

ORIGINAL ARTICLE

Treating Childhood Acute Lymphoblastic Leukemia without Cranial Irradiation

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ABSTRACT

BACKGROUND

Prophylactic cranial irradiation has been a standard treatment in children with acute lymphoblastic leukemia (ALL) who are at high risk for central nervous system (CNS) relapse.

METHODS

We conducted a clinical trial to test whether prophylactic cranial irradiation could be omitted from treatment in all children with newly diagnosed ALL. A total of 498 patients who could be evaluated were enrolled. Treatment intensity was based on presenting features and the level of minimal residual disease after remission-induction treatment. The duration of continuous complete remission in the 71 patients who previously would have received prophylactic cranial irradiation was compared with that of 56 historical controls who received it.

RESULTS

The 5-year event-free and overall survival probabilities for all 498 patients were 85.6% (95% confidence interval [CI], 79.9 to 91.3) and 93.5% (95% CI, 89.8 to 97.2), respectively. The 5-year cumulative risk of isolated CNS relapse was 2.7% (95% CI, 1.1 to 4.3), and that of any CNS relapse (including isolated relapse and combined relapse) was 3.9% (95% CI, 1.9 to 5.9). The 71 patients had significantly longer continuous complete remission than the 56 historical controls ($P=0.04$). All 11 patients with isolated CNS relapse remained in second remission for 0.4 to 5.5 years. CNS leukemia (CNS-3 status) or a traumatic lumbar puncture with blast cells at diagnosis and a high level of minimal residual disease ($\geq 1\%$) after 6 weeks of remission induction were significantly associated with poorer event-free survival. Risk factors for CNS relapse included the genetic abnormality $t(1;19)(TCF3-PBX1)$, any CNS involvement at diagnosis, and T-cell immunophenotype. Common adverse effects included allergic reactions to asparaginase, osteonecrosis, thrombosis, and disseminated fungal infection.

CONCLUSIONS

With effective risk-adjusted chemotherapy, prophylactic cranial irradiation can be safely omitted from the treatment of childhood ALL. (ClinicalTrials.gov number, NCT00137111.)

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CLINICAL TRIALS HAVE YIELDED 5-YEAR event-free survival rates as high as 79 to 82% among children with acute lymphoblastic leukemia (ALL).¹⁻³ A major challenge is to reduce treatment-related late effects, which can occur in more than two thirds of long-term survivors.⁴ In a growing proportion of patients, prophylactic cranial irradiation, once a standard treatment, is being replaced by intrathecal and systemic chemotherapy to reduce radiation-associated late complications such as second cancers, cognitive deficits, and endocrinopathy.⁴⁻⁸

Two pediatric clinical trials tested whether prophylactic cranial irradiation could be completely omitted from treatment.^{9,10} Although the cumulative risks of isolated central nervous system (CNS) relapse in these trials were relatively low (4% and 3%), event-free survival rates were only 68.4% and 60.7%, respectively. In another study, prophylactic cranial irradiation appeared to improve the outcome of children with T-cell ALL.¹¹ Thus, there is a persistent concern that residual leukemic cells after insufficient CNS treatment could cause relapse not only in the CNS but also in the bone marrow. For this reason, virtually all study groups continue to use prophylactic cranial irradiation in up to 20% of patients.¹²

In our Total Therapy XIIIa study, 22% of the patients received prophylactic cranial irradiation; the overall 5-year event-free survival rate was 77.6%, and the cumulative risk of isolated CNS relapse was 1.2%.¹³ We replaced prednisone with dexamethasone in postremission therapy and limited prophylactic cranial irradiation to 12% of the patients in the subsequent Total Therapy XIIIb study, resulting in a 5-year event-free survival of 80.8% and a cumulative risk of an isolated CNS relapse of 1.7%.³ In the Total Therapy XV study reported here, we tested whether intensification of systemic drugs that affect control of ALL in the CNS, together with optimal intrathecal treatment, would allow for the complete omission of prophylactic cranial irradiation without compromising overall survival. These modifications were made in the context of risk assignment based on sequential measurements of minimal residual disease and adjustment of chemotherapy dosages on the basis of pharmacogenetics and pharmacokinetics.

METHODS

PATIENTS

From June 2000 to October 2007, a total of 501 consecutive patients (1 to 18 years of age) with newly diagnosed ALL were enrolled in the Total Therapy XV study; 411 patients were enrolled at St. Jude Children's Research Hospital and 90 patients were enrolled at Cook Children's Medical Center. Three patients were subsequently excluded because of a revised diagnosis of myeloid leukemia. The protocol was approved by the institutional review boards of both hospitals, and written informed consent was obtained from the patients who were 18 years old and, in the case of younger patients, from the parents or guardians, with assent from the patients, as appropriate.

The diagnostic criteria for ALL were described previously.¹⁴ CNS status was defined as CNS-1 (no detectable blast cells in a sample of cerebrospinal fluid), CNS-2 (<5 leukocytes per cubic millimeter with blast cells in a sample with <10 erythrocytes per cubic millimeter), CNS-3 (≥5 leukocytes per cubic millimeter with blast cells in a sample with <10 erythrocytes per cubic millimeter), or traumatic lumbar puncture with blast cells (≥10 erythrocytes per cubic millimeter with blast cells).¹² Minimal residual disease was determined by means of flow cytometry, polymerase chain reaction, or both.^{15,16}

STUDY AIMS AND MONITORING

Our major aims were to determine whether prophylactic cranial irradiation can be safely omitted from treatment in all patients (especially those patients who would have received this treatment after approximately 1 year of continuous complete remission, according to published criteria^{3,13}) and to estimate the overall event-free survival. The study was monitored by an independent data and safety monitoring board. Group-sequential designs were used to provide guidelines for decisions to discontinue treatment on the basis of safety and efficacy (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

RISK CLASSIFICATION

Risk classification was based on presenting characteristics of the patients and treatment response.

Patients with B-cell–precursor ALL who were between 1 and 10 years of age and who had a leukocyte count of less than 50×10^9 per liter, a DNA index (the ratio of DNA content in leukemic cells to that in normal diploid G_0/G_1 cells) of 1.16 or more, or the translocation $t(12;21)(ETV6-RUNX1)$ were provisionally classified as having low-risk ALL. Patients with $t(9;22)(BCR-ABL1)$ were considered to have high-risk ALL, and the remaining patients were provisionally classified as having standard-risk (intermediate-risk) ALL. The final risk status was determined on the basis of the level of minimal residual disease. Any patient with a level of minimal residual disease of 1% or more in the bone marrow aspirate on day 19 of remission induction or 0.10 to 0.99% minimal residual disease after completion of 6 weeks of induction therapy was considered to have standard-risk ALL. A level of minimal residual disease of 1% or more after completion of induction therapy indicated high-risk ALL.

TREATMENT

Remission Induction and Consolidation

Patients were randomly assigned to receive initial treatment with methotrexate over a period of 4 or 24 hours. Four days later, remission-induction therapy was instituted with prednisone, vincristine, daunorubicin, and asparaginase (Table 1 in the Supplementary Appendix). Patients with a level of minimal residual disease of 1% or more on day 19 received three additional doses of asparaginase. Subsequent induction therapy consisted of cyclophosphamide, mercaptopurine, and cytarabine. On hematopoietic recovery (between days 43 and 46), the minimal residual disease was assessed, and consolidation therapy was begun (Table 1 in the Supplementary Appendix).

Continuation Therapy

During initial continuation therapy (Table 1 in the Supplementary Appendix), patients with low-risk disease received daily mercaptopurine and weekly methotrexate with pulses of mercaptopurine, dexamethasone, and vincristine. Two reinduction treatments were given between weeks 7 and 9 and between weeks 17 and 19. Patients with standard-risk disease received weekly asparaginase and daily mercaptopurine with pulses of doxorubicin plus vincristine plus dexamethasone. They also received two reinduction treatments between weeks 7 and 9 and between weeks 17 and 20.

For the remaining continuation therapy (Table 2 in the Supplementary Appendix), patients with low-risk disease received mercaptopurine and methotrexate, with pulses of dexamethasone, vincristine, and mercaptopurine, and patients with standard-risk disease received three rotating drug pairs (mercaptopurine plus methotrexate, cyclophosphamide plus cytarabine, and dexamethasone plus vincristine). Dosages of mercaptopurine and methotrexate were adjusted according to the tolerance and according to the phenotype and genotype of thiopurine methyltransferase.¹⁷ Total scheduled dosages of anthracyclines were limited to 110 mg per square meter of body-surface area and 230 mg per square meter, and total scheduled dosages of cyclophosphamide were limited to 1 g per square meter and 4.6 g per square meter, in patients with low-risk disease and patients with standard-risk disease, respectively. Continuation treatment lasted 120 weeks in girls and 146 weeks in boys.

Therapy Directed to the CNS

Intrathecal cytarabine was instilled immediately after a diagnostic lumbar puncture, and triple intrathecal chemotherapy was used in all subsequent treatments (Table 1 in the Supplementary Appendix). Depending on the presenting patient characteristics and the CNS status, patients with low-risk disease received 13 to 18 intrathecal treatments, and patients with standard-risk disease received 16 to 25 intrathecal treatments.

Allogeneic Hematopoietic Stem-Cell Transplantation

Allogeneic hematopoietic stem-cell transplantation was an option in patients with high-risk leukemia (whose early treatment was identical to that in patients with standard-risk disease). Intensification therapy (Table 3 in the Supplementary Appendix) was given to maximize the reduction in minimal residual disease before transplantation. The median time to transplantation after remission induction was 4.1 months (range, 2 to 12).

STATISTICAL ANALYSIS

All analyses were prespecified in the protocol. To assess the effect of omitting prophylactic cranial irradiation, we compared the rate of continuous complete remission after 1 year of continuation therapy in the subgroup of patients who met our previous criteria for prophylactic cranial irradiation at 1 year with the rate for historical controls

who had received irradiation,^{3,13} using an unstratified Mantel-Haenszel test.

Event-free survival and overall survival distributions were compared with the use of the Mantel-Haenszel test. A Cox proportional-hazards model was used to identify independent prognostic factors without the use of any variable-selection methods. The cumulative incidence of isolated CNS relapse or any CNS relapse (isolated plus combined), as well as other adverse events, was calculated according to the method of Kalbfleisch and Prentice and was compared between groups with the use of Gray's test. Fine and Gray's model and the weighted logistic-regression model¹⁸ were used to identify independent factors for prognosis and toxic effects, respectively.

The database on January 5, 2009, was used for analysis; 97% of the survivors had been seen within 1 year. The median follow-up time was 4.0 years (range, 1.2 to 8.4). All reported P values are two-sided and were not adjusted for multiple tests.

RESULTS

Table 1 summarizes the characteristics of the 498 patients who could be evaluated. The median age at diagnosis was 5.3 years (range, 1.0 to 18.9), and the median leukocyte count was 11.7×10^9 per liter (range, 0.4×10^9 to 1014.0×10^9 per liter). There were increased proportions of patients with T-cell ALL (15.3%) or $t(1;19)(TCF3-PBX1)$ (5.8%), probably owing to the overrepresentation of black patients in our study population relative to other series.¹⁹ On the basis of levels of minimal residual disease, which were successfully measured in all patients, we reclassified the risk status of 58 patients: 30 patients from low to standard risk, 6 patients from low to high risk, and 22 patients from standard to high risk.

TREATMENT OUTCOME

Outcomes were similar in patients treated in the two centers. Of the 498 patients, 492 (98.8%) entered complete remission (low-risk, 99.6%; standard-risk, 99.5%; and high-risk, 90.4%). Induction failures were due to fatal infections in two patients and refractory leukemia in four patients. Three of the latter four patients remained in remission for 4.6, 4.6, and 6.1 years after allogeneic transplantation.

Thirty-three patients received allogeneic trans-

plants (9 from matched-sibling donors, 17 from matched-unrelated donors, and 7 from haploidentical donors) 2 to 12 months after remission induction (median, 4.1). Transplantation was performed in 6 patients for $t(9;22)(BCR-ABL1)$ ALL, in 21 patients for minimal residual disease of 1% or more at the end of induction, in 5 patients for persistent minimal residual disease on week 16 after remission, and in 1 patient for near-haploidy. Of these 33 patients, 24 were alive and in remission; 7 died of complications, and 2 had relapses.

A total of 33 relapses occurred: 17 hematologic, 11 isolated CNS, 4 combined CNS and hematologic, and 1 testicular. In addition, there was 1 case of secondary myelodysplastic syndrome, and 12 deaths occurred in patients who were in remission (including 6 patients who had undergone hematopoietic stem-cell transplantation). The 5-year cumulative risk of isolated CNS relapse was 2.7% (95% confidence interval [CI], 1.1 to 4.3), of any CNS relapse, 3.9% (95% CI, 1.9 to 5.9) (Fig. 1), and of any relapse, 9.3% (95% CI, 6.0 to 12.6). Table 4 in the Supplementary Appendix summarizes pertinent characteristics of the 11 patients with isolated CNS relapse. Notably, all 11 patients were alive and in a second remission for 0.4 to 5.5 years (median, 2.5); 10 were not receiving therapy (3 after transplantation) for 1 month to 4.1 years (median, 2.0). The estimated 5-year rate of event-free survival was 85.6% (95% CI, 79.9% to 91.3), and the rate of overall survival was 93.5% (95% CI, 89.8 to 97.2) for all 498 patients (Fig. 1). All 30 patients with low-risk disease who were reclassified as being in the standard-risk group remained free of relapse.

Among the 71 patients who met our previous criteria for receiving prophylactic CNS irradiation, 2 had a bone marrow relapse, 1 had a CNS relapse, and 1 died in remission. The duration of continuous complete remission after 1 year of continuation therapy in these 71 patients was significantly longer than that for the 56 historical controls ($P=0.04$)^{3,13}; the 5-year rate was 90.8% (95% CI, 76 to 100) versus 73.0% (95% CI, 61.2 to 84.8) (Fig. 1 in the Supplementary Appendix), and the relative risk was 0.34 (95% CI, 0.11 to 1.02).

PROGNOSTIC FACTORS

Table 1 shows treatment outcomes according to selected features. As compared with other variables, only CNS-3 status or traumatic lumbar puncture with blast cells and minimal residual disease

Table 1. Treatment Outcome According to Selected Clinical and Biologic Characteristics.*

Variable	No. of Patients	5-Yr Event-free Survival %	P Value	5-Yr Overall Survival %	P Value
Randomization group					
4-hr group	177	88.2±4.2	0.22	95.0±2.7	0.20
24-hr group	180	85.6±4.6		94.0±2.9	
Not randomly assigned†	141	82.4±6.8		91.2±4.9	
Risk group					
Low	239	95.4±2.6	<0.001	98.7±1.3	<0.001
Standard	217	82.4±4.5		92.5±3.0	
High	42	47.2±15.3		67.9±12.8	
NCI risk group (B-cell–precursor ALL)					
Standard	258	89.7±3.7	0.01	97.7±1.7	0.002
High	164	82.4±5.2		89.7±4.0	
NCI risk group (T-cell ALL)					
Standard	16	73.9±15.4	0.71	93.8±8.9	0.44
High	60	79.6±8.7		86.0±7.6	
Sex					
Male	279	83.5±4.1	0.16	93.6±2.4	0.64
Female	219	88.8±4.3		93.3±3.1	
Age					
1–10 yr	372	87.8±3.1	0.005	96.7±1.6	<0.001
>10 yr	126	79.1±6.4		83.8±5.5	
Leukocyte count					
<10×10 ⁹ /liter	227	86.8±4.1	0.1	93.7±2.8	0.33
10×10 ⁹ to 49×10 ⁹ /liter	144	85.9±5.4		95.9±3.0	
50×10 ⁹ to 99×10 ⁹ /liter	64	83.9±7.9		91.0±6.0	
100×10 ⁹ to 300×10 ⁹ /liter	44	86.1±8.9		90.4±7.5	
≥300×10 ⁹ /liter	19	73.3±18.9		89.2±12.0	
Race or ethnic group‡					
White	340	87.8±3.2	0.02	94.8±2.0	0.23
Black	79	77.8±8.2		88.3±6.2	
Hispanic	60	74.2±13.3		89.1±8.9	
Asian or other	19	100±0.0		100±0.0	
Immunophenotype					
B-cell precursor	422	86.9±3.1	<0.001	94.6±1.9	0.013
T-cell	76	78.4±7.8		87.6±6.3	
CNS status§					
CNS-1	359	87.5±3.1	<0.001	94.6±2.0	0.02
CNS-2	102	86.2±7.5		95.1±4.3	
Traumatic lumbar puncture with blast cells	28	81.4±14.3		81.9±13.2	
CNS-3	9	43.2±23.0		71.1±22.1	

Table 1. (Continued.)

Variable	No. of Patients	5-Yr Event-free Survival %	P Value	5-Yr Overall Survival %	P Value
DNA index¶					
≥1.16	121	91.2±4.6	0.02	96.2±3.0	0.09
<1.16	377	83.8±3.5		92.8±2.5	
Genetic abnormality					
t(9;22) (BCR-ABL1)					
Present	10	40.0±21.9	<0.001	48.0±20.0	<0.001
Absent	488	86.7±2.8		94.5±1.8	
t(1;19) (TCF3-PBX1)					
Present	28	85.9±11.4	0.99	100±0.0	0.18
Absent	470	85.6±3.0		93.1±2.0	
t(12;21) (ETV6-RUNX1)					
Present	96	97.6±3.2	0.004	98.9±2.0	0.03
Absent	402	83.0±3.3		92.2±2.3	
t(4;11) (MLL-AF4)					
Present	3	100±0.0	0.59	100±0.0	0.70
Absent	495	85.6±2.9		93.5±1.9	
Minimal residual disease					
On day 19 of induction					
<0.01%	198	92.6±3.2	<0.001	97.5±1.9	<0.001
0.01–0.99%	192	87.8±5.1		93.8±3.2	
1.00–4.99%	43	77.4±10.6		96.8±4.5	
≥5.00%	55	56.8±4.1		78.1±10.6	
On remission date					
<0.01%	392	89.6±2.9	<0.001	94.5±1.9	<0.001
0.01–0.99%	77	79.5±8.0		90.9±5.4	
1.00–4.99%	14	38.1±21.2		71.4±27.0	
≥5.00%	9	55.6±26.2		87.5±13.8	

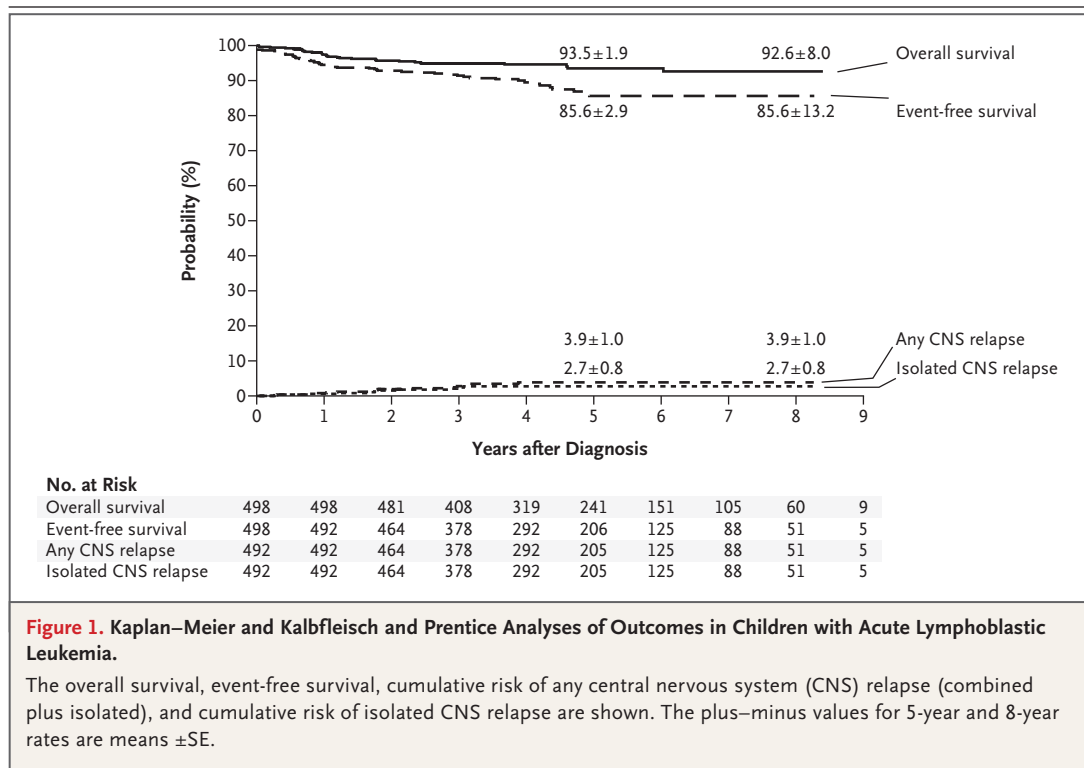
* Plus–minus values are estimates ±SE. ALL denotes acute lymphoblastic leukemia, CNS central nervous system, and NCI National Cancer Institute.

† Patients were not randomly assigned to treatment because of the decision by the patient or parent or guardian to decline (in 62 patients), completion of accrual for this part of the randomized study (21 patients), the presence of a mediastinal mass or respiratory distress (17 patients), the decision by the physician (17 patients), Down's syndrome (12 patients), organ dysfunction or infection (11 patients), and an unknown reason (1 patient).

‡ Race or ethnic group was reported by parents or guardians.

§ CNS status was classified as: CNS-1 (no detectable blast cells in a sample of cerebrospinal fluid), CNS-2 (less than 5 leukocytes per cubic millimeter with blast cells in a sample with less than 10 erythrocytes per cubic millimeter), CNS-3 (5 or more leukocytes per cubic millimeter with blast cells in a sample with less than 10 erythrocytes per cubic millimeter or the presence of a cranial-nerve palsy), and traumatic lumbar puncture with blast cells (10 or more erythrocytes per cubic millimeter with blast cells).¹²

¶ The DNA index is the ratio of DNA content, as measured by flow cytometry, in leukemic cells to that in normal diploid G₀/G₁ cells.



of 1% or more at the end of induction were independently associated with poorer event-free survival (Table 2). Features independently associated with isolated CNS relapse included T-cell ALL, black race, $t(1;19)(TCF3-PBX1)$, and any CNS involvement (i.e., CNS-2, CNS-3, or traumatic lumbar puncture with blast cells) (Table 2).

TOXICITY

Table 3 summarizes the relevant toxic effects of treatment. The cumulative risk of death from toxic effects during chemotherapy was 1.4% (95% CI, 0.4 to 2.4). Patients with T-cell ALL had a higher risk of seizures than patients with B-cell precursor ALL. Osteonecrosis, thrombosis, and hyperglycemia occurred more often in the patients in the standard-risk and high-risk groups, who received higher doses of dexamethasone and asparaginase, than the low-risk group. An age of more than 10 years was independently associated with increased risks of severe infections, osteonecrosis, hyperglycemia, and thrombosis.

DISCUSSION

The 5-year survival rate in the Total Therapy XV study was 93.5%, which is superior to results of all major studies reported to date.^{1-3,13,20-27} This

outcome also compares favorably with the recent result (87.5%) reported by the Surveillance, Epidemiology, and End Results Program for patients younger than 15 years of age who were treated between 2000 and 2004.²⁸ The 5-year survival rates of 97.7% for National Cancer Institute (NCI) standard-risk and 89.7% for NCI high-risk B-cell-precursor ALL were especially gratifying. Our study showed that with intensification of systemic and intrathecal chemotherapy, prophylactic cranial irradiation can be totally omitted without compromising overall survival. Indeed, the 71 patients who met previous criteria to receive prophylactic cranial irradiation fared significantly better than 56 historical controls.^{3,13} Because etoposide and irradiation were given only to the small subgroup of patients who underwent hematopoietic stem-cell transplantation, we expect a very low rate of therapy-induced cancers. Extrapolating from the long-term results of reported studies,^{1-3,20-26} we predict that major adverse events will develop in no more than 4% of patients 5 to 10 years after diagnosis, and this treatment protocol should yield a 10-year survival rate, and perhaps a cure rate, of 90%.⁵

We attribute this improved outcome to the incorporation of effective treatment components from earlier clinical trials,^{1-3,13,20-26} coupled with

Table 2. Independent Risk Factors for Major Adverse Events, Death, and Isolated CNS Relapse.*

Variable	All Patients				Patients with B-Cell–Precursor ALL			
	No. of Patients	No. of Adverse Events	Hazard Ratio (95% CI)	P Value	No. of Patients	No. of Adverse Events	Hazard Ratio (95% CI)	P Value
Major adverse events								
Minimal residual disease								
≥1% on remission date	23	11	5.3 (2.5–11.3)	<0.001	15	8	8.7 (3.5–21.7)	<0.001
<1%	469	39	1.0		403	27	1.0	
CNS status								
CNS-3 or traumatic lumbar puncture with blast cells	37	9	2.5 (1.2–5.2)	0.02	26	4	1.8 (0.6–5.4)	0.29
CNS-1 or CNS-2	461	43	1.0		396	32	1.0	
Age								
>10 yr	126	21	1.5 (0.8–2.8)	0.16	98	17	2.1 (1.1–4.3)	0.04
≤10 yr	372	31	1.0		324	19	1.0	
Death								
Age								
>10 yr	126	17	3.8 (1.7–8.3)	0.001	98	14	8.6 (3.0–24.2)	<0.001
≤10 yr	372	11	1.0		324	5	1.0	
Genetic abnormality								
t(9;22) (<i>BCR-ABL1</i>)	10	3	4.7 (1.3–16.7)	0.02	10	3	4.0 (1.1–14.2)	0.04
Other	488	25	1.0		412	16	1.0	
CNS status								
CNS-3 or traumatic lumbar puncture with blast cells	37	6	2.6 (1.0–6.5)	0.05	26	3	2.3 (0.6–8.1)	0.20
CNS-1 or CNS-2	461	22	1.0		396	16	1.0	
Type of immunophenotype								
T-cell	76	9	2.1 (0.9–5.0)	0.07				
B-cell precursor	422	19	1.0					
Isolated CNS relapse								
Type of immunophenotype								
T-cell	74	6	7.7 (1.4–43.0)	0.02				
B-cell precursor	418	5	1.0					
Race or ethnic group†								
Black	79	5	3.9 (1.6–14.0)	0.04	63	4	9.5 (1.2–75.0)	0.03
Other	413	6	1.0		355	1	1.0	
Genetic abnormality								
t(1;19) (<i>TCF3-PBX1</i>)	28	3	15 (3.1–73.0)	0.001	28	3	11.7 (2.3–59.0)	0.003
Other	464	8	1.0		390	2		
CNS status								
CNS-1	358	3	1.0	0.005	317	2	1.0	0.1
Other‡	134	8	6.4 (1.7–23.0)		101	3	4.0 (0.8–20.0)	

* Major adverse events included induction failure, any relapse, death in remission, and the development of a second cancer. In B-cell–precursor ALL, the mean ($\pm$ SE) 5-year cumulative risk of isolated CNS relapse was 14.1 $\pm$ 8.0% among patients with t(1;19) (*TCF3-PBX1*) versus 0.8 $\pm$ 0.6% among all other patients; this risk was 8.6 $\pm$ 4.2% among black patients versus 0.4 $\pm$ 0.4% among other patients. ALL denotes acute lymphoblastic leukemia, and CNS central nervous system.

† Race or ethnic group was reported by parents or guardians.

‡ Other CNS status indicates any CNS involvement (CNS-2, CNS-3, or traumatic lumbar puncture with blast cells).

Table 3. Selected Toxic Effects of Treatment.*

Toxic Effect	No. of Patients	3-Yr Cumulative Risk (%)	P Value
Seizure (grade 2, 3, or 4) [†]			
All patients	22	4.7±1.0	
Standard-risk or high-risk group	14	5.8±1.5	0.19
Low-risk group	8	3.6±1.3	
Severe infection (grade 4 or 5) [‡]			
All patients	23	4.8±1.0	
Standard-risk or high-risk group	8	3.4±1.2	0.18
Low-risk group	13	6.4±1.7	
Disseminated fungal infection			
All patients	25	5.5±1.1	
Standard-risk or high-risk group	13	5.8±1.6	0.84
Low-risk group	12	5.3±1.5	
Allergic reaction to asparaginase (grade 2, 3, or 4)			
All patients	198	41.2±2.3	
Standard-risk or high-risk group	85	34.3±3.1	0.10
Low-risk group	113	47.6±3.3	
Osteonecrosis (grade 3 or 4) [§]			
All patients	32	8.8±1.6	
Standard-risk or high-risk group	28	15.5±2.8	<0.001
Low-risk group	4	2.4±1.3	
Thrombosis (grade 2, 3, or 4) [¶]			
All patients	36	7.5±1.2	
Standard-risk or high-risk group	31	12.9±2.2	<0.001
Low-risk group	5	2.1±0.9	
Hyperglycemia (grade 3 or 4)			
All patients	41	8.5±1.3	<0.001
Standard-risk or high-risk group	32	13.2±2.2	
Low-risk group	9	3.8±1.2	

* Plus-minus values are estimates ±SE.

[†] Seizures occurred during remission induction in six patients, during consolidation therapy in five patients, during re-induction treatment in one patient, during continuation therapy in nine patients, and after hematopoietic stem-cell transplantation in one patient. At 3 years, the cumulative risk of seizures among patients with T-cell acute lymphoblastic leukemia (ALL) was 9.6% (95% confidence interval [CI], 2.7 to 16.5), as compared with 3.8% (95% CI, 1.8 to 5.8) among patients with B-cell precursor ALL (P=0.02). A grade 3 leukoencephalopathy developed in a child after therapeutic cranial irradiation for relapse in the central nervous system.

[‡] Two patients died of *Bacillus cereus* sepsis during remission induction, one died of typhilitis during consolidation treatment, two died of bacterial sepsis and one died of hepatic failure during reinduction, and one died of bacterial sepsis during continuation therapy. An age of more than 10 years was independently associated with a cumulative risk of severe infection: 7.5% (95% CI, 2.8 to 12.2) at 3 years, as compared with 3.8% (95% CI, 1.6 to 6.0) among younger patients (P=0.005).

[§] An age of more than 10 years was independently associated with an increased cumulative risk of osteonecrosis: 30.1% (95% CI, 18.9 to 41.3), as compared with 2.6% (95% CI, 0.6 to 4.6) among younger patients (P<0.001). Of the 32 patients with grade 3 or 4 osteonecrosis, 14 underwent core decompression, with subsequent arthroplasty in 6 patients and joint resurfacing procedures in 2 patients.

[¶] An age of more than 10 years was independently associated with an increased cumulative risk of thrombosis: 16.3% (95% CI, 9.4 to 23.2), as compared with 4.7% (95% CI, 2.5 to 6.9) among younger patients (P=0.03).

^{||} An age of more than 10 years was independently associated with an increased cumulative risk of hyperglycemia: 21.7% (95% CI, 14.3 to 29.2), as compared with 4.2% (95% CI, 2.0 to 6.4) among younger patients (P<0.001).

a stringent risk classification based on minimal residual disease and dose adjustments according to the pharmacogenetic and pharmacodynamic characteristics. We increased the dosage of methotrexate in patients with T-cell ALL or t(1;19)(TCF3-PBX1) ALL because the blasts in these subtypes accumulate methotrexate polyglutamates less avidly than do blasts in other subtypes.²⁹ Indeed, high-dose methotrexate is associated with an improved outcome in patients with T-cell ALL,³⁰ whereas relatively lower doses appear to be sufficient for those with low-risk B-cell-precursor ALL.³¹ We targeted methotrexate doses individually (a strategy that improved the outcome in our previous trial³¹), and we administered two courses of reinduction treatment that has been shown to benefit patients with intermediate-risk ALL.³²

Intensified asparaginase treatment was used because this approach has improved the outcome in previous trials.^{2,33} In patients with hypersensitivity reactions to native *Escherichia coli* asparaginase, erwinia asparaginase was substituted at high and frequent doses because an insufficient dose of this drug led to an inferior outcome.³⁴ Because we used a relatively high dose of mercaptopurine, we prospectively identified patients with inherited deficiency of thiopurine-S-methyltransferase and lowered the dosage of mercaptopurine accordingly to avoid toxic effects.¹⁷ We regularly monitored levels of thioguanine nucleotides to assess mercaptopurine treatment and administered methotrexate intravenously to ensure compliance. Dosages of mercaptopurine and methotrexate were administered to the limits of tolerance, but they were not adjusted overzealously in order to avoid undue interruptions of therapy.^{27,35} Dexamethasone was used after remission induction because it has yielded better outcomes than prednisone or prednisolone.^{36,37}

We relied on high-dose methotrexate, intensive asparaginase, dexamethasone, and optimal intrathecal therapy to control CNS leukemia. Intrathecal therapy was intensified in patients with blasts in the cerebrospinal fluid, even if the blasts were from traumatic lumbar puncture, which has been associated with poor outcome.³⁸⁻⁴¹ Special precautions¹² were taken to decrease the rate of traumatic lumbar punctures from 24% in previous studies⁴² to 8% in this study. We administered a large volume of intrathecal therapy (8 ml or more, depending on the patient's age), and pa-

tients remained in the prone position for at least 60 minutes after intrathecal therapy¹² in order to improve intraventricular distribution.^{43,44} Finally, we used triple intrathecal therapy, which proved to be more effective than intrathecal methotrexate for CNS control.⁴⁵ With these measures, the rate of isolated CNS relapse was 2.7%, well within the 1.5 to 4.5% range in clinical trials that used prophylactic cranial irradiation.^{1-3,13,20-26,37} CNS relapse developed in only one of our nine patients with CNS-3 status. Although a remarkably low rate (0.6%) of isolated CNS relapse was achieved in one study, approximately two thirds of those patients received cranial irradiation.²

Our improved therapy has made most of the important routinely used prognostic factors, including leukocyte count, moot. Even though high levels of minimal residual disease (i.e., $\geq 1\%$) at the end of induction were still associated with a poor outcome, the use of this measure for risk-directed therapy undoubtedly contributed to the improved results in this study. Indeed, although patients with levels of minimal residual disease between 0.01 and 0.99% had a cumulative risk of relapse of 43% in our previous trials,¹⁵ patients with the same levels had a 5-year event-free survival rate of 79.5% in this study. Vigilant supportive care resulted in a rate of death from toxic effects of only 1.4%, despite intensive treatment. Rates of disseminated fungal infection and thrombosis were substantial, but no patient died of these complications. Severe infection, osteonecrosis, thrombosis, and hyperglycemia were more likely to develop in children older than 10 years of age than in younger patients; this finding may be explained by slower clearance of dexamethasone in older patients.⁴⁶

The complete omission of prophylactic cranial irradiation allowed us to clearly identify risk factors for CNS relapse — that is, any CNS involvement, t(1;19)(TCF3-PBX1), and T-cell ALL. We would argue against the use of prophylactic cranial irradiation even in patients with these features because in our study, approximately 90% of such patients would have received unnecessary irradiation. Furthermore, since CNS and hematologic relapses are competing events, eradication of occult CNS leukemia by means of cranial irradiation alone may allow overt systemic relapse from residual leukemia in the bone marrow or other sites; systemic relapse is more difficult to treat with salvage therapy than is CNS relapse. Indeed, in one

study, triple intrathecal treatment, as compared with intrathecal methotrexate, reduced the frequency of CNS relapse, but it was associated with increased rates of relapse in the bone marrow and testicles, leading to poor overall survival.⁴⁵ Moreover, patients with isolated relapse in the CNS who have not received prophylactic irradiation are eminently curable, especially if there is no involvement of the bone marrow, as assessed by determination of minimal residual disease.^{47,48} In this regard, all of our 11 patients with an isolated CNS relapse remained in second remission, and most were probably cured after one course of therapeutic irradiation. In patients at high risk for CNS relapse, we have further intensified early intrathecal treatments in our ongoing clinical trial.

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