Improved CNS Control of Childhood Acute Lymphoblastic Leukemia Without Cranial Irradiation: St Jude Total Therapy Study 16

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PURPOSE Despite contemporary treatment, up to 10% of children with acute lymphoblastic leukemia still experience relapse. We evaluated whether a higher dosage of PEG-asparaginase and early intensification of triple intrathecal therapy would improve systemic and CNS control.

PATIENTS AND METHODS Between 2007 and 2017, 598 consecutive patients age 0 to 18 years received risk-directed chemotherapy without prophylactic cranial irradiation in the St Jude Total Therapy Study 16. Patients were randomly assigned to receive PEG-asparaginase 3,500 U/m² versus the conventional 2,500 U/m². Patients presenting features that were associated with increased risk of CNS relapse received two extra doses of intrathecal therapy during the first 2 weeks of remission induction.

RESULTS The 5-year event-free survival and overall survival rates for the 598 patients were 88.2% (95% CI, 84.9% to 91.5%) and 94.1% (95% CI, 91.7% to 96.5%), respectively. Cumulative risk of any—isolated or combined—CNS relapse was 1.5% (95% CI, 0.5% to 2.5%). Higher doses of PEG-asparaginase did not affect treatment outcome. T-cell phenotype was the only independent risk factor for any CNS relapse (hazard ratio, 5.15; 95% CI, 1.3 to 20.6; *P* = .021). Among 359 patients with features that were associated with increased risk for CNS relapse, the 5-year rate of any CNS relapse was significantly lower than that among 248 patients with the same features treated in the previous Total Therapy Study 15 (1.8% [95% CI, 0.4% to 3.3%] v 5.7% [95% CI, 2.8% to 8.6%]; *P* = .008). There were no significant differences in the cumulative risk of seizure or infection during induction between patients who did or did not receive the two extra doses of intrathecal treatment.

CONCLUSION Higher doses of PEG-asparaginase failed to improve outcome, but additional intrathecal therapy during early induction seemed to contribute to improved CNS control without excessive toxicity for high-risk patients.

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INTRODUCTION

Contemporary treatment of pediatric acute lymphoblastic leukemia (ALL) yields 5-year event-free survival rates of 80% or higher.¹ In addition to further advancing cure rates, current trials increasingly focus on improving the patients' quality of life and preventing long-term sequelae. A major recent accomplishment has been the elimination of prophylactic cranial irradiation without jeopardizing leukemia control in the CNS. The St Jude Total Therapy Study 15 resulted in a 5-year event-free survival rate of 86%, with an isolated CNS relapse rate of 2.7% and a combined CNS relapse rate of 1.2%.² Corresponding rates for the Dutch Childhood Oncology Group Protocol ALL-9 were 81%, 2.6%, and 2.0%, respectively.³ Both studies, reported in 2009, featured intensive dexamethasone, vincristine, asparaginase, and triple intrathecal therapy—with methotrexate, hydrocortisone, and cytarabine—without prophylactic cranial irradiation,

previously considered the standard treatment of patients with high-risk ALL.^{2,3} Since then, three other major studies omitting prophylactic cranial irradiation have been reported, with 5-year rates of event-free survival rates ranging from 72% to 85%, isolated CNS relapse rates from 1.7% to 4.1%, and combined CNS relapse rates from approximately 1% to 1.8%.⁴⁻⁶ These results are comparable to those of six other studies during the same period⁷⁻¹² that used prophylactic cranial irradiation in 0.6% to 42.8% of patients.¹³ These findings notwithstanding, 3.5% to 5.4% of patients not treated with prophylactic cranial irradiation required subsequent therapeutic irradiation because of CNS relapse.²⁻⁶

In the Total Therapy Study 16, we sought to improve event-free survival and CNS control by refining risk-directed therapy and intensifying systemic and intrathecal chemotherapy.¹⁴ It has been proposed that the degree of asparagine depletion from the CSF by

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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asparaginase is important for the treatment and prevention of CNS leukemia. Several studies have demonstrated that PEG-asparaginase 2,500 U/m² usually achieves complete depletion of asparagine from the blood but not necessarily from the CSF.¹⁵⁻¹⁷ We therefore reasoned that a higher dose of PEG-asparaginase may be more effective in depleting asparagine from the blood and CSF and might improve systemic and CNS control. We also tested whether intensification of triple intrathecal chemotherapy during early remission induction in patients with presenting features that were associated with increased CNS relapse could improve CNS control. This strategy was prompted by our experience in Total Therapy Study 15,² where triple intrathecal treatment reduced the frequency of CNS relapse but did not seem to have reached maximum intensification, and was supported by its success in patients with advanced Burkitt lymphoma or Burkitt leukemia,¹⁸ lymphoid malignancies that are associated with a high risk of CNS relapse. Here, we present the outcome of these two therapeutic interventions and the overall results of this study.

PATIENTS AND METHODS

Participants

Between October 29, 2007, and March 26, 2017, 598 eligible patients younger than age 19 years with newly diagnosed ALL were enrolled in the Total Therapy Study 16 (Appendix, online only). The protocol was approved by the institutional review board, and written informed consent was obtained from the parents, guardians, or patients, with assent from the patients, as appropriate.

Diagnosis and Risk Classification

Diagnosis of ALL was based on immunophenotypic and genetic features of leukemic cells. Patients were classified as having low-risk, standard-risk (intermediate-risk), or high-risk leukemia on the basis of presenting characteristics and treatment response as determined by levels of minimal residual disease (MRD) measured by flow cytometry during remission induction and consolidation (Appendix and Fig 1). CNS status was defined as CNS-1, CNS-2, CNS-3, or traumatic lumbar puncture with blast cells (Appendix and Table 1).

Study Design and Outcomes

For the primary objective, 420 evaluable patients were planned to be stratified and randomly assigned (1:1) on the first day of continuation treatment to receive PEG-asparaginase at the conventional dose (2,500 U/m²) or at a higher dose (3,500 U/m²; Appendix). The primary end point was continuous complete remission. A secondary objective was to evaluate whether early intensification of triple intrathecal chemotherapy during early remission induction reduced the rate of isolated or any—isolated or combined—CNS relapse in patients at high risk for this complication. Because of the low rate of CNS relapse, a randomized study of any treatment intervention to

improve CNS control was not feasible; therefore, data from patients with similar characteristics enrolled in the preceding Total Therapy Study 15 were used for comparison.² The study was originally powered for the primary objective only, but we performed a post hoc power calculation for the CNS secondary objective (Appendix).

Treatment

Treatment on Total Therapy Study 16 was based on that used in Study 15 with several modifications (Appendix). Remission induction consisted of prednisone, vincristine, daunorubicin, and PEG-asparaginase, followed by cyclophosphamide, cytarabine, and a thiopurine (Appendix Table A1, online only). Patients with Philadelphia chromosome-positive ALL received dasatinib 40 mg/m² twice daily from day 22 until the end of all treatment. Upon hematopoietic recovery—between days 43 and 46—consolidation therapy consisting of four courses of high-dose methotrexate, mercaptopurine, and triple intrathecal therapy was administered (Appendix Table A2, online only). All patients received antimetabolite-based continuation therapy for 120 weeks. During initial continuation therapy, low-risk patients received two reinduction cycles plus pulses of dexamethasone and vincristine, whereas standard-risk or high-risk patients received PEG-asparaginase every 2 weeks for 15 doses interrupted with pulses of doxorubicin plus vincristine plus dexamethasone and two reinduction cycles, followed by three rotating drug pairs (Appendix Table A3, online only).

Triple intrathecal chemotherapy was instilled at an age-appropriate dose with the number of doses varied according to presenting characteristics and CNS status that historically affected the risk of CNS relapse (Appendix Table A1). All patients received intrathecal therapy on days 1 and 15 of induction with additional doses on days 8 and 22 in patients with Philadelphia chromosome, *KMT2A* rearrangement, hypodiploidy < 44 chromosomes, or leukocyte count > 100,000/μL at presentation, and on days 4, 8, 11, and 22 for those with features associated with an increased risk of CNS relapse in Total Therapy Study 15, including T-cell ALL, the presence of *TCF3-PBX1*, CNS-2 or CNS-3 status, or traumatic lumbar puncture with blasts.² During continuation therapy, intrathecal therapy was also administered according to risk features (Appendix Table A3). Hence, patients with low-risk ALL received a total of 13 to 21 intrathecal treatments, and those with standard-risk ALL received 16 to 27 treatments.

Allogeneic hematopoietic stem-cell transplantation was an option for patients with high-risk leukemia. These patients received 1-2 courses of reintensification therapy before transplantation (Appendix Table A4, online only).

Statistical Analysis

We used the Kaplan-Meier method to estimate the probabilities of continuous complete remission, event-free survival, or overall survival with SE calculated according

FIG 1. CONSORT diagram. MRD, minimal residual disease.

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

Characteristic	No. of Patients	5-Year Overall Survival, % (95% CI)	P	5-Year Event-Free Survival, % (95% CI)	P
Risk group*					
Low	260	98.8 (97.0 to 100)	< .001	96.1 (93.0 to 99.2)	< .001
Standard	280	95.6 (92.7 to 98.5)		88.0 (83.3 to 92.7)	
High	58	65.4 (50.3 to 80.5)		55.8 (40.9 to 70.7)	
NCI risk group (B-cell ALL)					
Standard	295	98.3 (96.3 to 100)	< .001	95.1 (92.0 to 98.2)	< .001
High	199	91.7 (86.8 to 96.6)		82.1 (75.2 to 89.0)	
NCI risk group (T-cell ALL)					
Standard	22	86.6 (67.8 to 100)	.527	86.4 (67.6 to 100)	.553
High	82	86.5 (77.7 to 95.3)		79.8 (69.6 to 90.0)	
Age at diagnosis, years					
< 1	12	58.3 (25.4 to 91.2)	< .001	50.0 (19.0 to 81.0)	< .001
1-10	443	96.3 (94.1 to 98.5)		91.5 (88.2 to 94.8)	
> 10	143	90.6 (84.5 to 96.7)		81.5 (73.7 to 89.3)	
Sex					
Male	350	94.3 (91.2 to 97.4)	.945	87.6 (83.3 to 91.9)	.987
Female	248	93.9 (90.2 to 97.6)		89.2 (84.3 to 94.1)	
Race					
White	394	96.5 (94.1 to 98.9)	.007	91.0 (87.5 to 94.5)	.019
Black	81	90.0 (82.0 to 98.0)		82.8 (72.6 to 93.0)	
Others	123	89.4 (82.3 to 96.5)		83.1 (74.7 to 91.5)	
Leukocyte count, cells/ μ L					
< 10,000	249	95.5 (92.2 to 98.8)	< .001	92.2 (87.9 to 96.5)	< .001
10,000 to < 50,000	210	96.9 (94.0 to 99.8)		92.8 (88.3 to 97.3)	
50,000 to < 100,000	57	89.2 (79.6 to 98.8)		77.0 (64.1 to 89.9)	
$\geq$ 100,000	82	86.5 (77.1 to 95.9)		73.3 (61.3 to 85.3)	
CNS status†					
CNS1	343	96.4 (94.0 to 98.8)	< .001	90.7 (87.0 to 94.4)	.034
CNS2	200	93.5 (89.0 to 98.0)		86.4 (80.1 to 92.7)	
CNS3	21	85.7 (68.6 to 100)		85.7 (68.6 to 100)	
Traumatic with blasts	34	79.4 (61.8 to 97.0)		75.4 (56.4 to 94.4)	
Immunophenotype					
B-lineage	494	95.6 (93.2 to 98.0)	.001	89.8 (86.5 to 93.1)	.009
T-lineage	104	87.0 (79.0 to 95.0)		81.0 (71.8 to 90.2)	
DNA index					
$\geq$ 1.16	124	99.2 (97.0 to 100)	.005	96.6 (92.3 to 100)	< .001
< 1.16	474	92.8 (89.9 to 95.7)		86.1 (82.2 to 90.0)	
Ploidy					
Hyperdiploidy > 50	154	99.4 (97.6 to 100)	< .001	94.7 (90.0 to 99.4)	.001
Others	444	92.3 (89.2 to 95.4)		86.0 (82.1 to 89.9)	
t(9;22)(BCR-ABL1)					
Present	15	75.4 (47.8 to 100)	.023	71.1 (42.9 to 99.3)	.003
Absent	583	94.6 (92.2 to 97.0)		88.7 (85.4 to 92.0)	

(continued on following page)

TABLE 1. Treatment Outcome According to Selected Clinical and Biologic Characteristics* (continued)

Characteristic	No. of Patients	5-Year Overall Survival, % (95% CI)	P	5-Year Event-Free Survival, % (95% CI)	P
<i>KMT2A</i> rearrangement					
Present	38	78.9 (61.7 to 96.1)	< .001	64.9 (46.1 to 83.7)	< .001
Absent	560	95.2 (93.0 to 97.4)		89.8 (86.7 to 92.9)	
<i>KMT2A-AFF1</i>					
Present	12	75.0 (45.0 to 100)	.008	55.6 (23.1 to 88.1)	< .001
Absent	586	94.5 (92.1 to 96.9)		88.9 (85.8 to 92.0)	
t(1;19)(<i>TCF3-PBX1</i>)					
Present	16	87.1 (69.5 to 100)	.348	87.1 (69.5 to 100)	.378
Absent	582	94.3 (91.9 to 96.7)		88.3 (85.0 to 91.6)	
t(12;21)(<i>ETV6-RUNX1</i>)					
Present	127	99.2 (97.2 to 100)	.004	98.4 (95.7 to 100)	< .001
Absent	471	92.8 (89.9 to 95.7)		85.6 (81.7 to 89.5)	
MRD on day 15 of induction, %					
< 0.01	187	97.3 (94.2 to 100)	< .001	94.9 (90.6 to 99.2)	< .001
0.01-0.99	232	97.8 (95.4 to 100)		91.7 (87.4 to 96.0)	
1-4.99	99	90.4 (83.3 to 97.5)		84.6 (76.0 to 93.2)	
≥ 5	78	82.9 (73.1 to 92.7)		70.4 (58.6 to 82.2)	
MRD on remission date, %					
< 0.01	515	96.8 (94.8 to 98.8)	< .001	92.0 (89.1 to 94.9)	< .001
0.01-0.99	63	87.2 (76.6 to 97.8)		75.2 (61.5 to 88.9)	
1-4.99	10	54.9 (22.6 to 87.2)		45.0 (12.3 to 77.7)	
≥ 5	5	60.0 (7.5 to 100)		20.0 (0.0 to 44.7)	

Abbreviations: ALL, acute lymphoblastic leukemia; MRD, minimal residual disease; NCI, National Cancer Institute.

*Patients with B-ALL between age 1 and 10 years and with a leukocyte count of < 50,000/ μ L, a DNA index (the ratio of DNA content in leukemic cells to that in normal diploid G0/G1 cells) of ≥ 1.16 , or the translocation t(12;21) (*ETV6-RUNX1*) were provisionally classified as having low-risk ALL. Infants with *KMT2A* rearrangement, patients with t(9;22) (*BCR-ABL1*), and those with early T-cell precursor ALL were considered to have high-risk ALL. Remaining patients were provisionally classified as having standard-risk (intermediate-risk) ALL. The final risk status of patients with provisional low-risk or provisional standard-risk ALL was determined by the level of MRD. Any patient with a level of MRD of $\geq 1\%$ in the bone marrow aspirate on day 15 of remission induction or 0.01% to 0.99% after completion of 6 weeks of induction therapy was classified as having standard-risk ALL. A level of MRD of $\geq 1\%$ after completion of induction therapy indicated high-risk ALL.

†CNS status was classified as follows: CNS-1 (no detectable blast cells in a sample of CSF), CNS-2 status (< 5 leukocytes/ μ L of CSF with blasts), CNS-3 status (≥ 5 leukocytes/ μ L of CSF with blasts or cranial palsy), and traumatic lumbar puncture with blast cells (≥ 10 erythrocytes/ μ L of CSF with blast cells).

to Peto and Pike.¹⁹ Independent prognostic factors were identified using the Cox proportional hazards regression model. The cumulative incidence functions of isolated CNS relapse and any CNS relapse were estimated according to Kalbfleisch and Prentice²⁰ and compared with those in the Total Therapy Study 15 using Gray's test²¹; death in remission and second neoplasm were regarded as competing events. All reported *P* values were two sided and not adjusted for multiple comparisons. Outcome data updated on May 1, 2019, were used in all analyses; 98% of survivors had been seen within 1 year. Median follow-up time for the 561 patients who were alive at the time of analysis was 6.26 years (interquartile range, 4.41 years; range, 1.15 to 11.43 years). All statistical analyses were based on intent-to-treat population and performed with SAS (version 9.4;

SAS Institute, Cary, NC) and R version 3.3.0 (www.r-project.org).

RESULTS

Treatment Outcome

Of the 598 patients, including 12 infants, 590 (98.66%) entered complete morphologic remission (low risk, 99.62%; standard risk, 99.64%; high risk, 89.66%). There were 8 induction failures, 4 as a result of fatal infections and the other 4 refractory leukemia; 2 of these 4 patients were alive and in remission 2.2 and 4.5 years later, the latter after undergoing transplantation.

Allogeneic transplantation was performed in 24 patients at 1.58 to 30.35 months (median, 4.46 months) after

remission induction (Appendix). Sixteen of the 24 patients were alive and in remission. There were 36 relapses including 26 hematologic, 7 isolated CNS, 1 isolated testicular, 1 combined CNS and ocular, and 1 combined hematologic and testicular. Six patients developed secondary malignancies (Appendix). There were 17 deaths in remission: 3 transplantation-related toxicities, 7 infections, 2 hepatic failures, 1 saddle pulmonary embolus, 2 respiratory failures, 1 systemic inflammatory response, and 1 cerebral hemorrhagic infarct.

The probability of 5-year event-free survival was 88.2% (95% CI, 84.9% to 91.5%), overall survival 94.1% (95% CI, 91.7% to 96.5%; Fig 2), and cumulative risk of any relapse 6.6% (95% CI, 4.4% to 8.7%), including 4.6% (95% CI, 2.8% to 6.5%) for an isolated hematologic relapse. The death-in-remission rate was 2.7% (95% CI, 1.4% to 4.0%).

Impact of Presenting Features and Early Treatment Response

Table 1 lists the 5-year event-free survival and overall survival rates according to presenting features, risk assessment, and response to initial treatment. Because infants had a significantly poorer outcome than older patients, and patients with T-cell ALL had inferior outcomes compared with those with B-cell ALL, we analyzed prognostic factors separately in cases of T-cell ALL and B-cell ALL in noninfants (Table 2). Among patients with B-cell ALL, the only factors associated with inferior event-free survival and overall survival rates were MRD at the end of remission induction, black race, and *KMT2A*

rearrangement, whereas *ETV6-RUNX1* predicted a better outcome. Among patients with T-cell ALL, the only significant adverse predictor was the presence of any blasts in the CSF at diagnosis. Of note, the 15 patients with Philadelphia chromosome-positive ALL had an excellent 5-year event-free survival rate of 71.1% (95% CI, 42.9% to 99.3%), with 3 patients experiencing hematologic relapses, including the only patient who underwent transplantation for high MRD and subsequently died of relapse, and 1 who died of infection. The 5-year event-free survival rate for the 10 patients with early T-cell precursor ALL, one of whom died of infection during induction and another of relapse after transplantation, was 80.0% (95% CI, 53.5% to 100%).

Treatment Toxicity

The cumulative risk of death from toxic effects during remission induction and continuation chemotherapy was 3.2% (95% CI, 1.8% to 4.6%). Table 3 summarizes the most notable toxic effects of treatment. Apart from allergic reactions to PEG-asparaginase, all toxic effects occurred more often among standard-risk and high-risk patients than among low-risk patients. Age greater than 10 years was associated with an increased risk of severe infection (11.5% [95% CI, 6.0% to 17.0%] v 5.9% [95% CI, 3.6% to 8.1%]; $P = .027$), osteonecrosis (31% [95% CI, 22.6% to 39.4%] v 2.2% [95% CI, 0.8% to 3.6%]; $P < .001$), hyperglycemia (27.3% [95% CI, 19.8% to 34.7%] v 7.2% [95% CI, 4.7% to 9.6%]; $P < .001$), and thrombosis (29.9% [95% CI, 22.1% to 37.7%] v 10.6% [95% CI, 7.7%

TABLE 2. Independent Risk Factors for Any Major Adverse Events (n = 66) or Deaths (n = 37) Among All Patients and Among Noninfant Patients With B-ALL or T-ALL

Variable	All Patients (including infants)				Patients With B-ALL (excluding infants)				Patients With T-ALL (excluding infants)			
	No. of Patients	No. of Adverse Events	HR (95% CI)	P	No. of Patients	No. of Events	HR (95% CI)	P	No. of Patients	No. of Events	HR (95% CI)	P
Major adverse event*												
MRD level on remission date, %												
0.01-0.99	63	15	3.4 (1.9 to 6.2)	< .001	49	10	4.1 (1.9 to 8.8)	< .001	11	3	3.8 (1.0 to 14.5)	.048
1-4.99	10	5	6.2 (2.4 to 15.8)	.001	4	3	20.7 (5.9 to 72.7)	< .001	6	2	3.0 (0.7 to 13.8)	.154
≥ 5	5	4	37.7 (12.9 to 110)	< .001	3	2	28.5 (6.5 to 126)	< .001	2	2	83.7 (7.3 to 960)	.001
< 0.01	515	39	1.0		424	26	1.0		83	10	1.0	
t(12;21)(ETV6-RUNX1)†												
Present	127	2	0.1 (0.0 to 0.6)	.012	127	2	0.1 (0.0 to 0.6)	.016	—	—	—	—
Absent	471	65	1.0		356	41	1.0		—	—	—	—
CNS status†												
CNS2/CNS3/traumatic with blasts	—	—	—	—	—	—	—	—	55	15	4.9 (1.3 to 18.2)	.016
CNS1	—	—	—	—	—	—	—	—	48	3	1.0	
KMT2A†												
Present	38	13	3.0 (1.6 to 5.7)	.001	21	6	3.3 (1.3 to 7.9)	.009	—	—	—	—
Absent	560	54	1.0		462	37	1.0		—	—	—	—
Race†												
Black	81	14	2.2 (1.1 to 4.1)	.017	57	8	3.0 (1.3 to 6.9)	.016	—	—	—	—
Other	123	19	1.6 (0.9 to 3.0)	.135	104	13	1.6 (0.7 to 3.4)	.225	—	—	—	—
White	394	34	1.0		322	22	1.0		—	—	—	—

(continued on following page)

TABLE 2. Independent Risk Factors for Any Major Adverse Events (n = 66) or Deaths (n = 37) Among All Patients and Among Noninfant Patients With B-ALL or T-ALL (continued)

Variable	All Patients (including infants)				Patients With B-ALL (excluding infants)				Patients With T-ALL (excluding infants)			
	No. of Patients	No. of Adverse Events	HR (95% CI)	P	No. of Patients	No. of Events	HR (95% CI)	P	No. of Patients	No. of Events	HR (95% CI)	P
Deaths												
MRD level on remission date, %												
0.01-0.99	63	10	5.2 (2.4 to 11.4)	< .001	49	6	6.9 (2.3 to 20.2)	.001	11	2	3.6 (0.7 to 18.2)	.120
1-4.99	10	5	14.2 (5.2 to 38.4)	< .001	4	3	45.2 (11.2 to 182)	< .001	6	2	3.1 (0.6 to 15.1)	.157
≥ 5	5	2	17.0 (3.7 to 77.3)	< .001	3	1	44.7 (5.2 to 381)	< .001	2	1	5.3 (0.6 to 44.2)	.125
< 0.01	515	18	1.0		424	9	1.0		83	7	1.0	
KMT2A†												
Present	38	8	3.3 (1.4 to 7.7)	.006	21	3	4.6 (1.3 to 16.7)	.019	—	—	—	—
Absent	560	31	1.0		462	18	1.0		—	—	—	
Race†												
Black	81	8	2.5 (1.1 to 5.9)	.035	57	2	2.0 (0.4 to 9.8)	.396	—	—	—	—
Other	123	14	2.4 (1.1 to 5.4)	.034	104	10	3.0 (1.1 to 8.5)	.037	—	—	—	—
White	394	17	1.0		322	9	1.0		—	—	—	
CNS status†												
CNS1	—	—	—	—	—	—	—	—	48	2	1.0	.047
CNS2/CNS3/traumatic with blast	—	—	—	—	—	—	—	—	55	11	5.0 (1.0 to 24.3)	

Abbreviations: ALL, acute lymphoblastic leukemia; HR, hazard ratio; MRD, minimal residual disease.

*Any major events included induction failure, any relapse, death in remission, and the development of a second cancer.

†Data not shown for multivariable analysis because univariable analyses were not significant or the numbers of patients were too small for analyses.

TABLE 3. Selected Major Toxic Effects of Treatment

Toxic Effect	No. of Patients	3-Year Cumulative Risk, % (95% CI)	P
Seizure (grade 2, 3, or 4)			
All patients	36	6.2 (4.3 to 8.2)	.035
Standard-risk or high-risk group	26	8.1 (5.1 to 11.1)	
Low-risk group	10	3.9 (1.5 to 6.3)	
Severe infection (grade 4 or 5)			
All patients	47	8.3 (6.0 to 10.5)	.006
Standard-risk or high-risk group	35	11.2 (7.7 to 14.7)	
Low-risk group	12	4.7 (2.1 to 7.3)	
Allergic reaction to asparaginase (grade 2, 3, or 4)			
All patients	104	18.0 (14.9 to 21.2)	.219
Standard-risk or high-risk group	63	19.7 (15.3 to 24.1)	
Low-risk group	41	16.0 (11.5 to 20.5)	
Osteonecrosis (grade 3 or 4)			
All patients	46	8.5 (6.1 to 10.8)	< .001
Standard-risk or high-risk group	42	14.5 (10.5 to 18.6)	
Low-risk group	4	1.6 (0.0 to 3.1)	
Thrombosis (grade 2, 3, or 4)			
All patients	89	15.6 (12.6 to 18.6)	< .001
Standard-risk or high-risk group	64	20.2 (15.7 to 24.7)	
Low-risk group	25	9.9 (6.2 to 13.5)	
Hyperglycemia (grade 3 or 4)			
All patients	69	11.8 (9.2 to 14.4)	.001
Standard-risk or high-risk group	51	15.6 (11.6 to 19.5)	
Low-risk group	18	7.0 (3.9 to 10.1)	
Pancreatitis (grade 2, 3, or 4)			
All patients	57	10.0 (7.5 to 12.4)	< .001
Standard-risk or high-risk group	45	14.3 (10.4 to 18.1)	
Low-risk group	12	4.6 (2.1 to 7.2)	

to 13.6%]; $P < .001$) compared with findings in younger patients. Whereas none of the 12 infants experienced a reaction to PEG-asparaginase, hyperglycemia, or pancreatitis, they had a higher cumulative risk of grade 4 or 5 infections (58.3% [95% CI, 28.4% to 88.3%] v 7.2% [95% CI, 5.0% to 9.3%]; $P < .001$), seizures (16.7% [95% CI, 0.0% to 38.7%] v 6.0% [95% CI, 4.1% to 8.0%]; $P = .08$), and thrombosis (37.5% [95% CI, 5.9% to 69.1%] v 15.2% [95% CI, 12.2% to 18.2%]; $P = .038$) than did older children.

PEG-Asparaginase Randomization and CNS Relapse

Of the 598 evaluable patients, 414 patients were randomly assigned for the primary study objective to receive PEG-asparaginase 2,500 U/m² (n = 208) or 3,500 U/m² (n = 206). A total of 184 patients were not randomly assigned for various reasons (Fig 1). Although there were no significant differences in the presenting features between the 2

randomly assigned groups, the non-randomly assigned patients were more likely to have high-risk disease and less likely to have *ETV6-RUNX1* ALL and CNS-3 status (Appendix Table A5, online only). There were no differences in the 5-year continuous complete remission rate (90.4% [95% CI, 85.7% to 95.1%] v 91.2% [95% CI, 86.7% to 95.7%]; $P = .91$), cumulative risk of isolated CNS relapse (1.1% [95% CI, 0.0% to 2.7%] v 0.5 [95% CI, 0.0% to 1.4%]; $P = .98$), and cumulative risk of any CNS relapse (1.1% [95% CI, 0.0% to 2.7%] v 1.0% [95% CI, 0.0% to 2.3%]; $P = .55$) between patients who were randomly assigned to receive 2,500 U/m² or 3,500 U/m². There was no difference in treatment outcome between any subsets of patients within the 2 randomly assigned groups (Appendix Table A6, online only).

Seven of 598 patients experienced isolated CNS relapse and 1 a combined CNS and ocular relapse. Six of these

TABLE 4. Cumulative Risk of Isolated or Any CNS Relapse According to Selected Clinical and Biologic Characteristics

Variable	No. Total	No. Any CNS Relapse	5-Year Cumulative Risk of Any CNS Relapse, % (95% CI)	P	No. Isolated CNS Relapse	5-Year Cumulative Risk of Isolated CNS Relapse, % (95% CI)	P
Age at diagnosis, years			0	.209		0	.111
< 1	11	0	1.0 (0.0 to 1.9)		0	0.7 (0.0 to 1.5)	
1-10	440	4	3.2 (0.1 to 6.3)		3	3.2 (0.1 to 6.3)	
> 10	139	4			4		
Sex							
Male	345	7	2.3 (0.6 to 3.9)	.091	6	1.9 (0.4 to 3.5)	.140
Female	245	1	0.4 (0.0 to 1.2)		1	0.4 (0.0 to 1.2)	
Race							
White	391	5	1.4 (0.2 to 2.7)	.940	5	1.4 (0.2 to 2.7)	.927
Black	80	1	1.3 (0.0 to 3.8)		1	1.3 (0.0 to 3.8)	
Others	119	2	1.9 (0.0 to 4.5)		1	0.8 (0.0 to 2.5)	
Leukocyte count (cells/ μ L)							
< 10,000	247	0	0	.005	0	0	.027
10,000-49,000	207	4	2.0 (0.1 to 3.9)		4	2.0 (0.1 to 3.9)	
50,000-99,000	57	0	0		0	0	
> 100,000	79	4	5.8 (0.2 to 11.4)		3	4.3 (0.0 to 9.3)	
CNS status							
CNS1	340	3	1.0 (0.0 to 2.1)	.328	2	0.6 (0.0 to 1.5)	.180
CNS2	195	4	2.3 (0.0 to 4.6)		4	2.3 (0.0 to 4.6)	
CNS3	21	1	4.8 (0.0 to 14.1)		1	4.8 (0.0 to 14.1)	
Traumatic with blast	34	0	0		0	0	
Immunophenotype							
B	490	4	0.9 (0.0 to 1.7)	.013	3	0.6 (0.0 to 1.4)	.005
T	100	4	4.3 (0.1 to 8.6)		4	4.3 (0.1 to 8.6)	
DNA index		0					
≥ 1.16	124	0	0	.150	0	0	.178
< 1.16	466	8	1.9 (0.6 to 3.1)		7	1.6 (0.4 to 2.8)	
Ploidy							
Hyperdiploidy > 50	154	0	0	.095	0	0	.119
Others	436	8	2.0 (0.6 to 3.4)		7	1.7 (0.4 to 3.0)	
t(9;22)(BCR-ABL1)							
Present	14	0	0	.665	0	0	.686
Absent	576	8	1.5 (0.5 to 2.6)		7	1.3 (0.3 to 2.3)	
KMT2A rearrangement							
Present	36	1	2.8 (0.0 to 8.2)	.460	1	2.8 (0.0 to 8.2)	.371
Absent	554	7	1.4 (0.4 to 2.4)		6	1.2 (0.2 to 2.1)	
t(4;11)(KMT2A-AFF1)							
Present	12	0	0	.675	0	0	.698
Absent	578	8	1.5 (0.5 to 2.6)		7	1.3 (0.3 to 2.3)	
t(1;19)(TCF3-PBX1)							
Present	16	0	0	.632	0	0	.654
Absent	574	8	1.5 (0.5 to 2.6)		7	1.3 (0.3 to 2.3)	

(continued on following page)

TABLE 4. Cumulative Risk of Isolated or Any CNS Relapse According to Selected Clinical and Biologic Characteristics (continued)

Variable	No. Total	No. Any CNS Relapse	5-Year Cumulative Risk of Any CNS Relapse, % (95% CI)	P	No. Isolated CNS Relapse	5-Year Cumulative Risk of Isolated CNS Relapse, % (95% CI)	P
t(12;21)(ETV6-RUNX1)							
Present	126	0	0	.141	0	0	.169
Absent	464	8	1.9 (0.6 to 3.2)		7	1.6 (0.4 to 2.8)	
MRD on day 15 of induction, %							
< 0.01	186	2	1.2 (0.0 to 2.8)	.461	1	0.5 (0.0 to 1.6)	.293
0.01-0.99	231	4	1.9 (0.0 to 3.9)		4	1.9 (0.0 to 3.9)	
1-4.99	99	0	0		0	0	
≥ 5	74	2	2.7 (0.0 to 6.4)		2	2.7 (0.0 to 6.4)	
MRD on remission date, %							
< 0.01	515	6	1.3 (0.3 to 2.4)	.599	5	1.1 (0.1 to 2.0)	.479
0.01-0.99	63	2	3.2 (0.0 to 7.5)		2	3.2 (0.0 to 7.5)	
1-4.99	9	0	0		0	0	
≥ 5	2	0	0		0	0	

Abbreviation: MRD, minimal residual disease.

patients remained in second remission for 0.57 to 4.25 years, but 2 died of progressive disease (Appendix Table A7, online only). Five-year cumulative risk of isolated CNS relapse was 1.3% (95% CI, 0.3% to 2.2%) and of any CNS relapse 1.5% (95% CI, 0.5% to 2.5%; Fig 2). Whereas presenting leukocyte count > 100,000/ μ L and T-cell ALL were associated with an increased risk of isolated or any CNS relapse (Table 4), only T-cell ALL retained independent significance in the multivariable analysis for any CNS relapse (hazard ratio, 5.15 [95% CI, 1.3 to 20.6]; $P = .021$) and for isolated CNS relapse (hazard ratio, 6.83 [95% CI, 1.5 to 30.5]; $P = .012$).

There were 359 patients in the current study with presenting features that were associated with an increased risk of CNS relapse defined in Total Therapy Study 15,² and they had significantly lower CNS relapse rates than the corresponding 248 patients enrolled in Study 15 (5-year cumulative risk of any CNS relapse, 1.8% [95% CI, 0.4% to 3.3%] v 5.7% [95% CI, 2.8% to 8.6%]; $P = .008$; isolated CNS relapse, 1.5% [95% CI, 0.2% to 2.9%] v 4.0% [95% CI, 1.6% to 6.5%]; $P = .049$; Fig 3). There were no significant differences in the cumulative risk of grade 2 to 4 seizure (5.9% [95% CI, 3.2% to 8.7%] v 6.5% [95% CI, 3.7% to 9.4%]; $P = .78$) or grade 4 or 5 infections (8.1% [95% CI, 4.9% to 11.3%] v 8.4% [95% CI, 5.2% to 11.7%]; $P = .95$) between the 293 patients who received two to four intrathecal treatments and the 305 who received six intrathecal treatments during remission induction.

DISCUSSION

The results of this study suggest that early intensification of intrathecal therapy improves CNS control. Compared with historical controls treated in Total Therapy Study 15, the

two extra doses of intrathecal therapy administered during the first 2 weeks of remission induction seemed to significantly reduce CNS relapse without excessive toxicity in patients with features that were previously associated with an increased risk of CNS relapse, such as black race, the presence of *TCF3-PBX1*, or any CNS involvement, including a CNS-2, CNS-3, or traumatic lumbar puncture with blasts status at diagnosis.² Despite the omission of prophylactic cranial irradiation in each of these subgroups, rates of isolated CNS or any CNS relapse were only 1.5% and 1.8%, respectively, significantly lower than the 4.0% and 5.7%, respectively, observed among historical controls treated in the Total Therapy Study 15.² The overall isolated CNS relapse rate of 1.3% and any CNS relapse rate of 1.5% in this study also compared favorably with those reported rates from studies conducted during the same time period, many of which still used prophylactic cranial irradiation for high-risk patients.³⁻¹² In this regard, the strategy of early intensification of intrathecal therapy for patients with CNS-2 or CNS-3 status has also been used in other clinical trials with improved results.^{9,12}

Our study enrolled consecutive patients without exclusion of any high-risk cases, such as infant or Philadelphia chromosome-positive ALL. Remarkably, none of the patients in some of the higher-risk categories experienced CNS relapse, including 34 patients with a traumatic lumbar puncture with blasts, 15 with Philadelphia chromosome, 16 with *TCF3-PBX1*, 12 with *KMT2A-AFF1*, and 12 with infant ALL. Only one of 21 patients with CNS-3 status at diagnosis experienced an isolated CNS relapse, but massive cerebral involvement did not preclude cure without cranial irradiation (Appendix Fig A1, online only). In contrast, these factors were still associated with increased CNS relapse in

FIG 3. Cumulative risk of (A) any CNS relapse and (B) isolated CNS relapse in the Total Therapy 15 and 16 Studies.

other contemporary clinical trials, even with the use of prophylactic cranial irradiation.²²⁻²⁴ For example, in the Children's Oncology Group (COG) AALLL0331 and AALL0232 trials, CNS-2, CNS-3, and traumatic lumbar puncture status were associated with increased CNS relapse and poorer event-free survival rates.²² In the 2 most recent clinical trials for Philadelphia chromosome-positive ALL, which included treatment with dasatinib, isolated or

combined CNS relapse occurred in 7% of patients in one study²³ and 15.4% in the other.²⁴ Finally, in the Interfant-99 and Interfant-06 trials in which cranial irradiation was omitted, isolated CNS relapse occurred in 3% and 4.5%, and combined CNS relapse in 5% and 4.9% of infants, respectively.^{25,26}

It is likely that other treatment components of our trial also contributed to CNS control, not only for those with particularly

high-risk features identified in Study 15, but also for all other patients. For example, high-dose methotrexate has been shown to improve CNS outcome in standard-risk or high-risk patients.^{22,27} Dasatinib can cross the blood-brain barrier,²⁸ and our use of a dosage that was higher than that of other studies^{23,24} (80 mg/m² per day v 60 mg/m² per day) may have resulted in higher drug levels in the CNS, preventing CNS relapse in our patients with Philadelphia chromosome-positive ALL. Dexamethasone and asparaginase treatment were used in all patients and intensified in those with standard- or high-risk ALL in this study. Both drugs have been shown to improve CNS control, and asparaginase potentiates the effect of dexamethasone.²⁹

There is no consensus regarding the optimal dose or number of doses of PEG-asparaginase that should be administered in patients with any ALL subtype. Two recent studies tested the effect of extra doses of PEG-asparaginase after remission induction.^{30,31} In the COG AALL0331 study for standard-risk ALL, after remission induction with dexamethasone, vincristine, and 1 dose of PEG-asparaginase 2,500 U/m², patients were randomly assigned to receive consolidation treatment with or without 4 additional doses.³⁰ In the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 study for non-high-risk ALL, after remission induction and consolidation treatment, including 5 doses of PEG-asparaginase 1,000 U/m², patients who tolerated asparaginase were randomly assigned to receive an additional 10 doses administered every 2 weeks versus 3 doses every 6 weeks during early continuation treatment.³¹ Extra doses of PEG-asparaginase failed to improve outcomes for standard-risk or non-high-risk patients in both studies.^{30,31} The optimal number of doses for high-risk ALL was uncertain. In our study, we found that increasing PEG-asparaginase to 3,500 U/m² had no excessive toxicity but did not improve systemic or CNS control for any subgroup of patients, which suggests that a threshold level of asparaginase exposure may have been reached at 2,500 U/m².

Our results corroborate the outcome of a 10-study meta-analysis that indicated that cranial radiotherapy has no important effect on the overall risk of relapse or survival in

childhood ALL.³² In the trial reported here, an isolated CNS relapse occurred in 7 patients, 5 of whom remained alive in second remission for 2.3 to 6.2 years (median, 4.04 years). Of the 498 patients treated in our Total Therapy Study 15, isolated CNS relapse occurred in 11 patients, all of whom were alive in second remission for 5.8 to 16.0 years (median, 13.9 years) from diagnosis (Pui et al, unpublished data). Thus, among 916 patients with B-cell ALL and 180 with T-cell ALL treated in our 2 consecutive trials omitting prophylactic cranial irradiation, only 1 each with B-cell ALL and T-cell ALL died because of CNS relapse. With the recent advent of chimeric antigen receptor–modified T-cell therapy, it is possible that even patients who experience CNS relapse can be cured without the use of therapeutic cranial irradiation.^{33,34} Indeed, the patient with a combined CNS and ocular relapse in this study was treated only with remission induction treatment, including intrathecal therapy followed by CD19 chimeric antigen receptor–modified T-cell therapy, and has remained in second remission for 25 months. The only risk factor for CNS relapse in this study was T-cell ALL with a cumulative risk of 4.3%. The recent improved overall outcome of T-cell ALL in the COG AALL0434 study suggests that nelarabine may be used to improve CNS control of this leukemia subtype.³⁵

Despite the reduction of CNS relapse and a corresponding increase in event-free survival, the overall survival rate reported here was similar to that of the Total Therapy Study 15.² This finding can be explained, in part, by the inclusion of infants in the current study, whose 5-year event-free survival was 50.0% (95% CI, 19.0% to 81.0%) and overall survival 58.3% (95% CI, 25.4% to 91.2%) compared with 89.0% (95% CI, 85.9% to 92.1%) and 94.9% (95% CI, 92.5% to 97.3%) for children older than 1 year. However, a more compelling explanation is that the intensity of conventional chemotherapy had reached its limit. Indeed, the cumulative risk of toxic death reported here was higher than in our earlier study (3.2% v 1.4%). Thus, additional improvement in outcome will need to rely more heavily on molecular therapeutic and cellular immunotherapy approaches.³⁶

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Improved CNS Control of Childhood Acute Lymphoblastic Leukemia Without Cranial Irradiation: St Jude Total Therapy Study 16**

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Research Funding: Servier

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Consulting or Advisory Role: Adaptive Biotechnologies

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APPENDIX

Patients and Methods

Participants. Of the 600 consecutive patients younger than age 19 years with newly diagnosed acute lymphoblastic leukemia (ALL) enrolled in the Total Therapy Study 16 at St Jude Children's Research Hospital, 2 patients registered in the study were subsequently excluded because of revised diagnoses of acute bilineal leukemia and chronic myeloid leukemia in blast crisis.

Diagnosis and risk classification. Diagnosis of ALL was based on immunophenotypic and genetic features of leukemic cells. Patients with B-cell ALL between age 1 and 10 years, with a leukocyte count of $< 50,000/\mu\text{L}$, a DNA index (the ratio of DNA content in leukemic cells to that in normal diploid G0/G1 cells) of ≥ 1.16 , or the translocation $t(12;21)$ (*ETV6-RUNX1*) were provisionally classified as having low-risk ALL. Infants with *KMT2A* rearrangement, patients with $t(9;22)$ (*BCR-ABL1*), and those with early T-cell precursor ALL were considered to have high-risk ALL. The remaining patients were provisionally classified as having standard-risk (intermediate-risk) ALL.

Final risk classification was determined by the level of minimal residual disease (MRD) measured during remission and consolidation induction by flow cytometry. Provisional low-risk patients with an MRD level of $\geq 1\%$ in bone marrow aspirate on day 15 of remission induction or 0.01% to 0.99% after the completion of 6 weeks of induction therapy were considered to have standard-risk ALL. An MRD level of $\geq 1\%$ after the completion of induction therapy or persistent, re-emergent, or increased MRD during consolidation therapy indicated high-risk ALL, regardless of provisional risk classification.

CNS status was classified as follows: CNS-1 status (no detectable blast cells in a sample of cerebrospinal fluid), CNS-2 status (< 5 leukocytes/ μL of CSF with blasts), CNS-3 status (≥ 5 leukocytes/ μL of CSF with blasts or cranial palsy), and traumatic lumbar puncture with blast cells (≥ 10 erythrocytes/ μL of CSF with blast cells).

Study design and outcomes. For the primary objective, patients were randomly assigned (1:1) on the first day of continuation treatment to receive PEG-asparaginase at the conventional dose ($2,500 \text{ U/m}^2$) or at a higher dose ($3,500 \text{ U/m}^2$). Randomization was stratified by risk group (low v standard/high risk), immunophenotype (T v B), and MRD level on day 15 of induction ($< 0.01\% \text{ v } \geq 0.01\%$) among patients with T-cell ALL. Patients with Down syndrome were not randomly assigned and were treated with the conventional dosage. The number of patients with presenting features that were associated with a high risk of CNS relapse—black race, any CNS involvement, T-cell ALL, and *TCF3-PBX1*—was equally distributed between the 2 randomized arms (149 in the conventional dose and 151 in the higher dose arm). Neither investigators, nor patients were masked to treatment assignment. The accrual goal for the primary objective was 420 evaluable patients, which would provide 80% statistical power ($\alpha = .05$; 2-sided log-rank test) to detect an improvement of 8.5% in the 5-year continuous complete remission rate. Two interim analyses were planned, and the final analysis was performed 3 years after the last patient was randomly assigned.

The primary objective of the randomization of dosage of PEG-asparaginase had 2 end points. The primary end point was continuous complete remission assessed from the randomization date to the first adverse event, including relapse at any site, death during remission, or second malignant neoplasm. The secondary end point was overall survival time from the randomization date to death from any cause.

A secondary objective was to evaluate whether early intensification of triple intrathecal chemotherapy during early remission induction would reduce the rate of isolated or any (isolated or combined) CNS relapse in patients who were at high risk for this complication compared with the cohort in the preceding Total Therapy Study 15.² Because it was difficult to determine a priori the number of patients (out of the total enrollment for the primary objective) who would satisfy the high-risk criteria for CNS relapse to receive early intensification of triple intrathecal chemotherapy during early remission induction, power analysis was not performed for this objective. Post hoc power analysis

on the basis of realized sample size ($n_1 = 359$ [Study 16] and $n_2 = 248$ [Study 15]) and the observed 5-year any-CNS relapse rates (0.018 [Study 16] and 0.057 [Study 15]) showed that the log-rank test has the post hoc power 0.869 at the .05 significant level. The post hoc power for isolated CNS relapse was 0.682. Despite this relatively low power, the comparison nonetheless showed borderline significance ($P = .049$).

Event-free survival time was calculated from the date of diagnosis to any first adverse event, including death during remission induction and induction failure as a result of drug resistance. Overall survival was measured as the time from diagnosis to death from any cause. Patients without an event were censored at the last day they were known to be alive.

Treatment. Total Therapy Study 16 was similar to that used in Study 15 with several modifications (Tables A1, A2, A3, and A4). Intramuscular native *Escherichia coli* asparaginase was replaced by intravenous PEG-asparaginase, which was intensified in standard- and high-risk patients. Mercaptopurine during days 22 to 35 of remission induction was replaced with thioguanine for patients with wild-type thiopurine methyltransferase activity. Cyclophosphamide was intensified to 4 fractionated doses (300 mg/m^2 every 12 hours for four doses) instead of 1 g/m^2 for 1 dose for standard- or high-risk patients with poor early treatment response—that is, 5% or more leukemia cells on day 15 of remission induction. Two extra doses of triple intrathecal therapy on days 4 and 11 of remission induction were administered to patients with increased risk of CNS relapse. Dasatinib instead of imatinib was administered for patients with Philadelphia chromosome-positive ALL. To improve quality of life, dexamethasone dose was decreased to 6 mg/m^2 per day for all patients after week 69 of continuation treatment, and the duration of continuation treatment was shortened from 146 weeks to 120 weeks for boys.

Remission induction and consolidation. Remission induction began with prednisone, vincristine, daunorubicin, and PEG-asparaginase (Table A1). Patients with an MRD level of $\geq 1\%$ after 2 weeks of induction were administered an additional dose of PEG-asparaginase on day 15. Subsequent induction therapy between days 22 and 35 consisted of cyclophosphamide, thioguanine (or mercaptopurine in thiopurine methyltransferase intermediate or poor metabolizers), and cytarabine for all patients, except infants with *KMT2A* fusion, who were treated with a 5-day course of clofarabine, cyclophosphamide, and etoposide. For patients with Philadelphia chromosome-positive ALL, dasatinib (40 mg/m^2 twice daily) was started on day 22 and continued until the end of all treatment. Upon hematopoietic recovery—between days 43 and 46—MRD was assessed and consolidation therapy consisting of 4 courses of high-dose methotrexate, mercaptopurine, and triple intrathecal therapy was administered (Table A2).

Continuation therapy. Continuation therapy for low-risk patients consisted of daily mercaptopurine and weekly methotrexate interrupted with pulses of mercaptopurine, dexamethasone, and vincristine, in addition to 2 reinduction cycles with dexamethasone, vincristine, and PEG-asparaginase with 1 dose of doxorubicin added to the first reinduction (Table A3). Patients with standard-risk or high-risk disease received PEG-asparaginase every 2 weeks for a total of 15 doses and daily mercaptopurine with pulses of doxorubicin plus vincristine plus dexamethasone (Table A3). Patients also received 2 reinduction cycles that consisted of dexamethasone, vincristine, and PEG-asparaginase, together with doxorubicin in the first reinduction and high-dose cytarabine in the second reinduction. They then received 3 rotating drug pairs (mercaptopurine plus methotrexate, cyclophosphamide plus cytarabine, and dexamethasone plus vincristine). Doses of mercaptopurine and methotrexate were adjusted according to the tolerance, the phenotype and genotype of thiopurine methyltransferase, and erythrocyte thioguanine metabolites. Total scheduled doses of anthracyclines were limited to 80 mg/m^2 and 230 mg/m^2 , and cyclophosphamide to 1 g/m^2 and 4.8 g/m^2 in low-risk disease and standard-risk patients, respectively. Continuation treatment lasted 120 weeks for all patients.

CNS-directed therapy. Triple intrathecal chemotherapy was instilled at an age-appropriate dose immediately after the collection of CSF with a diagnostic lumbar puncture and was repeated on day 15 (Table A1). Additional intrathecal therapy was administered on days 8 and 22 of remission induction in patients with Philadelphia chromosome, *KMT2A* rearrangement, hypodiploidy less than 44 chromosomes, or leukocyte count $> 100,000/\mu\text{L}$ at presentation, and on days 4, 8, 11, and 22 for patients with features associated with an increased risk of CNS relapse in Total Therapy Study 15, including T-cell ALL, presence of *TCF3-PBX1*, CNS-3 status, CNS-2 status, or traumatic lumbar puncture with blasts. Leucovorin rescue (5 mg/m² per dose, max 5 mg) was administered orally 24 and 30 hours after each intrathecal treatment during remission induction. Intrathecal therapy was administered every 2 weeks during consolidation therapy and according to risk features thereafter—every 4 or 8 weeks in low-risk patients and every 4 weeks in standard-risk or high-risk patients during the first year of continuation therapy (Table A3). Patients who were at high risk of CNS relapse continued to receive intrathecal therapy until week 97 of continuation therapy. Patients with low-risk ALL received a total of 13 to 21 intrathecal treatments, and those with standard-risk ALL, 16 to 27 treatments.

Allogeneic hematopoietic stem-cell transplantation.

Transplantation was an option for patients with high-risk leukemia whose treatment before transplantation was identical to that of patients with standard-risk disease. To maximize the reduction of MRD before transplantation, we administered reintensification therapy to all patients and 1 or 2 additional courses of clofarabine, etoposide, cyclophosphamide, and dexamethasone to those who experienced suboptimal responses to the initial reintensification (Table A4).

Results

Treatment outcome. The 598 evaluable patients included 12 infants, 9 of whom had *KMT2A* rearrangements. Median age at diagnosis was 6.04 years (range, 0.12 to 18.89 years), and median leukocyte count was 13,900/ μL (range, 200 to 905,300/ μL). On the basis of

MRD measurements (available for 596 patients), we reclassified the risk status of 94 patients: 70 patients from provisional low risk to standard risk and 24 from provisional standard risk to high risk (Fig 1).

Of 598 patients, 590 (98.66%) entered complete morphologic remission (low risk, 99.62%; standard risk, 99.64%; high risk, 89.66%). There were 8 induction failures—4 because of fatal infections and the other 4 refractory leukemia; 2 of these 4 patients were alive and in remission 2.2 and 4.5 years later (the latter after transplantation). Twenty-four patients, including 3 with induction failure, underwent allogeneic stem-cell transplantation (4 from matched-sibling donors, 15 from matched-unrelated donors, 4 from haploidentical donors, and 1 cord blood) at 1.58 to 30.35 months (median, 4.46 months) after remission induction. Transplantation was performed in these patients because of an MRD level of $\geq 1\%$ at the end of induction therapy ($n = 10$), persistent MRD at week 16 after remission induction ($n = 2$), increasing MRD ($n = 6$), and early T-cell precursor ALL ($n = 6$). Among the latter, 3 patients had an MRD level $< 0.01\%$, one 0.01%, and one 3.82% at the end of induction, as well as 1 patient with increasing MRD to 0.077% during consolidation. Sixteen (66.7%) of 24 patients who underwent transplantation, including 1 nonresponder, were alive and in remission. Two nonresponders died of progressive disease and cardiopulmonary failure, 3 died of complications, 2 patients with relapsed disease died of progressive disease, and 1 patient who developed a second malignancy died as a result of respiratory failure.

There were 36 cases of relapses, including 26 hematologic, 7 isolated CNS, 1 isolated testicular, 1 combined CNS and ocular, and 1 combined hematologic and testicular. Six patients developed secondary malignancies: T-lymphoblastic lymphoma after the completion of therapy for B-cell ALL, renal-cell carcinoma and squamous-cell carcinoma after transplantation, low-grade cerebellar glioma, myelodysplastic syndrome with germline *ETV6* variant, glioblastoma multiforme with constitutional mismatch repair deficiency syndrome, and acute myeloid leukemia with monosomy 7. There were 17 deaths in remission: 3 transplantation-related toxicities, 7 infections, 2 hepatic failures, 1 saddle pulmonary embolus, 2 respiratory failures, 1 systemic inflammatory response, and 1 cerebral hemorrhagic infarct.

FIG A1. T1 postcontrast sagittal and coronal images of an 8-month-old girl with *KMT2A*-rearranged ALL presenting with massive cerebral involvement, scalp lesions and leukocyte count of 31,100/ μL . Cytospin on CSF showed 0 RBC/ μL and 93 WBC/ μL with 99% blasts. Images show an extensive parieto-occipital dural-based tumor involving superior sagittal sinus, bilateral brain parenchyma, and erosion through the skull. Superior sagittal sinus was displaced but not occluded on venogram. There was a smaller scalp lesion (arrow) involving the dura, but not the brain. Lesions resolved completely after 3 months of chemotherapy. She has remained in continuous first remission for 11.3 years.

TABLE A1. Remission Induction Therapy

Total Therapy Study 16				Total Therapy Study 15			
Participant	Agent	Doses and Routes	No. of Doses	Schedules	Doses and Routes	No. of Doses	Schedules
All participants							
	Methotrexate	none			1 g/m ² IV over 4 v 24 hours	1	Day 1
	Prednisone	40 mg/m ² per day orally three times per day*	84	Days 1-28	40 mg/m ² per day orally 3 times per day	84	Days 5-32
	Vincristine	1.5 mg/m ² IV (max 2 mg)	4	Days 1, 8, 15, 22†	1.5 mg/m ² IV (max 2 mg)	4	Days 5, 12, 19, 26
	Daunorubicin	25 mg/m ² IV	2	Days 1 and 8	25 mg/m ² IV	2	Days 5 and 12
	PEG-asparaginase	3,000 U/m ² IV	1-2	Day 3, (15)‡	Asparaginase 10,000 U/m ² 3 times weekly IM	6-9	Days 6, 8, 10, 12, 14, 16 (19, 21, 23)‡
	Triple intrathecal§	Age dependent	2-6	Days 1, (4), (8), (11), 15, (22)	Age dependent	2-4	Day 1 (intrathecal cytarabine only), 19 (8, 26)
Day 15 MRD < 5% (excluding infants with KMT2A)							
	Cyclophosphamide	1,000 mg/m ² IV	1	Day 22	1,000 mg/m ² IV	1	Day 26
	Cytarabine	75 mg/m ² IV	8	Days 23-26, 30-33	75 mg/m ² IV	8	Days 27-30, 34-37
	Thioguanine (mercaptopurine for thiopurine methyltransferase intermediate or poor metabolizers)	60 mg/m ² per dose orally	14	Days 22-35	Mercaptopurine for all; 60 mg/m ² per dose orally	14	Days 26-39
Day 15 MRD ≥ 5% (excluding infants with KMT2A)							
	Cyclophosphamide	300 mg/m ² IV‡	4	Every 12 hours, days 22-23	—	—	—
	Cytarabine	75 mg/m ² /dose IV	8	Days 23-26, 30-33	—	—	—
	Thioguanine (Mercaptopurine for thiopurine methyltransferase intermediate or poor metabolizers)	60 mg/m ² /dose orally	14	Days 22-35	—	—	—
(continued on following page)							

TABLE A1. Remission Induction Therapy (continued)

Participant	Agent	Total Therapy Study 16			Total Therapy Study 15		
		Doses and Routes	No. of Doses	Schedules	Doses and Routes	No. of Doses	Schedules
Infants with <i>KMT2A</i>	Clofarabine	40 mg/m ² /dose IV	5	Days 22-26	—	—	—
	Etoposide	100 mg/m ² /dose IV	5	Days 22-26	—	—	—
	Cyclophosphamide	300 mg/m ² /dose IV	5	Days 22-26	—	—	—

NOTE. In Study 16, except for vincristine, all doses administered to infants (age < 1 year) were based on body surface area. For infants age < 1 month or < 3 months and born prematurely, a 50% reduction in doses of daunomycin, asparaginase, etoposide, methotrexate, thiopurines, cyclophosphamide, clofarabine, and cytarabine were made. The vincristine dose for patients age < 12 months or < 10 kg weight was 0.05 mg/kg per dose.

Abbreviations: IM, intramuscular; IV, intravenous; MRD, minimal residual disease.

*Prednisone was substituted by dexamethasone (10 mg/m² per day on days 1-21, 4 mg/m² per day on days 22-24, and 2 mg/m² per day on days 25-28) in patients with early T-cell precursor acute lymphoblastic leukemia.

†Day 22 vincristine omitted for infants with *KMT2A* rearrangement in Total Therapy Study 16.

‡Extra dose of PEG-asparaginase or an extra 3 doses of asparaginase were administered to patients with ≥ 1% residual leukemia cells in the bone marrow on day 15 in Study 16 and on day 19 in Study 15, respectively.

§Triple intrathecal treatment (methotrexate 6, 8, 10, or 12 mg; hydrocortisone 12, 16, 20, or 24 mg; and cytarabine 18, 24, 30, or 36 mg for age < 1, 1-1.99, 2-2.99 and ≥ 3 years, respectively). Leucovorin rescue (5 mg/m² per dose, max 5 mg) was administered orally at 24 and 30 hours after each triple intrathecal treatment during remission induction. In patients presenting with renal function impairment, serum methotrexate level was measured 24 hours after intrathecal therapy and those with delayed methotrexate clearance were rescued with leucovorin until the level was no longer measurable. In Study 16, extra triple intrathecal treatment was administered on days 8 and 22 for patients with Philadelphia chromosome, *KMT2A* rearrangement, hypodiploidy (< 44 chromosomes), or WBC > 100,000/μL at presentation. Extra triple intrathecal treatment was administered on days 4, 8, 11, and 22 for patients with T-cell acute lymphoblastic leukemia, *TCF3-PBX1*, CNS-2 status, CNS-3 status, or traumatic lumbar puncture with blasts. In Study 15, extra triple intrathecal treatment was administered on days 8 and 26 for patients with CNS-2, CNS-3, or traumatic lumbar puncture with blasts, T-cell acute lymphoblastic leukemia with WBC > 50,000/μL, B-cell acute lymphoblastic leukemia with WBC > 100,000/μL, Philadelphia chromosome, *KMT2A* rearrangement, or hypodiploidy (< 45 chromosomes).

TABLE A2. Consolidation Therapy: Total Therapy Study 16 and Study 15

Agent	Dose and Route	No. of Doses	Schedule
High-dose methotrexate*	2.5 g/m ² (or targeted 33 μ M, low risk), 5.0 g/m ² (or targeted 65 μ M, standard/high risk)	4	Days 1, 15, 29, and 43
Mercaptopurine	50 mg/m ² /d	56	Days 1 to 56
Triple intrathecal	Age dependent	4	Days 1, 15, 29, and 43

NOTE. Methotrexate dose was adjusted according to pharmacokinetic data to achieve a steady-state concentration of 65 μ M in standard-risk or high-risk patients and to 33 μ M in some low-risk patients. Leucovorin 15 mg/m² (intravenous or orally) for standard-risk or high-risk patients and 10 mg/m² (orally or intravenous) for low-risk patients was initiated 42 hours after the start of methotrexate infusion and repeated every 6 hours for a total of 3 doses. For the first methotrexate course in Study 15 or for any patients having prior mucositis, leucovorin rescue was administered for 5 doses. For all courses, leucovorin was adjusted on the basis of plasma methotrexate levels.

*Patients with Down syndrome received 500 mg/m² irrespective of risk group. Dasatinib was held 24 hours before the administration and resumed when the methotrexate level was below the threshold for stopping leucovorin rescue.

TABLE A3. Continuation/Reinduction Therapy

Total Therapy Study 16			Total Therapy Study 15	
Week	Low-Risk Patients	Standard- or High-Risk Patients	Low-Risk Patients	Standard- or High-Risk Patients
1	Mercaptopurine + dexamethasone + vincristine	PEG-asparaginase + mercaptopurine + dexamethasone + vincristine + doxorubicin	Mercaptopurine + dexamethasone + vincristine	Asparaginase + mercaptopurine + dexamethasone + vincristine + doxorubicin
2	Mercaptopurine + methotrexate	Mercaptopurine	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
3*	Mercaptopurine + methotrexate	PEG-asparaginase + mercaptopurine	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
4	Mercaptopurine + dexamethasone + vincristine	Mercaptopurine + dexamethasone + vincristine + doxorubicin	Mercaptopurine + dexamethasone + vincristine	Asparaginase + mercaptopurine + dexamethasone + vincristine + doxorubicin
5	Mercaptopurine + methotrexate	PEG-asparaginase + mercaptopurine	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
6	Mercaptopurine + methotrexate	Mercaptopurine	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
7*	Reinduction I PEG-asparaginase + dexamethasone + vincristine + doxorubicin	Reinduction I PEG-asparaginase + dexamethasone + vincristine + doxorubicin (excluding KMT2A+ infants) [†]	Reinduction I	Reinduction I
8	Reinduction I	Reinduction I	Reinduction I	Reinduction I
9	Vincristine Reinduction I PEG-asparaginase + dexamethasone + vincristine	Vincristine + doxorubicin Reinduction I PEG-asparaginase + dexamethasone + vincristine (excluding KMT2A+ infants) [†]	Asparaginase + vincristine Reinduction I Asparaginase + dexamethasone + vincristine + doxorubicin	Asparaginase + vincristine + doxorubicin Reinduction I Asparaginase + dexamethasone + vincristine
10	Mercaptopurine + methotrexate	Mercaptopurine	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
11	Mercaptopurine + methotrexate	PEG-asparaginase + mercaptopurine + vincristine + doxorubicin	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine + vincristine + doxorubicin
12*	Mercaptopurine + methotrexate	Mercaptopurine	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
13	Mercaptopurine + methotrexate	PEG-asparaginase + mercaptopurine	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
14	Mercaptopurine + dexamethasone + Vincristine	Mercaptopurine + dexamethasone + vincristine + doxorubicin	Mercaptopurine + dexamethasone + vincristine	Asparaginase + mercaptopurine + dexamethasone + vincristine + doxorubicin
15	Mercaptopurine + methotrexate	PEG-asparaginase + mercaptopurine	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
16	Mercaptopurine + methotrexate	Mercaptopurine	Mercaptopurine + methotrexate	Asparaginase + mercaptopurine
17*	Reinduction II PEG-asparaginase + dexamethasone + vincristine	Reinduction II PEG-asparaginase + dexamethasone + vincristine	Reinduction II Asparaginase + dexamethasone + vincristine + doxorubicin	Reinduction II Asparaginase + dexamethasone + vincristine
18	Reinduction II Vincristine	Reinduction II Vincristine	Reinduction II	Reinduction II
19	Reinduction II PEG-asparaginase + dexamethasone + vincristine	Reinduction II PEG-asparaginase + dexamethasone + vincristine + high-dose cytarabine	Reinduction II Asparaginase + vincristine	Reinduction II Asparaginase + dexamethasone + vincristine + high-dose cytarabine
20	Mercaptopurine + methotrexate	—	Mercaptopurine + methotrexate	—

(continued on following page)

TABLE A3. Continuation/Reinduction Therapy (continued)

Total Therapy Study 16			Total Therapy Study 15	
Week	Low-Risk Patients	Standard- or High-Risk Patients	Low-Risk Patients	Standard- or High-Risk Patients
21	Mercaptopurine + methotrexate	PEG-asparaginase + mercaptopurine	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate
22	Mercaptopurine + methotrexate	Mercaptopurine	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate
23	Mercaptopurine + methotrexate	PEG-asparaginase + mercaptopurine	Mercaptopurine + methotrexate	Cyclophosphamide + cytarabine
24	Mercaptopurine + methotrexate	Cyclophosphamide + cytarabine	Mercaptopurine + dexamethasone + vincristine	Dexamethasone + vincristine
25*	Mercaptopurine + dexamethasone + vincristine	PEG-asparaginase + dexamethasone + vincristine	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate
26	Mercaptopurine + methotrexate	Mercaptopurine	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate
27	Mercaptopurine + methotrexate	PEG-asparaginase + mercaptopurine	Mercaptopurine + methotrexate	Cyclophosphamide + cytarabine
28	Mercaptopurine + methotrexate	Cyclophosphamide + cytarabine	Mercaptopurine + dexamethasone + vincristine	Vincristine + dexamethasone
29*	Mercaptopurine + dexamethasone + vincristine	PEG-asparaginase + vincristine + dexamethasone	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate
30	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate
31	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate	Cyclophosphamide + cytarabine
32	Mercaptopurine + methotrexate	Cyclophosphamide + cytarabine	Mercaptopurine + dexamethasone + vincristine	Dexamethasone + vincristine
33*	Mercaptopurine + dexamethasone + vincristine	Dexamethasone + vincristine	Mercaptopurine + methotrexate	Mercaptopurine + methotrexate

NOTE. After week 30, low-risk patients received daily mercaptopurine and weekly methotrexate, which were interrupted by pulses of dexamethasone, vincristine, and mercaptopurine every 4 weeks up to week 101, after which only mercaptopurine and methotrexate were administered until week 120; whereas standard-risk and high-risk (not transplanted) patients received three drug pairs administered in 4-week blocks: mercaptopurine plus methotrexate in the first and second weeks, cyclophosphamide plus cytarabine in the third week (replaced by mercaptopurine plus methotrexate after week 68), and dexamethasone plus vincristine in the fourth week (replaced by mercaptopurine plus methotrexate after week 101). In Study 15, boys received mercaptopurine plus methotrexate from weeks 121 to 146. Mercaptopurine: 75 mg/m² orally daily for 7 days for the low-risk group; 50 mg/m² orally daily for 7 days between weeks 1 and 19 and 75 mg/m² after week 19 for standard- and high-risk groups. The starting dose for patients with heterozygous deficiency (intermediate metabolizers) of thiopurine methyltransferase was 60 mg/m² instead of 75 mg/m². The starting dose for poor metabolizers of thiopurine methyltransferase was 10 mg/m² 3 times per week instead of 75 mg/m² per day. Dexamethasone: 8 mg/m² orally per day in 3 divided doses for 5 days for the low-risk group and 12 mg/m² for standard-risk and high-risk groups until week 69; 8 mg/m² on days 1 to 8 and days 15 to 21 during reinduction I (weeks 7 to 9) and reinduction II (weeks 17 to 19) for both groups. In Study 16, the dose was reduced to 6 mg/m² orally per day in 3 divided doses for 5 days for both groups in weeks 69 to 101. Methotrexate, 40 mg/m² intravenously; doxorubicin, 30 mg/m² intravenously; vincristine, 2 mg/m² intravenously and 1.5 mg/m² intravenously during reinductions I and II (maximum 2 mg; 0.05 mg/kg for patients age < 1 year or < 10 kg in body weight); cyclophosphamide, 300 mg/m² intravenously; cytarabine, 300 mg/m² intravenously. In Study 16, PEG-asparaginase 2,500 U/m² or 3,500 U/m² was administered intravenously on the basis of randomization. In Study 15, asparaginase 25,000 U/m² weekly intramuscularly for 19 doses for standard- and high-risk patients and 10,000 U/m² 3 times per week intramuscularly for nine doses in low-risk patients. High-dose cytarabine: 2 g/m² intravenously every 12 hours × 4 doses on days 15 and 16 of reinduction II in standard-risk and high-risk groups.

*For low-risk acute lymphoblastic leukemia (ALL), triple intrathecal chemotherapy was administered to patients with CNS-1 status and WBC < 100,000/μL on weeks 7, 12, 17, 25, 33, 41, and 49, and to those with CNS-2 status, traumatic lumbar puncture with blasts status, or WBC > 100 × 10⁹/L at presentation on weeks 3, 7, 12, 17, 25, 29, 33, 37, 41, 45, and 49. For standard-risk or high-risk ALL, triple intrathecal treatment was administered on weeks 7, 12, 17, 25, 29, 33, 37, 41, 45, and 49 and to those with additional WBC > 100,000/μL at presentation, T-cell immunophenotype, *TCF3-PBX1*, Philadelphia chromosome, *KMT2A* rearrangement, hypodiploidy < 44, CNS-2 status, CNS-3 status, or traumatic lumbar puncture with blasts on weeks 3, 7, 12, 17, 25, 29, 33, 37, 41, 45, 49, 57, 65, 73, 81, 89, and 97. Leucovorin was not administered routinely after consolidation therapy.

†In Study 16, for infants with *KMT2A* rearrangement, vincristine and doxorubicin were substituted with clofarabine, etoposide, and cyclophosphamide (same doses as administered during the initial remission induction). The dexamethasone and PEG-asparaginase dose schedule was not altered.

TABLE A4. Reintensification Therapy

Agent	Dose and Route	No. of Doses	Schedule
First reintensification therapy before transplantation			
Dexamethasone	20 mg/m ² /d orally or IV (divided 3 times per day)	18	Days 1-6
Cytarabine	2 g/m ² , 3-hour IV infusion every 12 hours	4	Days 1-2
Etoposide	100 mg/m ² , 1-hour IV infusion every 12 hours	5	Days 3-5
Triple intrathecal	Age dependent	1	Day 5
PEG-asparaginase	3,000 U/m ² IV	1	Day 6
Second reintensification therapy for patients with suboptimal response to first reintensification			
Clofarabine	40 mg/m ² /d, 2-hour IV infusion	5	Days 1-5
Etoposide	100 mg/m ² /d, 2-hour IV infusion	5	Days 1-5
Cyclophosphamide	300 mg/m ² /d, 30- to 60-minute IV infusion	5	Days 1-5
Dexamethasone	8 mg/m ² /d (divided 3 times per day)	15	Days 1-5

Abbreviation: IV, intravenous.

TABLE A5. Comparisons of Presenting Features Between Non-Randomly Assigned and Randomly Assigned Patients and Between the Two Randomly Assigned Groups

Clinical Feature	Not Randomly Assigned		P*	PEG-Asparaginase 3,500 U/m ²		PEG-Asparaginase 2,500 U/m ²		P†
	No.	%		No.	%	No.	%	
Risk group								
Low	82	44.57	< .001	88	42.72	90	43.27	.987
Standard	69	37.50		106	51.46	105	50.48	
High	33	17.93		12	5.83	13	6.25	
NCI risk group (B-cell ALL)								
Standard	82	56.55	.366	103	59.54	110	62.50	.585
High	63	43.45		70	40.46	66	37.50	
NCI risk group (T-cell ALL)								
Standard	9	23.08	.805	8	24.24	5	15.63	.537
High	30	76.92		25	75.76	27	84.38	
Age at diagnosis, year								
< 1	4	2.17	.506	5	2.43	3	1.44	.643
1-10	131	71.20		152	73.79	160	76.92	
> 10	49	26.63		49	23.79	45	21.63	
Sex								
Male	112	60.87	.472	115	55.83	123	59.13	.551
Female	72	39.13		91	44.17	85	40.87	
Race								
White	118	64.13	.662	135	65.53	141	67.79	.862
Black	24	13.04		30	14.56	27	12.98	
Other	42	22.83		41	19.90	40	19.23	
Leukocyte count, cells/μL								
< 10,000	77	41.85	.473	85	41.26	87	41.83	.774
10, 000 to < 50,000	58	31.52		78	37.86	74	35.58	
50,000 to < 100,000	19	10.33		16	7.77	22	10.58	
≥ 100,000	30	16.30		27	13.11	25	12.02	
CNS status†								
CNS1	96	52.17	.016	126	61.17	121	58.17	.183
CNS2	72	39.13		56	27.18	72	34.62	
CNS3	2	1.09		13	6.31	6	2.88	
Traumatic with blast	14	7.61		11	5.34	9	4.33	
Immunophenotype								
B	145	78.80	.104	173	83.98	176	84.62	.893
T	39	21.20		33	16.02	32	15.38	
DNA index								
≥ 1.16	43	23.37	.325	36	17.48	45	21.63	.322
< 1.16	141	76.63		170	82.52	163	78.37	
Ploidy								
Hyperdiploidy > 50	50	27.17	.613	49	23.79	55	26.44	.572
Other	134	72.83		157	76.21	153	73.56	

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TABLE A5. Comparisons of Presenting Features Between Non-Randomly Assigned and Randomly Assigned Patients and Between the Two Randomly Assigned Groups (continued)

Clinical Feature	Not Randomly Assigned		P*	PEG-Asparaginase 3,500 U/m ²		PEG-Asparaginase 2,500 U/m ²		P†
	No.	%		No.	%	No.	%	
t(9;22)(BCR-ABL1)								
Present	6	3.26	.411	5	2.43	4	1.92	.750
Absent	178	96.74		201	97.57	204	98.08	
KMT2A rearrangement								
Present	14	7.61	.468	11	5.34	13	6.25	.834
Absent	170	92.39		195	94.66	195	93.75	
KMT2A-AFF1								
Present	4	2.17	1.000	3	1.46	5	2.40	.724
Absent	180	97.83		203	98.54	203	97.60	
t(1;19)(TCF3-PBX1)								
Present	5	2.72	1.000	8	3.88	3	1.44	.139
Absent	179	97.28		198	96.12	205	98.56	
t(12;21)(ETV6-RUNX1)								
Present	28	15.22	.017	46	22.33	53	25.48	.490
Absent	156	84.78		160	77.67	155	74.52	

Abbreviations: ALL, acute lymphoblastic leukemia; MRD, minimal residual disease; NCI, National Cancer Institute.

**P* values in the column between non-randomly assigned and randomly assigned patients reflect the comparisons between the 2 groups.

†*P* values at the last column reflect the comparisons between the 2 randomly assigned groups.

TABLE A6. Comparisons of Continuous Complete Remission Duration of Patients With Selected Clinical and Biologic Features Between the 2 Randomly Assigned Groups

	PEG-Asparaginase 3,500 U/m ²		PEG-Asparaginase 2,500 U/m ²		
Variable	No. of Patients	5-Year CCR, % (95% CI)	No. of Patients	5-Year CCR, % (95% CI)	P
Risk group					
Low	88	96.3 (91.6 to 100)	90	97.5 (93.6 to 100)	.632
Standard/high	118	87.6 (80.7 to 94.5)	118	85.0 (77.4 to 92.6)	.749
Age at diagnosis, years					
1-10	152	93.8 (89.3 to 98.3)	160	91.4 (86.1 to 96.7)	.699
> 10	49	86.4 (73.9 to 98.9)	45	88.4 (77.4 to 99.4)	.840
Sex					
Male	115	90.0 (83.5 to 96.5)	123	88.8 (82.3 to 95.3)	.821
Female	91	92.7 (86.2 to 99.2)	85	92.6 (85.7 to 99.5)	.995
Race					
White	154	92.5 (87.6 to 97.4)	167	91.1 (86.0 to 96.2)	.656
Black	34	90.9 (79.3 to 100)	29	86.2 (71.5 to 100)	.536
Other	18	82.1 (62.5 to 100)	12	91.7 (73.3 to 100)	.709
Leukocyte count, cells/ μ L					
< 10,000	85	94.8 (89.3 to 100)	87	91.8 (85.3 to 98.3)	.527
10,000 to < 50,000	78	94.6 (88.5 to 100)	74	95.6 (89.7 to 100)	.713
50,000 to < 100,000	16	73.1 (49.6 to 96.6)	22	81.3 (63.5 to 99.1)	.131
$\geq$ 100,000	27	81.5 (64.3 to 98.7)	25	78.2 (59.0 to 97.4)	.804
CNS status†					
CNS1	126	91.4 (85.7 to 97.1)	121	94.0 (89.1 to 98.9)	.297
CNS2/CNS3/traumatic with blasts	80	91.1 (83.5 to 98.7)	87	85.0 (75.4 to 94.6)	.197
Immunophenotype					
B-lineage	173	92.0 (87.1 to 96.9)	176	91.6 (86.7 to 96.5)	.883
T-lineage	33	87.1 (74.0 to 100)	32	83.3 (68.0 to 98.6)	.649
DNA index					
$\geq$ 1.16	36	96.8 (89.9 to 100)	45	94.6 (87.0 to 100)	.659
< 1.16	170	90.1 (84.8 to 95.4)	163	89.1 (83.4 to 94.8)	.984
Ploidy					
Hyperdiploidy > 50	49	97.7 (92.4 to 100)	55	91.3 (82.3 to 100)	.158
Other	157	89.3 (83.6 to 95.0)	153	89.9 (84.2 to 95.6)	.576
KMT2A rearrangement					
Absent	195	91.7 (87.2 to 96.2)	195	91.8 (87.3 to 96.3)	.930
Present	11	81.8 (57.7 to 100)	13	68.4 (37.6 to 99.2)	.893
t(1;19)(TCF3-PBX1)					
Absent	198	91.4 (86.7 to 96.1)	205	90.2 (85.3 to 95.1)	.773
Present	8	87.5 (66.1 to 100)	3	100 (100 to 100)	.513
t(12;21)(ETV6-RUNX1)					
Absent	160	88.8 (83.1 to 94.5)	155	87.8 (81.7 to 93.9)	.969
Present	46	100 (100 to 100)	53	98.1 (93.8 to 100)	.340

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TABLE A6. Comparisons of Continuous Complete Remission Duration of Patients With Selected Clinical and Biologic Features Between the 2 Randomly Assigned Groups (continued)

Variable	PEG-Asparaginase 3,500 U/m ²		PEG-Asparaginase 2,500 U/m ²		<i>P</i>
	No. of Patients	5-Year CCR, % (95% CI)	No. of Patients	5-Year CCR, % (95% CI)	
MRD on day 15 of induction, %					
< 0.01	61	94.1 (86.8 to 100)	63	96.8 (91.3 to 100)	.515
≥ 0.01	145	89.9 (84.2 to 95.6)	145	87.7 (81.6 to 93.8)	.763
MRD on remission date, %					
< 0.01	181	92.9 (88.6 to 97.2)	183	93.8 (89.7 to 97.9)	.741
≥ 0.01	181	92.9 (88.6 to 97.2)	183	93.8 (89.7 to 97.9)	.741

Abbreviations: CCR, continuous complete remission; MRD, minimal residual disease.

TABLE A7. Clinical and Biologic Features of the 7 Patients With Isolated and 1 With Combined CNS Relapse

Patient No.	Risk Group	Age at Diagnosis, Years	WBC Cells/ μ L	Sex	Race	Subtype	Day 15 MRD, %	Day 46 MRD, %	CNS Status at Diagnosis	Current Status
1	Standard	17.87	148,100	Male	White	T cell	0.94	0.00	CNS-2	Died of progressive disease 4.25 years after relapse and 8.85 years from diagnosis
2	Standard	18.02	13,400	Male	White	B others	0.05	0.00	CNS-1	Alive in remission > 6.29 years from diagnosis
3	High	1.60	805,700	Male	White	T cell	0.07	0.00	CNS-2	Alive in remission > 4.5 years from diagnosis
4*	High	6.41	15,400	Male	Other	T cell	16.30	0.32	CNS-2	Alive in remission > 4.04 years from diagnosis
5	Low	9.41	42,700	Male	White	<i>KMT2A-AFF1</i>	0.08	0.00	CNS-1	Alive in remission > 2.8 years from diagnosis
6	Standard	18.54	12,300	Male	Black	B others	33.35	0.56	CNS-3	Died of progressive disease 0.5 years after relapse and 2.5 years from diagnosis
7	High	14.11	244,000	Female	White	T cell	0.00	0.00	CNS-2	Alive in remission > 2.26 years from diagnosis
8†	Standard	1.76	224,800	Male	Other	B others	0.00	0.00	CNS-1	Alive in remission > 5.54 years from diagnosis

*Underwent transplantation in first remission.

†Combined CNS and ocular relapse, received chimeric antigen receptor–modified T-cell therapy after relapse.