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Treatment of Childhood Acute Lymphoblastic Leukemia Without Prophylactic Cranial Irradiation

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Abstract

Background—We conducted a clinical trial to test whether prophylactic cranial irradiation could be omitted in all children with newly diagnosed acute lymphoblastic leukemia.

Methods—A total of 498 evaluable patients were enrolled. Treatment intensity was based on presenting features and the level of minimal residual disease after remission induction treatment. Continuous complete remission was compared between the 71 patients who previously would have received prophylactic cranial irradiation and the 56 historical controls who received it.

Results—The 5-year event-free and overall survival probabilities (95% confidence interval) for all 498 patients were 85.6% (79.9% to 91.3%) and 93.5% (89.8% to 97.2%), respectively. The 5-year cumulative risk of isolated central-nervous-system (CNS) relapse was 2.7% (1.1% to 4.2%), and that of any CNS relapse (isolated plus combined) was 3.9% (1.9% to 5.9%). The 71 patients had significantly better continuous complete remission than the 56 historical controls ($P=0.04$). All 11 patients with isolated CNS relapse remain in second remission for 0.4 to 5.5 years. CNS leukemia (CNS-3 status) or a traumatic lumbar puncture with blasts 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 presence of the $t(1;19)[TCF3-PBX1]$, any CNS involvement at diagnosis, and T-cell immunophenotype. Common adverse effects included allergic reactions to L-asparaginase, osteonecrosis, thrombosis, and disseminated fungal infection.

Conclusions—With effective risk-adjusted chemotherapy, prophylactic cranial irradiation can be safely omitted in the treatment of childhood acute lymphoblastic leukemia.

Contemporary clinical trials have yielded 5-year event-free survival rates of 79% to 82% for children with acute lymphoblastic leukemia (ALL).^{1–3} A major challenge is to reduce treatment-related late effects that may occur in more than two-thirds of long-term survivors.⁴

For 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, neurocognitive deficits, and endocrinopathy.⁴⁻⁸

Two pediatric clinical trials tested whether prophylactic cranial irradiation could be completely omitted.^{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 outcome of children with T-cell ALL.¹¹ Thus, there is a persistent concern that residual leukemic cells remaining after inadequate CNS treatment could not only cause CNS relapse but also reseed bone marrow, leading to hematologic relapse. Thus, virtually all study groups continue to use prophylactic cranial irradiation for up to 20% of patients.¹²

In our Total XIII A study, 22% of the patients received prophylactic cranial irradiation, overall 5-year event-free survival rate was 77.6%, and cumulative risk of isolated CNS relapse was 1.2%.¹³ We substituted prednisone with dexamethasone in post-remission therapy and limited prophylactic cranial irradiation to 12% of the patients in the subsequent Total XIII B 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 XV study reported here, we tested whether intensification of systemic drugs that affect CNS control, together with optimal intrathecal treatment, would allow 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 (MRD), and adjustment of chemotherapy dosages based on pharmacogenetics and pharmacokinetics.

METHODS

PATIENTS

From June 2000 to October 2007, 501 consecutive patients (1 to 18 years old) with newly diagnosed ALL were enrolled in Total XV Study at St. Jude Children's Research Hospital (n=411) or at Cook Children's Medical Center (n=90). Three patients were subsequently excluded because of a revised diagnosis of myeloid leukemia. The protocol was approved by the institutional review boards and registered at ClinicalTrials.gov, number NCT00137111. Signed informed consent was obtained from the parents or guardians, with assent from the patients, as appropriate.

The diagnostic criteria of ALL was described previously.¹⁴ CNS status was defined as CNS-1, CNS-2, CNS-3, or traumatic lumbar puncture with blasts.¹² MRD was determined by flow cytometry and/or polymerase-chain-reaction.^{15,16}

STUDY AIMS AND MONITORING

Our major therapeutic aims were (i) to determine whether prophylactic cranial irradiation can be safely omitted in all patients, especially those who would have received this treatment at approximately 1 year of continuous complete remission based on previous criteria (presenting leukocyte count $\geq 100 \times 10^9/L$, Philadelphia chromosome, CNS-3 status, or T-cell ALL with leukocyte count $\geq 50 \times 10^9/L$),^{3,13} and (ii) to estimate the overall event-free survival. The study was monitored by an independent Data Safety Monitoring Board. Group-sequential designs were used to provide guidelines for stopping decisions based on safety and efficacy (See Supplementary Appendix for details).

RISK CLASSIFICATION

Risk classification was based on presenting features and treatment response. B-cell precursor cases with age between 1 and 10 years and leukocyte count $<50 \times 10^9/L$, DNA index ≥ 1.16 , or $t(12;21)[ETV6-RUNX1]$ were provisionally classified as low-risk ALL. Cases with $t(9;22)[BCR-ABL1]$ were considered to have high-risk ALL, while the remaining cases were provisionally classified as standard (intermediate)-risk ALL. The final risk status was determined by MRD levels. Any patient with $\geq 1\%$ bone marrow MRD on day 19 of remission induction, or 0.1% to 0.99% MRD after completion of 6-week induction therapy was considered to have standard-risk ALL. MRD $\geq 1\%$ after completion of induction therapy denoted high-risk ALL.

TREATMENT

Remission induction/Consolidation—Patients who consented to the optional therapeutic window were randomized to receive upfront methotrexate over 4 or 24 hours. Four days after methotrexate treatment, remission induction therapy began with prednisone, vincristine, daunorubicin, and asparaginase (Table 1). Patients with $\geq 1\%$ MRD on day 19 received three additional doses of asparaginase. Subsequent induction therapy consisted of cyclophosphamide, mercaptopurine and cytarabine. Upon hematopoietic recovery (between days 43 and 46), MRD was assessed, and consolidation therapy began (Table 1).

Continuation therapy—During initial continuation therapy (Table 1), low-risk cases received daily mercaptopurine and weekly methotrexate with pulses of mercaptopurine, dexamethasone and vincristine. Two reinduction treatments were given between weeks 7–9 and weeks 17–19. Standard-risk cases received weekly asparaginase and daily mercaptopurine with pulses of doxorubicin plus vincristine plus dexamethasone. They also received two reinduction treatments between weeks 7–9 and weeks 17–20.

For the remaining continuation therapy (Supplementary Table 1), low-risk patients received mercaptopurine and methotrexate, with pulses of dexamethasone, vincristine and mercaptopurine, and standard-risk patients 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 thiopurine methyltransferase phenotype and genotypes.¹⁷ Total scheduled dosages of anthracyclines and cyclophosphamide were limited to 110 mg/m^2 and 230 mg/m^2 , and 1 g/m^2 and 4.6 g/m^2 , for low-risk and standard-risk patients, respectively. Continuation treatment lasted 120 weeks in girls and 146 weeks in boys.

CNS-directed therapy—Intrathecal cytarabine was instilled following diagnostic lumbar puncture and triple intrathecal chemotherapy was given for all subsequent treatments (Table 1). Depending on the presenting features and the CNS status, low-risk patients received 13 to 18, and standard-risk patients 16 to 25, intrathecal treatments.

Allogeneic hematopoietic stem-cell transplantation—This procedure was an option for patients with high-risk leukemia (whose early treatment was identical to that for standard-risk patients). Reintensification therapy (Supplementary Table 2) was given to maximize MRD reduction before transplantation. The median time to transplantation after remission induction was 4.1 months (range, 2 to 12 months).

STATISTICAL ANALYSIS

All analyses were pre-specified in the protocol. To assess the effect of omitting prophylactic cranial irradiation, we compared the continuous complete remission rate after 1 year of continuation therapy of the subset of patients who met our previous criteria for prophylactic

cranial irradiation at 1 year to that of historical controls who received irradiation,^{3,13} using an unstratified Mantel-Haenszel test.

Event-free survival and overall survival distributions were compared with the Mantel-Haenszel test. The Cox proportional hazards model was used to identify independent prognostic factors without using any variable selection methods. The cumulative incidence of isolated CNS or any CNS relapse (isolated plus combined), as well as other adverse events, were constructed by the method of Kalbfleisch and Prentice, and compared using Gray's test. Fine and Gray's model and the weighted logistic regression model¹⁸ were used to identify independent factors for prognosis and toxicities, 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 years). All reported P-values are 2-sided and not adjusted for multiple tests.

RESULTS

Presenting characteristics of the 498 evaluable patients are summarized in Table 2. Median age at diagnosis was 5.3 years (range, 1.0 to 18.9 years) and median leukocyte count was $11.7 \times 10^9/L$ (range, 0.4 to $1014 \times 10^9/L$). We had increased proportions of T-cell ALL (15.3%) or t(1;19)[*TCF3-PBX1*] (5.8%) cases, owing to the overrepresentation of African-American patients relative to other series.¹⁹ Based on MRD measurements successfully done on all patients, we reclassified the risk status of 58 patients: 30 from low to standard, 6 from low to high, and 22 from standard to high.

TREATMENT OUTCOME

Outcomes were similar for 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 2 fatal infections and 4 refractory leukemias. Three of the latter four patients remain in remission for 4.6, 4.6 and 6.1 years after allogeneic transplantation.

Thirty-three patients underwent allogeneic transplantation (9 from matched-sibling, 17 matched-unrelated and 7 haploidentical donors) 2 to 12 months after remission induction (median, 4.1 months). Transplantation was performed in 6 patients for t(9;22)[*BCR-ABL1*] ALL, 21 for MRD $\geq 1\%$ at the end of induction, 5 for persistent MRD on week 16 post-remission and 1 for near-haploidy. Twenty-four patients remain alive in remission, 7 died of complications, and 2 relapsed.

There were 17 hematologic, 11 isolated CNS, 4 combined CNS and hematologic, and 1 testicular relapses, 1 secondary myelodysplastic syndrome, and 12 deaths in remission (including those after transplantation). The 5-year cumulative risk (95% confidence interval) of isolated CNS relapse was 2.7% (1.1% to 4.3%), any CNS relapse was 3.9% (1.9% to 5.9%) (Fig. 1), and any relapse was 9.3% (6.0% to 12.6%). Pertinent features of the 11 patients with isolated CNS relapse are summarized in Supplementary Table 3. Notably, all 11 patients remain alive in second remission for 0.4 to 5.5 years (median, 2.5 years); 10 have been off therapy (3 after transplantation) for 1 month to 4.1 years (median, 2.0 years). The 5-year event-free survival and overall survival estimates were 85.6% (79.9% to 91.3%) and 93.5% (89.8% to 97.2%) for all 498 patients (Fig. 1). All 30 low-risk patients reclassified into the standard-risk group remain free of relapse.

Among the 71 patients who met our previous criteria for receiving prophylactic CNS irradiation, two had bone marrow relapse, one CNS relapse, and one remission death. Their continuous complete remission after 1 year of continuation therapy was significantly better

than that of the 56 historical controls ($P=0.04$).^{3,13} the 5-year rate was 90.8% (76% to 100%) versus 73.0% (61.2% to 84.8%) (Supplementary Fig. 1); the relative risk was 0.34 (0.11 to 1.02).

PROGNOSTIC FACTORS

Table 2 shows treatment outcome by selected features. Only CNS-3 status or traumatic lumbar puncture with blasts and MRD $\geq 1\%$ at the end of induction were independently associated with poorer event-free survival (Table 3). Features independently associated with isolated CNS relapse included T-cell ALL, African-American race, the $t(1;19)[TCF3-PBX1]$ and any CNS involvement (Table 3).

TOXICITY

Table 4 summarizes the most relevant toxicities. The cumulative risk of toxic death during chemotherapy was 1.4% (0.4% to 2.4%). T-cell cases had a higher risk of seizures than B-cell precursor cases. Osteonecrosis, thrombosis and hyperglycemia occurred more often in the standard- and high-risk arms, which featured higher doses of dexamethasone and asparaginase, than in the low-risk arm. Age >10 years was independently associated with an increased risk of severe infections, osteonecrosis, hyperglycemia, and thrombosis.

DISCUSSION

Total XV study achieved a 5-year survival rate of 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, End Results, and Epidemiology Program for patients less than 15 years old treated between 2000 and 2004.²⁸ The 5-year survival rates of 97.7% for low-risk and 89.7% for standard-risk B-cell precursor ALL were especially gratifying. Importantly, our study demonstrated 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 the 56 historical controls.^{3,13} Because etoposide and irradiation were given only to the small subgroup of patients who underwent 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 no more than 4% of patients might develop major adverse events 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 a stringent risk classification based on MRD and dose adjustments based on the pharmacogenetic and pharmacodynamic characteristics. We used increased dosage of methotrexate in T-cell or $t(1;19)[TCF3-PBX1]$ ALL because these blasts accumulate methotrexate polyglutamates less avidly than blasts of other subtypes.²⁹ Indeed, high-dose methotrexate has improved outcome in T-cell ALL,³⁰ whereas relatively lower doses appear adequate for low-risk B-cell precursor ALL.³¹ We targeted methotrexate dose individually, a strategy that improved outcome in our previous trial,³¹ and used two courses of reinduction treatment which have been shown to benefit patients with intermediate-risk ALL.³²

Intensified asparaginase treatment was used because this approach has improved outcome in previous trials.^{2,33} For patients with hypersensitivity reactions to native *E coli* asparaginase, *Erwinia* asparaginase was substituted at high and frequent doses because an inadequate dose of this drug led to 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 mercaptopurine dosage accordingly to avoid toxicities.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 adjusted to the limits of tolerance but not overzealously to avoid undue interruptions of therapy.^{27,35} Dexamethasone was used post-remission because it has yielded better outcome 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 CSF, even 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 gave intrathecal therapy in a large volume (8 mL or more, depending on age), and kept patients in the prone position for at least 60 minutes after intrathecal therapy,¹² which improves intraventricular distribution.^{43,44} Finally, we used triple intrathecal therapy, which proved more effective than intrathecal methotrexate for CNS control.⁴⁵ With these measures, the isolated CNS relapse rate 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} Only 1 of our 9 patients with CNS-3 status developed CNS relapse. 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 abolished most historically important prognostic factors, including leukocyte count. Even though high levels of MRD (i.e., $\geq 1\%$) at the end of induction were still associated with a poor outcome, use of this measure for risk-directed therapy has undoubtedly contributed to the improved results in this study. Indeed, while patients with MRD levels between 0.01% and 0.99% had a cumulative risk of relapse of 43% in our previous trials,¹⁵ those with the same levels had a 5-year event-free survival rate of 79.5% in this study. Despite intensive treatment, vigilant supportive care resulted in a toxic death rate of only 1.4%. Rates of disseminated fungal infection and thrombosis were relatively high but no patient died of these complications. Children over 10 years of age were more likely than younger patients to develop severe infection, osteonecrosis, thrombosis, and hyperglycemia, a finding that 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: any CNS involvement, the t(1;19)[*TCF3-PBX1*] and T-cell ALL. We would argue against using prophylactic cranial irradiation even in patients with these features because approximately 90% would have received unnecessary irradiation. Further, since CNS and hematologic relapses are competing events, eradication of occult CNS leukemia by cranial irradiation alone may allow overt systemic relapse from residual leukemia in the bone marrow or other sites, which is more difficult to salvage. Indeed, in one study, triple intrathecal treatment reduced the frequency of CNS relapse compared with intrathecal methotrexate, but was associated with increased bone marrow and testicular relapse rates, leading to a poor overall survival.⁴⁵ Moreover, patients with isolated CNS relapse who have not received prophylactic irradiation are highly curable, especially if their bone marrow is not involved, as assessed by MRD determination.^{47,48} In this regard, all of our 11 patients with an isolated CNS relapse remain in second remission, and most are likely cured after one course of therapeutic irradiation. For patients at high risk of CNS relapse, we have further intensified early intrathecal treatments in our ongoing clinical trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosure

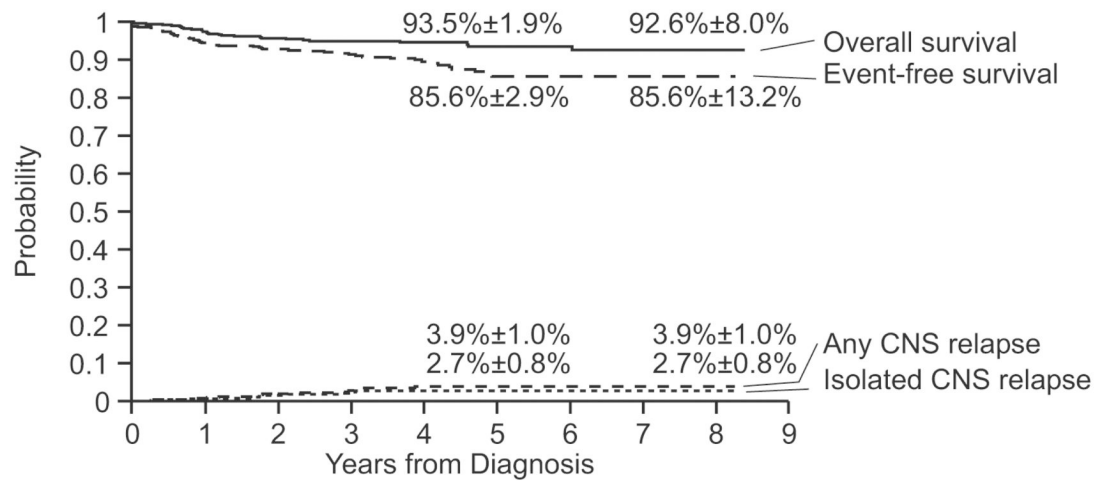
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Number at risk:	0	1	2	3	4	5	6	7	8	9
Overall survival	498	498	481	408	319	241	151	105	60	9
Event-free survival	498	492	464	378	292	206	125	88	51	5
Any CNS relapse	492	492	464	378	292	205	125	88	51	5
Isolated CNS relapse	492	492	464	378	292	205	125	88	51	5

Figure 1. Overall survival, event-free survival, cumulative risk of any CNS relapse (combined plus isolated), and cumulative risk of isolated CNS relapse for all patients. The 5-year and 8-year rates are means ± standard error.

TABLE 1

Remission Induction, Consolidation, and Early Continuation/Reinduction Therapy

A Remission induction		
Agent	Dosage	Schedule
Methotrexate	1 g/m ² IV over 4 or 24 hours	Day 1
Prednisone	40 mg/m ² /day	Days 5–32
Vincristine	1.5 mg/m ² per week	Days 5, 12, 19, 26
Daunorubicin	25 mg/m ² per week	Days 5, 12
L-asparaginase (Elspar)	10,000 U/m ² per dose IM (thrice weekly)	Days 6, 8, 10, 12, 14, 16, (19, 21, 23) *
Cyclophosphamide	1000 mg/m ² IV	Day 26
Cytarabine	75 mg/m ² per day IV	Days 27–30, 34–37
Mercaptopurine	60 mg/m ² per night	Days 26–39
Intrathecal cytarabine	Age-dependent	Day 1
Triple intrathecal	Age-dependent	Day 19 (8, 26) **

B Consolidation therapy		
Agent	Dosage	Schedule
High-dose methotrexate*	Targeted to 33μM (low-risk) or 65μM (standard-/or high-risk)	Days 1, 15, 29 and 43
Mercaptopurine	50 mg/m ² per night	Days 1 to 56
Triple intrathecal	Age-dependent	Day 1, 15, 29 and 43

C Early continuation/reinduction therapy		
Week	Low-risk Patients	Standard- or high-risk Patients
1	Mercaptopurine + dexamethasone + vincristine	Asparaginase + mercaptopurine + dexamethasone + vincristine + doxorubicin
2	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
3	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
4	Mercaptopurine + dexamethasone + vincristine	Asparaginase + mercaptopurine + dexamethasone + vincristine + doxorubicin
5	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
6	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
7	Dexamethasone + vincristine + asparaginase + doxorubicin	Asparaginase + dexamethasone + vincristine + doxorubicin
8	Vincristine + asparaginase	Asparaginase + vincristine + doxorubicin
9	Dexamethasone + vincristine + asparaginase	Asparaginase + dexamethasone + vincristine
10	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
11	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine + vincristine + doxorubicin
12	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
13	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
14	Mercaptopurine + dexamethasone + vincristine	Asparaginase + mercaptopurine + dexamethasone + vincristine + doxorubicin
15	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
16	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
17	Dexamethasone + vincristine + asparaginase + doxorubicin	Asparaginase + dexamethasone + vincristine
18	Vincristine + asparaginase	Asparaginase + vincristine
19	Dexamethasone + vincristine + asparaginase	Asparaginase + vincristine + dexamethasone + high-dose cytarabine

C Early continuation/reinduction therapy		
Week	Low-risk Patients	Standard- or high-risk Patients
20	Mercaptopurine + methotrexate	-----
21	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate
22	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate
23	Mercaptopurine + methotrexate	Cyclophosphamide + cytarabine
24	Mercaptopurine + dexamethasone + vincristine	dexamethasone + vincristine

Intrathecal cytarabine (40, 50 or 60 mg for ages 1 to 1.99, 2 to 2.99 and ≥ 3 years, respectively). Triple intrathecal treatments (methotrexate 8, 10 or 12 mg; hydrocortisone 16, 20 or 24 mg; and cytarabine 24, 30 or 36 mg for ages 1 to 1.99, 2 to 2.99 and ≥ 3 years, respectively)

** Extra triple intrathecal treatment on days 8 and 26 for patients with high-risk features of CNS relapse (CNS-2, CNS-3, traumatic lumbar puncture with blasts, T-cell ALL with leukocyte count $> 50 \times 10^9/L$, B-cell precursor ALL with leukocyte count $> 100 \times 10^9/L$, or the presence of t(9;22)[*BCR-ABL1*], *MLL* rearrangement, or hypodiploidy < 45 chromosomes).

* Extra asparaginase on days 19, 21, and 23 for patients with $\geq 1\%$ residual leukemia cells in the bone marrow on day 19.

Methotrexate dosage was adjusted according to prior patient-specific pharmacokinetic data to achieve a steady-state concentration of 65 μM (corresponding to an average dose of approximately 5 g/m^2) in standard-risk cases, and 33 μM (average 2.5 g/m^2) in low-risk cases.

Mercaptopurine – 75 mg/m^2 PO every evening for 7 days for low-risk group; 50 mg/m^2 in the first 16 weeks and 75 mg/m^2 thereafter for the standard- and high-risk groups. The starting dose for patients with heterozygous deficiency of thiopurine methyltransferase was 60 mg/m^2 instead of 75 mg/m^2 .

Dexamethasone – 8 mg/m^2 PO per day in 3 divided doses for 5 days for low-risk group and 12 mg/m^2 for standard-risk group; 8 mg/m^2 on days 1 to 8 and 15 to 21 during reinduction I (weeks 7 to 9) and reinduction II (weeks 17 to 19) for both groups.

Asparaginase – 10,000 U/ m^2 IM thrice weekly for 9 doses during each reinduction for low-risk group; and 25,000 units / m^2 IM weekly for 19 doses for the standard- and high-risk groups; in patients with allergic reactions to *E coli* asparaginase, *Erwinia* asparaginase 20,000 units / m^2 thrice weekly during reinduction treatment for the low-risk group, and 25,000 units / m^2 twice weekly in standard-risk group; in patients with allergic reactions to both *E coli* and *Erwinia* asparaginase, or in those for whom *Erwinia* asparaginase was not available, polyethylene glycol-asparaginase (Oncospar) 2500 units / m^2 per week.

Vincristine – 2 mg/m^2 IV, except for weeks 7–9 and 17–19 when given at 1.5 mg/m^2 ; Methotrexate - 40 mg/m^2 IV or IM; Doxorubicin 30 mg/m^2 IV; High-dose cytarabine - 2 g/m^2 IV every 12 hours for 4 doses; Cyclophosphamide - 300 mg/m^2 IV; Cytarabine - 300 mg/m^2 IV.

Triple intrathecal therapy – low-risk cases with CNS-1 status: weeks 7, 12, 17, 24, 32, 40, and 48; low-risk cases with CNS-2, traumatic lumbar punctures with blasts or leukocyte count $\geq 100 \times 10^9/L$: weeks 7, 12, 17, 24, 28, 32, 36, 40, 44, and 48; standard-risk cases: weeks 7, 12, 17, 24, 28, 32, 36, 40, 44 and 48; other standard-risk cases with leukocyte count $\geq 100 \times 10^9/L$, T-cell ALL with WBC $\geq 50 \times 10^9/L$, presence of Philadelphia chromosome, *MLL* rearrangement, hypodiploidy < 45 , or CNS-3 status: weeks 3, 7, 12, 17, 24, 28, 32, 36, 40, 44, 48, 56, 64, 72, 80, 88 and 96.

TABLE 2
Treatment outcome according to selected clinical and biologic features

Features	No. of patients	% 5-year event-free survival (SE)		% 5-year overall survival (SE)	
			P-value		P-value
Randomization arms					
4 - hour group	177	88.2 (4.2)	0.22	95.0 (2.7)	0.20
24 - hour group	180	85.6 (4.6)		94.0 (2.9)	
Not randomized*	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)					
NCI Standard	16	73.9 (15.4)	0.71	93.8 (8.9)	0.44
NCI 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 to 10 years	372	87.8 (3.1)	0.005	96.7 (1.6)	<0.001
>10 years	126	79.1 (6.4)		83.8 (5.5)	
Leukocyte count					
<10 × 10 ⁹ /L	227	86.8 (4.1)	0.1	93.7 (2.8)	0.33
10 to 49 × 10 ⁹ /L	144	85.9 (5.4)		95.9 (3.0)	
50 to 99 × 10 ⁹ /L	64	83.9 (7.9)		91.0 (6.0)	
100 to 300 × 10 ⁹ /L	44	86.1 (8.9)		90.4 (7.5)	
≥300 × 10 ⁹ /L	19	73.3 (18.9)		89.2 (12.0)	

Features	No. of patients	% 5-year event-free survival (SE)		% 5-year overall survival (SE)	
			P-value		P-value
Race					
White	340	87.8 (3.2)	0.02	94.8 (2.0)	0.23
African American	79	77.8 (8.2)		88.3 (6.2)	
Hispanic	60	74.2 (13.3)		89.1 (8.9)	
Asian or Others	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 with blasts	28	81.4 (14.3)		81.9 (13.2)	
CNS-3	9	43.2 (23.0)		71.1 (22.1)	
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)	
t(9;22)[<i>BCR-ABL1</i>]					
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)[<i>TCF3-PBX1</i>]					
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)[<i>ETV6-RUNX1</i>]					
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)[<i>MLL-AF4</i>]					
Present	3	100 (0.0)	0.59	100 (0.0)	0.70

Features	No. of patients	% 5-year event-free survival (SE)		% 5-year overall survival (SE)	
			P-value		P-value
Absent	495	85.6 (2.9)		93.5 (1.9)	
Minimal residual diseases on day 19 induction					
< 0.01%	198	92.6 (3.2)	<0.001	97.5 (1.9)	<0.001
0.01% to 0.99%	192	87.8 (5.1)		93.8 (3.2)	
1% to 4.99%	43	77.4 (10.6)		96.8 (4.5)	
≥ 5%	55	56.8 (14.1)		78.1(10.6)	
Minimal residual disease on remission date[‡]					
< 0.01%	392	89.6 (2.9)	<0.001	94.5 (1.9)	<0.001
0.01% to 0.99%	77	79.5 (8.0)		90.9 (5.4)	
1% to 4.99%	14	38.1 (21.2)		71.4 (27.0)	
≥ 5%	9	55.6 (26.2)		87.5 (13.8)	

* The reasons for not being randomized included parental refusal (n=62), completion of accrual for the pharmacologic study arms (n=21), the presence of mediastinal mass or respiratory distress (n=17), physician decision (n=17), Down syndrome (n=12), organ dysfunction or infection (n=11), and unknown reason (n=1).

[‡] CNS-1: no detectable blast cells in cerebrospinal fluid sample; CNS-2: <5 leukocytes/ μ L with blast cells in an atraumatic sample; CNS-3: \geq 5 leukocytes/ μ L with blast cells in an atraumatic sample or the presence of a cranial nerve palsy; and traumatic lumbar puncture with blasts (\geq 10 erythrocytes/ μ L with blasts.¹¹

^{††} Ratio of DNA content as measured by flow cytometry in leukemic cells versus normal diploid G₀/G₁ cells.

[‡] Flow cytometry, clone-specific PCR or both were used to study minimal residual disease (PCR studies were done only in patients with B-lineage ALL). 482 of 492 patients (98%) were studied by flow cytometry and 403 of 492 (82%) by PCR. Both studies yielded virtually identical results. In the few cases with discrepant results, we used the highest MRD value. The two methods could be applied to study 491 of 492 patients (99.8%) of the patients. The single patient with no available immunophenotypic or gene-rearrangement marker had a MLL-AF9 fusion transcript and was monitored by RT-PCR.

TABLE 3
Independent prognostic factors for event-free survival, overall survival, and isolated CNS relapse

	All Patients					B-cell precursor ALL				
	Total	Adverse Events	Hazard ratio	95% CI	P-value	Total	Adverse Events	Hazard ratio	95% CI	P-value
Event-free survival										
Minimal residual disease $\geq 1\%$ on remission date	23	11	5.3	2.5 to 11.3	<0.001	15	8	8.7	3.5 to 21.7	<0.001
Others	469	39	1.0	-----	-----	403	27	1.0	-----	-----
CNS-3 or traumatic with blasts	37	9	2.5	1.2 to 5.2	0.02	26	4	1.8	0.6 to 5.4	0.29
Others	461	43	1.0	-----	-----	396	32	1.0	-----	-----
Age > 10 years	126	21	1.5	0.8 to 2.8	0.16	98	17	2.1	1.1 to 4.3	0.04
Others	372	31	1.0	-----	-----	324	19	1.0	-----	-----
Overall survival										
Age > 10 years	126	17	3.8	1.7 to 8.3	0.001	98	14	8.6	3.0 to 24.2	<0.001
Others	372	11	1.0	-----	-----	324	5	1.0	-----	-----
t(9;22)[<i>BCR-ABL1</i>]	10	3	4.7	1.3 to 16.7	0.02	10	3	4.0	1.1 to 14.2	0.04
Others	488	25	1.0	-----	-----	412	16	1.0	-----	-----
CNS-3 or traumatic with blasts	37	6	2.6	1.0 to 6.5	0.05	26	3	2.3	0.6 to 8.1	0.20
Others	461	22	1.0	-----	-----	396	16	1.0	-----	-----
T-cell	76	9	2.1	0.9 to 5.0	0.07	-----	-----	-----	-----	-----
B-cell precursor	422	19	1.0	-----	-----	-----	-----	-----	-----	-----
Isolated CNS relapse										
T-cell	74	6	7.7	1.4 to 43	0.02	-----	-----	-----	-----	-----
B-cell precursor	418	5	1.0	-----	-----	-----	-----	-----	-----	-----
African American	79	5	3.9	1.6 to 14	0.04	63	4	9.5	1.2 to 75	0.03
Others	413	6	1.0	-----	-----	355	1	1.0	-----	-----
t(1;19)[<i>TCF3-PBX1</i>]	28	3	15	3.1 to 73	0.001	28	3	11.7	2.3 to 59	0.003
Others	464	8	1.0	-----	-----	390	2	-----	-----	-----
CNS-1	358	3	1.0	-----	0.005	317	2	1.0	0.8 to 20	0.1
Others CNS status*	134	8	6.4	1.7 to 23	-----	101	3	4.0	-----	-----

* any CNS involvement (CNS-2, CNS-3 or traumatic lumbar puncture with blasts)

In B-cell precursor ALL, the 5-year cumulative risk of isolated CNS relapse was 14.1% [8.0%] among cases with the t(1;19)[TCF3-PBX1] versus 0.8% [0.6%] among all other patients; and was 8.6% [4.2%] among African-American versus 0.4% [0.4%] among other patients.

TABLE 4

Summary of selected toxicities

Toxicity	No. of Patients	% 3-year cumulative risk (SE)	P-value
Seizures (grade 2, 3 or 4) *			
All patients	22	4.7 (1.0)	
standard - 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 - 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 - or high-risk group	13	5.8 (1.6)	} 0.84
low-risk group	12	5.3 (1.5)	
Allergic reactions to L-asparaginase (grade 2, 3 or 4)			
All patients	198	41.2 (2.3)	
standard - 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 - 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 - 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)	
standard - or high-risk group	32	13.2 (2.2)	} <0.001
low-risk group	9	3.8 (1.2)	

* Seizures occurred during remission induction in 6 patients, consolidation therapy in 5, reinduction treatment in 1, and continuation therapy in 9, and after transplantation in 1. T-cell cases had a higher cumulative risk of seizures than B-cell precursor cases (P=0.02; 9.6% [2.7% to 16.5%] versus 3.8% [1.8% to 5.8%] at 3 years). A grade 3 leukoencephalopathy developed in a child after therapeutic cranial irradiation for CNS relapse.

† Two patients died of *Bacillus cereus* sepsis during remission induction, one of typhlitis during consolidation treatment, two of bacterial sepsis and one of hepatic failure during reinduction, and one of bacterial sepsis during continuation therapy. Age >10 years was independently associated with an increased cumulative risk of severe infections (P=0.005, 7.5% [2.8% to 12.2%] versus 3.8% [1.6% to 6.0%] at 3 years).

‡ Age >10 years was independently associated with an increased cumulative risk of osteonecrosis (P<0.0001; 30.1% [18.9% to 41.3%] versus 2.6% [0.6% to 4.6%]). Of the 32 cases with grade 3 or 4 osteonecrosis, 14 underwent core decompression, with subsequent arthroplasty in six and joint resurfacing procedures in two.

§ Age >10 years was independently associated with an increased cumulative risk of thrombosis (P=0.03; 16.3% [9.4% to 23.2%] versus 4.7% [2.5% to 6.9%]).

¥ Age >10 years was independently associated with an increased cumulative risk of hyperglycemia (P<0.0001; 21.7% [14.3% to 29.2%] versus 4.2% [2.0% to 6.4%]).