patients who were treated with any tyrosine kinase inhibitor during front-line chemotherapy were excluded from the analysis. We accepted either cytogenetic or molecular tests to identify the Ph status; patients who were negative at diagnosis but positive at relapse were not included. A predefined set of data, collected for each patient, was then sent to a coordinating center, where the findings were reviewed for consistency and completeness. Follow-up observations extended through 2008, with a median follow-up time of 6.3 years (range, 0.1 to 11.5 years). By consensus, none of the participating groups will be identified with their data sets in this report.

Patients and Treatment

Of the 762 patients with Ph-positive ALL identified, 610 were eligible and evaluable. At most of the participating centers, these children were identified early in the clinical course and were assigned to therapy for high-risk ALL. Indications for HSCT for patients in first complete remission varied among the different study groups. Nonetheless, HSCT from an HLA-matched related donor was generally accorded the highest priority among alternatives to chemotherapy alone. The lack of information on the availability of donors prevented us from determining whether all patients with a suitable donor underwent HSCT. Definition of early response to chemotherapy was given by each group according to protocol criteria; good early response was defined by either peripheral-blood count on day 8 (prednisone good response: $< 1,000$ blasts/μL in peripheral blood after 7 days of glucocorticoid therapy and one injection of intrathecal methotrexate)[22] or bone marrow evaluation on day 8 or day 15 ($< 25\%$ blasts) or day 21 ($< 5\%$ blasts) of remission induction.[23]

Statistical Analysis

The principal end points in the analysis of treatment results were event-free survival (EFS), disease-free survival (DFS), and overall survival (OS). EFS was defined as the time from diagnosis to first failure, which was defined as death during induction therapy, lack of achievement of remission during protocol-specified induction period, relapse at any site, death during remission, or development of second malignant neoplasm. DFS was defined as the time from complete remission until relapse at any site, death during complete remission, or development of a second malignant neoplasm. OS was defined as the time from diagnosis (or time from complete remission, when stated) to

Table 1. Pattern of Treatment Failure in Children With Ph-Positive ALL Who Achieved Complete Remission After Induction Therapy by Treatment (N = 542)

			Hematopoietic Stem-Cell Transplantation (n = 325)											
	Chemotherapy Only (n = 217)		Matched Related Donor (n = 115)		Mismatched Related Donor (n = 15)		Unrelated Donor (n = 166)		Autologous (n = 10)		Not Known (n = 19)		All Patients (N = 542)	
Event	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Time from CR1 to HSCT, months														
Median			4.0		5.0		6.0		5.7		3.6			
First to third quartile			3.0-5.7		3.9-6.8		4.3-7.9		5.2-6.4		3.2-6.5			
Relapse	146	67	49	43	2	13	45	27	7	70	3	16	252	46
Bone marrow	110		37		2		32		5		3		189	
CNS	13		1		0		1		1		0		16	
Testis	2		1		0		4		0		0		7	
Bone marrow + other	16		3		0		4		1		0		24	
Other	5		6		0		3		0		0		14	
Unknown	0		1		0		1		0		0		2	
Death in CCR	16	7	18	16	8	53	31	19	0	0	6	32	79	15
Therapy related	15		0		0		0				0		15	
HSCT	0		17		6		26				5		54	
Other	0		1		0		4				1		6	
Unknown	1		0		2		1				1		4	
Second neoplasm	0		1		0		3		0		0		4	1
CCR	55	25	47	41	5	33	87	52	3	30	10	53	207	38

Abbreviations: Ph, Philadelphia chromosome; ALL, acute lymphoblastic leukemia; CR1, first complete remission; CCR, continuous complete remission; HSCT, hematopoietic stem-cell transplantation.

death from any cause. Observations of patients were censored at the date of last contact when no events were observed.

The Kaplan-Meier method was used to estimate the probabilities of EFS, DFS, and OS, with SEs calculated according to Greenwood. Curves were compared using the log-rank test. Statistical methods were used to minimize potential sources of bias in comparing DFS and OS (from date of first complete remission) after HSCT or intensive chemotherapy alone. Kaplan-Meier plots that compared HSCT with chemotherapy alone were adjusted to account for the waiting time to transplantation. The curves originate at a landmark (median time to transplantation) and thus do not include patients who had events or whose data were censored before that time; the curves account for patients who underwent transplantation after the landmark by delayed entry. To deal with lack of proportional hazards between the two treatment groups, univariate comparison between these curves was performed at a predefined time point of 5 years from remission based on log-log transformation.[24]

Differences in time to transplantation and in the prognostic factors used to assign patients to HSCT were accounted for in Cox regression analyses. Treatment was considered to be a time-dependent factor. Thus, each patient was included in the chemotherapy-only group until transplantation, at which point he or she was shifted to the transplantation group. The model also included the covariates of age (0 to 3, 3 to 6, 6 to 10, 10 to 15, $v > 15$ years), leukocyte count (0 to 10, 10 to 25, 25 to 50, 50 to 100, $v > 100 \times 10^3/\mu L$), sex, and early response (poor responders according to bone marrow result or peripheral-blood result, response not known, v good responders). The time dependence of the treatment effect (ie, nonproportional hazards) was accommodated by including a term for the interaction of time (log-transformed) and treatment in the regression analysis.[25] According to graphical checks, the proportional hazards assumption was reasonable for the prognostic factors. Two-tailed P values for differences in the risk of treatment failure (in terms of either DFS or OS) were derived from the likelihood ratio test. Estimated hazard ratios (HRs) were reported with 95% CIs.

Cumulative incidence of relapse or death was estimated in patients who underwent transplantation accounting for competing risks (censoring second malignant neoplasms). The logistic regression model was used to analyze the influence of age, leukocyte count, and early response on the odds of nonresponse to induction therapy.

RESULTS

The estimates of EFS and OS of the 610 patients with Ph-positive ALL were 32.0% ± 2.0% and 44.9% ± 2.2% at 7 years after diagnosis, respectively.

Clinical and Laboratory Characteristics

Appendix Table A1 (online only) summarizes the presenting features of the 610 evaluable patients. The median age at diagnosis was 7.8 years (range, 0.7 to 17.65 years); 72 patients (12%) were less than 2 years of age and only 1 was younger than 1 year of age. The leukocyte count at diagnosis was at least 50,000/μL in approximately 43% of the patients and less than 10,000/μL in 23%. Despite the relatively high proportion of patients with hyperleukocytosis, leukemic involvement of the CNS at diagnosis was observed in only 6% of the patients. Nine patients had a T-cell lineage immunophenotype.

Early Responses to Chemotherapy

Early response to treatment as measured by prednisone response was available in 177 patients, 33 (19%) of whom had a poor response, a proportion approximately twice that of unselected patients with ALL. Among the 338 patients for whom early response was evaluated by bone marrow aspirates, 134 (40%) had poor response (Appendix Table A1), a proportion also higher than that of unselected patients with childhood ALL.[9]

Induction of Complete Remission

A total of 542 patients (89%) achieved a complete remission after induction therapy; the remaining patients either died during induction (n = 5) or failed to achieve remission (n = 63). The induction failure rate of 11% is much higher than the 2% to 3% induction failure rate seen among children with Ph-negative ALL. In a multivariate analysis, poor early response was the strongest predictor of induction failure (odds ratio, 13.3; 95% CI, 5.73 to 31.02; $P < .001$), although WBC count retained predictive value (odds ratio, 1.86; 95% CI, 1.04 to 3.32; $P = .04$ for $\geq v < 100,000/\mu L$). Of the 63 patients with induction failure, 45 patients subsequently underwent HSCT, and 11 patients were alive at last follow-up (nine patients after HSCT).

Patterns of Treatment Failure

Of the 542 patients who achieved a complete remission after induction chemotherapy, 252 (46%) experienced a relapse, including

Table 2. Estimated HRs Associated With Different Types of HSCT and Chemotherapy Alone in Patients With Ph-Positive Childhood Acute Lymphoblastic Leukemia Who Achieved Complete Remission After Initial Induction Therapy (n = 540*)

Variable	DFS			Survival		
	HR	95% CI	P	HR	95% CI	P
Treatment			< .001			.003
Chemotherapy alone	1.00			1.00		
HSCT						
At 0.5 years	1.34	0.94 to 1.90		1.37	0.81 to 2.31	
At 1 year	0.87	0.69 to 1.10		0.96	0.71 to 1.31	
At 5 years	0.32	0.20 to 0.52		0.42	0.25 to 0.70	
Age at diagnosis, years			.03			< .001
0-3	0.45	0.27 to 0.77		0.26	0.14 to 0.48	
3-6	0.65	0.41 to 1.01		0.45	0.28 to 0.73	
6-10	0.72	0.47 to 1.12		0.56	0.35 to 0.89	
10-15	0.77	0.50 to 1.19		0.62	0.39 to 0.98	
≥ 15	1.00			1.00		
Leukocyte count at diagnosis, per μL			< .001			.003
0-10	0.47	0.34 to 0.64		0.48	0.33 to 0.70	
10-25	0.55	0.40 to 0.76		0.67	0.46 to 0.96	
25-50	0.63	0.44 to 0.89		0.77	0.52 to 1.15	
50-100	0.62	0.44 to 0.88		0.81	0.55 to 1.17	
≥ 100	1.00			1.00		
Sex						
Male	1.10	0.88 to 1.38	.40	1.01	0.79 to 1.30	.93
Female	1.00			1.00		
Early response						
Good responders in PB or BM	1.00		.03	1.00		.007
Poor responders in PB	2.00	1.26 to 3.18		2.41	1.47 to 3.95	
Poor responders in BM	1.19	0.88 to 1.61		1.30	0.94 to 1.81	
Early response unknown	1.27	0.93 to 1.73		1.34	0.95 to 1.89	

Abbreviations: HR, hazard ratio; HSCT, hematopoietic stem-cell transplantation; Ph, Philadelphia chromosome; DFS, disease-free survival; PB, peripheral blood; BM, bone marrow.

*The model was fitted on 540 patients as a result of missing values in leukocyte count at diagnosis in two patients.

