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Long-term results of Total Therapy studies 11, 12 and 13A for childhood acute lymphoblastic leukemia at St Jude Children's Research Hospital

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We present the long-term results of three consecutive clinical trials (Total Therapy studies 11, 12 and 13A) conducted for children with newly diagnosed acute lymphoblastic leukemia (ALL) between 1984 and 1994. In study 11 (1984–1988), the overall event-free survival rates (±1 s.e.) were 71.8 ± 2.4% and 69.3 ± 2.4%, and the cumulative risks of isolated central nervous system (CNS) relapse 5.6 ± 1.2% and 5.9 ± 1.3%, at 5 and 10 years, respectively. In study 12 (1988–1991), event-free survival rates were 67.6 ± 3.4% and 61.5± 9.0%, and isolated CNS relapse rates were 10.4 ± 2.3% and 10.4 ± 2.3%, respectively. Early intensive intrathecal therapy in study 13A (1991–1994) has yielded a very low 5-year isolated CNS relapse rate of 1.2 ± 0.9%, boosting the 5-year event-free survival rate to 76.9 ± 3.3%. Factors consistently associated with an adverse prognosis included male sex, infant or adolescent age group, leukocyte count >100 × 10^9/l, nonhyperdiploidy karyotype and poor early response to treatment. Risk classification based on age and leukocyte count had prognostic significance in B-lineage but not T-lineage ALL. Early therapeutic interventions or modifications for patients with specific genetic abnormalities or persistent minimal residual leukemia may further improve long-term results. *Leukemia* (2000) **14,** 2286–2294.
Keywords: CNS relapse; B-lineage ALL; T-lineage ALL; prognostic factors; leukemia; chemotherapy

Introduction

The St Jude Total Therapy program for childhood acute lymphoblastic leukemia (ALL) spans almost four decades. The long-term results of the first 10 consecutive clinical studies, conducted from 1962 to 1984, have been reported.[1,2] Since 1984, we have completed five other studies; the results of their primary research aims and the early outcome of the first three trials (Total Therapy studies 11, 12 and 13A) have also been published.[3–5]

Study 11 was designed to provide intensified induction therapy to all patients and to test the Goldie–Coldman model of tumor cell kinetics and drug resistance, which predicts that cancer cell killing would increase if maximum doses of active agents are given as early as possible.[3] The 4-year event-free survival rate did not differ significantly between the two randomized treatment groups, possibly because of the relatively small numbers of patients studied or the ostensibly minor differences between treatment schedules. Nonetheless, the early result of treatment was excellent overall and was attributed to reinforcement of early therapy, including both the induction and consolidation phases, with additional effective agents. The leukemogenic effects of the epipodophyllotoxins, which are schedule-dependent,[6] were also identified in study 11.

In study 12, we tested the hypothesis that treatment outcome would be improved if doses of chemotherapeutic agents were individualized to prevent low systemic exposure to the drugs in patients with fast clearance.[4] Doses were also adjusted to avoid high systemic exposure, and hence undue toxicities, in patients with slow clearance. We found that among B-lineage ALL cases, individualizing therapy based on clearance improved the early treatment outcome without increasing toxicity. Failure to improve outcome in T-lineage cases with individualized therapy may have been due to an inadequately targeted systemic exposure to methotrexate. In this regard, several studies have shown that T-lineage blasts accumulate methotrexate and its active metabolites (methotrexate polyglutamates) less avidly than do B-lineage blasts and that higher doses could result in greater accumulation of the drug.[7–9]

Based on the premise that early intensification of systemic chemotherapy can forestall the emergence of drug-resistant blast cells, we reasoned that the same approach applied to intrathecal chemotherapy should further reduce the central nervous system (CNS) relapse hazard, leading to an improved outcome overall. Indeed, in study 13A, this strategy reduced the early CNS relapse hazard to near zero, boosting the overall effectiveness of ALL treatment.[5] Here, we report the long-term results of these three clinical trials and the clinical outcomes according to prognostic features for each of the three treatment eras.

Materials and methods

Patients

From 1984 to 1994, 711 consecutive patients aged 18 years or younger with newly diagnosed ALL were enrolled in three successive treatment protocols (Total Therapy studies 11, 12, and 13A)[3–5] at St Jude Children's Research Hospital. Patients were not eligible for the studies if they had received more than 1 week of prior therapy or treatment other than glucocorticoids, vincristine or emergency mediastinal irradiation. The diagnosis of ALL was based on immunophenotyping with panels of monoclonal antibodies directed toward lineage-associated antigens. Based on the pattern of reactivity, leukemic lymphoblasts were classified as B-lineage ($CD19^+$, $CD22^{\pm}$, $CD7^-$, $CD5^-$) or T cell ($CD7^+$, $CD5^+$, $CD19^-$).[10] Bone marrow samples for cytogenetic analysis were prepared by a direct method, with or without overnight culture. A modified trypsin–Wright technique was used for chromosome banding. Chromosomes were described according to the International System for Human Cytogenetic Nomenclature.[11] Each protocol was approved by an institutional review board and written informed consent was obtained for all patients.

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Treatment (Table 1)

Details of the Total Therapy studies have been given in earlier publications.[3–5] In study 11 (1984–1988), 361 patients were enrolled; two had incorrect diagnoses (acute myeloid leukemia) and one refused treatment.[3] The 358 eligible patients received the same intensive multidrug remission induction therapy. In this study, cases were defined as high risk if the presenting leukocyte count was $\geqslant 100 \times 10^9$/l or if two or more of the following features were present: leukocyte count $\geqslant 25 \times 10^9$/l, age <2 years or $\geqslant 10$ years, nonWhite race, DNA index $\leqslant 1.15$ or unknown, or any chromosomal translocation. All other cases were considered to have lower risk ALL. On attaining complete remission, lower risk patients were randomized to receive antimetabolite-based therapy or four pairs of drugs given in rotation weekly, whereas higher risk groups were randomly assigned to receive the same four pairs of drugs in rotation weekly or every 6 weeks for 120 weeks. Cranial irradiation was administered at 1 year to 63% of patients, either with higher risk leukemia (18 Gy) or CNS leukemia at diagnosis (24 Gy).

In study 12 (1988–1991), 188 patients received remission induction therapy identical to that in the preceding trial.[4] Patients entering complete remission were stratified (by age, presenting leukocyte count, race and DNA index) and randomized to receive either conventional doses (based on body surface area) or individualized doses (targeted to achieve an area under the plasma concentration-versus-time curve between the 50th and 90th percentiles of that in the conventional arm) of high-dose methotrexate and teniposide plus cytarabine, given as alternating pulses for five courses each during the first year of continuation therapy with mercaptopurine and methotrexate (120 weeks). Thirty percent of the patients with high-risk leukemia or CNS leukemia at diagnosis received cranial irradiation (18 or 24 Gy, respectively) during weeks 59 to 61. Three of the six patients with Philadelphia chromosome-positive ALL underwent allogeneic hematopoietic stem cell transplantation.[12]

Study 13A (1991–1994) enrolled 167 patients; two patients were ineligible (one had an incorrect diagnosis of acute myeloid leukemia, and the other was too ill to be treated).[5] Remission induction therapy closely followed previous regimens, except that methotrexate was given before the primary induction phase and etoposide was substituted for teniposide. All patients received 2 weeks of consolidation therapy with high-dose methotrexate and mercaptopurine upon achieving complete remission. Continuation therapy was risk directed. Lower risk cases (DNA index 1.16 to 1.60, age 1 to 10 years, leukocyte count $<25 \times 10^9$/l, and CNS-1 status, in the absence of the t(1;19), and the Philadelphia chromosome) received antimetabolite-based therapy for 120 weeks with pulses of high-dose methotrexate every 8 weeks (for the first year) and prednisone plus vincristine every 4 weeks. The other cases with high risk ALL received continuation therapy modeled on the weekly rotation regimens of study XI, with the addition of L-asparaginase, high-dose methotrexate and a reinduction phase during the first year. All patients received early intensification of intrathecal therapy; patients with one or more blast cells in cytocentrifuged preparations of cerebrospinal fluid at diagnosis and those with higher risk leukemia received additional doses of intrathecal chemotherapy during remission induction and first year of continuation treatment. Cranial irradiation was given during weeks 56 to 59 to approximately 17% of the patients with high-risk leukemia (18 Gy) or CNS leukemia at diagnosis (24 Gy). Only one of the six patients with Philadelphia chromosome-positive ALL had hematopoietic stem cell transplantation.[12]

Table 1 Treatment schema of total studies 11, 12, and 13A

Treatment component	*Study 11*		*Study 12*	*Study 13A*	
	Higher risk	*Lower risk*		*Higher risk*	*Lower risk*
Induction Consolidation Continuation	PVDA → T+C HDMTX E+Cy → MP+MTX → T+C → P+V rotated weekly or every 6 weeks	PVDA → T+C HDMTX Same 4 drugs pairs rotated weekly, or MP+MTX × 3 weeks → P+V × 1 week	PVDA → T+C MP+MTX weekly with T+C or HDMTX pulse, alternating every 6 weeks ×5 pulses each	HDMTX → PVDA → E+C HDMTX+MP E+Cy → MP+MTX → MTX+C → P+V+A[a] E+Cy → MP+HDMTX[b] → E+C → P+V+A roated weekly	HDMTX → PVDA → E+C HDMTX+MP MP+MTX → MP+MTX → MP+MTX → P+V → MP+MTX → MP+MTX → MP+HDMTX[b] → P+V
Reinduction	No	No	No	PVDA → E+C → HDMTX from weeks 32 to 37	Same
CNS Therapy	TIT (13–15)[c] CRT	TIT (9)[c]	TIT (13–20)[c] CRT	TIT (22–26)[c] CRT	TIT (15)[c]

P, prednisone; V, vincristine; D, daunorubicin; A, asparaginase; HDMTX, high-dose methotrexate; T, teniposide; C, cytarabine; E, etoposide; MP, mercaptopurine; Cy, cyclophosphamide; MTX, methotrexate; TIT, triple intrathecal therapy with methotrexate, hydrocortisone and cytarabine; CRT, cranial irradiation for patients with high-risk leukemia or CNS leukemia at diagnosis.
[a]Asparaginase discontinued after week 28 of continuation therapy.
[b]High-dose methotrexate discontinued after 1 year of continuation therapy.
[c]Number in parenthesis represents the number of intrathecal treatments. In all studies, intrathecal therapy was given only during the first year of continuation treatment. Patients with CNS leukemia received 4 weekly doses of intrathecal therapy during remission induction. Five intrathecal treatments were given during cranial irradiation. In study 12, lower risk cases received 13 intrathecal treatments and higher risk cases 18 to 20.

Statistical analysis

The duration of event-free survival (EFS) is defined as the time from diagnosis until the date of failure (induction failure, relapse, death, or the development of a second malignancy) for patients who failed, or until the date of last contact for all others. Patients who did not attain a complete remission were considered failures at time zero. The duration of continuous complete remission (CCR) is defined as EFS, contingent upon induction of a complete remission. EFS and CCR rates were estimated by the method of Kaplan and Meier and were compared with the Mantel–Haenszel test.[13] All analyses were performed on the basis of 'intent-to-treat'; only patients who remained failure-free were censored on the date of last contact.

Cumulative incidence functions of isolated CNS and CNS relapses were constructed by the method of Kalbfleish and Prentice[14] for patients who achieved complete remission, and the functions were compared with Gray's test.[15] An isolated CNS relapse is defined as one without simultaneous relapse at another site and without another type of failure. CNS relapses included isolated CNS relapses and CNS relapses accompanying another type of relapse or failure. All other failures were considered competing events in the estimation of cumulative incidence functions. The databases for studies 11 and 12 were 'frozen' on 17 November 1999, and that for study 13A on 15 April 2000.

Long-term follow-up

The routine follow-up procedures for long-term survivors at our institution have been described previously.[16] Briefly, after completion of therapy, remission status and late effects are comprehensively assessed at least annually. Patients who are at least 18 years old and remain in remission for at least 10 years after diagnosis are discharged from the institution and followed thereafter by their community physicians. The status of these patients is monitored by a questionnaire mailed annually by the institution's tumor registry. No patients have been lost to follow-up during treatment. When the databases were frozen for analyses, 83.8%, 83.6% and 94.4% of event-free survivors in studies 11, 12 and 13A, respectively, had been seen within 12 months, and only 1.6%, 3.5% and 1.6% had not been contacted for more than 2 years.

Results

Protocol-specific treatment outcome

Of the 358 patients enrolled in study 11, 341 (95.3%) attained a complete remission. The overall EFS rate (±1 s.e.) was 71.8 ± 2.4% at 5 years and 69.3 ± 2.4% at 10 years (Figure 1). The adverse events included 17 induction failures (five deaths from infection, two excessive toxicities and 10 refractory leukemia), 52 isolated or combined hematologic relapses, 20 isolated CNS relapses, one isolated testicular relapse, three other extramedullary relapses, 11 second malignancies (10 acute myeloid leukemia and one Ewing sarcoma) and six deaths in remission (one accident). The median (minimum, maximum) follow-up duration for patients remaining free of adverse events was 12.9 (9.4, 15.4) years. The cumulative risk of isolated CNS relapse at 10 years was 5.9 ± 1.3% and that of CNS relapse 7.3 ± 1.4%. The overall survival was 79.1 ± 2.1% at 5 years and 76.5 ± 2.2% at 10 years. The type of post-remission therapy had no impact on the CCR duration for either the lower risk or higher risk group (Figure 2).

Complete remission was achieved in 182 (96.8%) of the 188 patients in study 12. The overall EFS rate was 67.6 ± 3.4% at 5 years and 61.5 ± 9.0% at 10 years (Figure 3). The adverse events consisted of six induction failures (two deaths from infection and four refractory leukemia), 30 isolated or combined hematologic relapses, 19 isolated CNS relapses, two testicular relapses, one other extramedullary relapse, 11 second malignancies (six brain tumors and five myeloid malignancies) and three deaths in remission (one accident). The median (minimum, maximum) follow-up duration for patients remaining event-free was 8.9 (6.4, 10.8) years. The 10-year cumulative risk of isolated CNS relapse was 10.4 ± 2.3%, compared with 14.9 ± 2.7% for CNS relapse. The overall survival was 83.5 ± 2.7% at 5 years and 79.5 ± 6.9% at 10 years. Individualized therapy improved outcome in patients with B-lineage ALL but not those with T-lineage ALL (Figure 4).

In study 13A, 162 (98.2%) of the 165 patients entered complete remission. The overall 5-year EFS rate was 76.9 ± 3.3% (Figure 5). The adverse events included three induction failures (one death from infection and two refractory leukemia), 23 isolated or combined hematologic relapses, two isolated CNS relapses, 12 second malignancies (11 myeloid malignancies and one osteosarcoma), and two deaths in remission (one accident). The median (minimum, maximum) follow-up of the event-free survivors was 5.7 (4.2, 7.5) years. The 5-year cumulative risk of isolated CNS relapse was 1.2 ± 0.9% and that of CNS relapse 3.7 ± 1.5%. The overall survival was 83.0 ± 2.9% at 5 years.

Treatment results according to presenting features in each era (Tables 2–4)

All consecutive patients in each treatment era were enrolled in a single treatment protocol. Hence, clinical and biologic features of patients in each study were identical to those of overall patients referred to our institution in the corresponding era. Notably, only 50.9% to 52.7% of our B-lineage cases had standard risk leukemia by NCI/Rome criteria (ages 1 to 9 years, leukocytes count $<50 \times 10^9$/l), as compared to 68% of the cases from the Children's Cancer Group and the Pediatric Oncology Group,[17] suggesting a preferential referral of higher risk cases to our center.

Factors consistently associated with a favorable prognosis in these three eras included female sex, age 1 to 9 years, lower leukocyte count, B-lineage phenotype, DNA index of 1.16 to 1.60, and <5% bone marrow blasts on day 15 of remission induction. Importantly, risk classification according to NCI/Rome criteria demonstrated prognostic significance for B-lineage but not T-lineage ALL in each of the three eras.

Discussion

This retrospective analysis demonstrates that contemporary risk-directed therapy can cure at least 70% of children with ALL. Despite the overall improvement in treatment outcome, male sex, infant or adolescent age group, hyperleukocytosis, T-lineage phenotype, nonhyperdiploidy and a delayed or poor early response to treatment consistently conferred an unfavorable prognosis, regardless of Total Therapy study. Given the

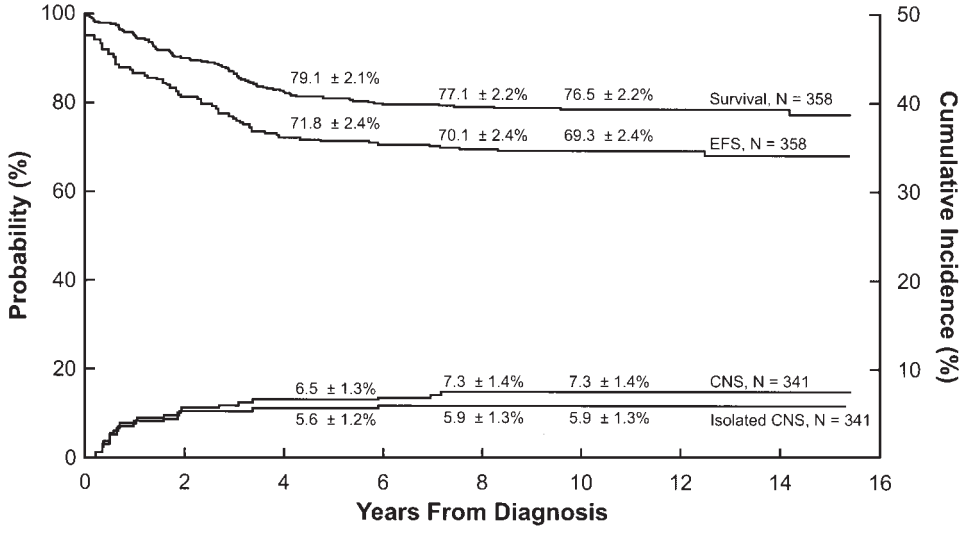

Figure 1 Event-free survival (EFS), survival and cumulative incidence of CNS or isolated CNS relapse in Total Therapy study 11.

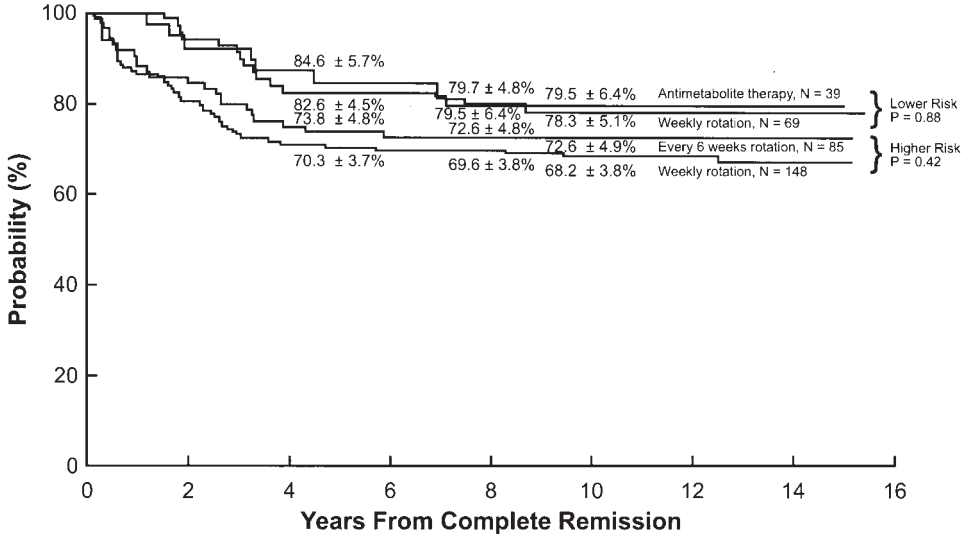

Figure 2 Duration of continuous complete remission according to post-remission therapy in patients with lower risk or higher risk ALL treated on Total Therapy study 11.

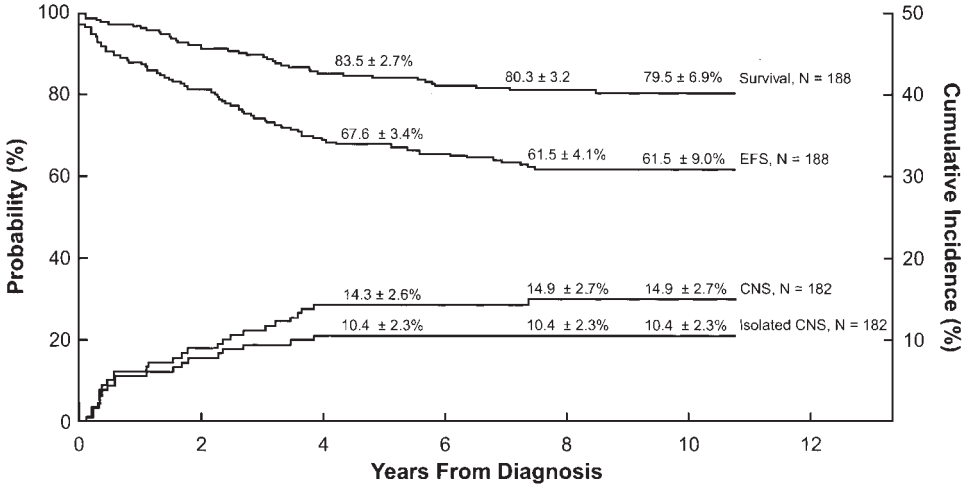

Figure 3 Event-free survival (EFS), survival and cumulative incidence of CNS or isolated CNS relapse in Total Therapy study 12.

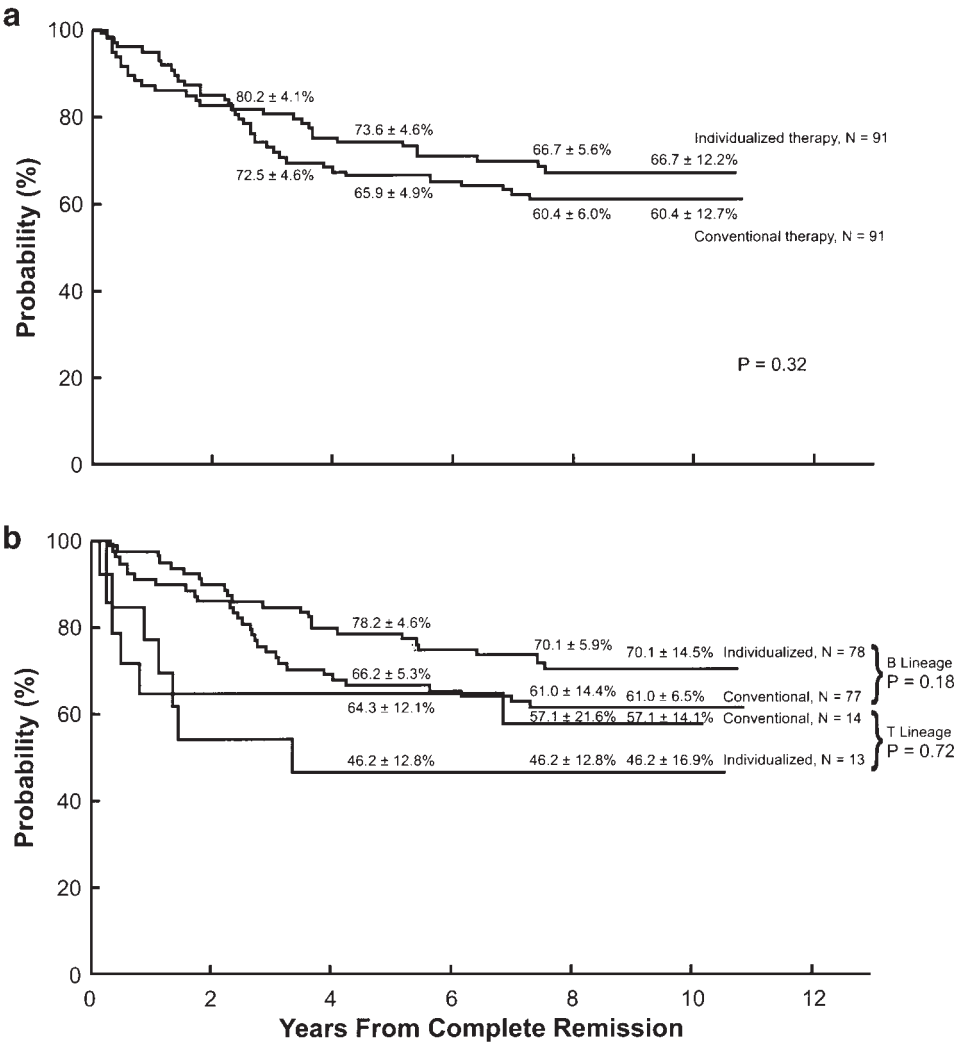

Figure 4 Duration of continuous complete remission according to postremission therapy for all patients in Total Therapy study 12 (a), and for B-lineage or T-lineage cases, respectively (b). Twelve patients with unsuccessful immunophenotyping were included in the B-lineage cases.

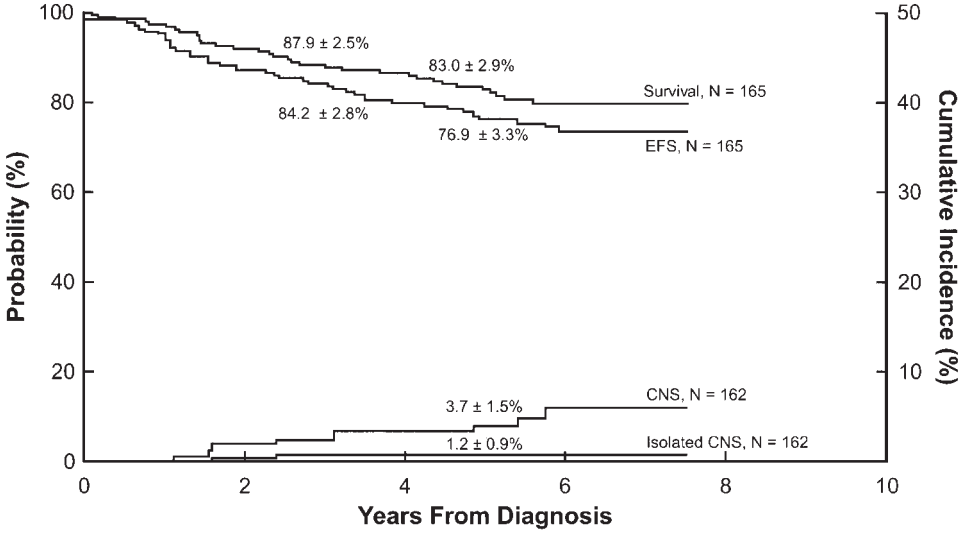

Figure 5 Event-free survival (EFS), survival and cumulative incidence of CNS or isolated CNS relapse in Total Therapy study 13A.

Table 2 Treatment results according to presenting features in patients treated in study 11 (1984–1988)

Feature	*No. of patients (n = 358)*	*EFS (% ± s.e.)*		
		5 year	*8 year*	*10 year*
Non-T lineage				
NCI risk group[a]				
Standard	183 (51.1%)	85.2 ± 2.6	83.1 ± 2.8	82.0 ± 2.8
High	102 (28.5%)	64.7 ± 4.7	63.7 ± 4.7	62.7 ± 4.8
T lineage				
NCI risk group[a]				
Standard	10 (2.8%)	40.0 ± 13.9	40.0 ± 13.9	40.0 ± 15.5
High	52 (14.5%)	51.9 ± 6.8	50.0 ± 6.8	50.0 ± 6.8
Sex				
Male	186 (52.0%)	67.7 ± 3.4	65.1 ± 3.5	64.0 ± 3.5
Female	172 (48.0%)	76.2 ± 3.2	75.6 ± 3.3	75.0 ± 3.3
Age at diagnosis (years)				
<1	11 (3.1%)	36.4 ± 13.0	36.4 ± 13.0	36.4 ± 13.0
1–9	257 (71.8%)	76.3 ± 2.6	74.3 ± 2.7	73.5 ± 2.8
⩾10	90 (25.1%)	63.3 ± 5.0	66.2 ± 5.1	61.1 ± 5.1
Race				
White	314 (87.7%)	72.6 ± 2.5	70.1 ± 2.6	70.1 ± 2.6
Black	43 (12.0%)	65.1 ± 7.1	62.8 ± 7.2	62.8 ± 7.2
Other	1 (0.3%)	100.0	100.00	100.0
WBC ($\times 10^9$/l)				
<10	154 (40.0%)	80.5 ± 3.2	79.2 ± 3.3	78.6 ± 3.3
10–49	109 (30.4%)	75.2 ± 4.1	73.4 ± 4.2	71.6 ± 4.3
50–99	30 (8.4%)	66.7 ± 8.4	63.3 ± 8.6	63.3 ± 8.6
⩾100	65 (18.2%)	47.7 ± 6.1	46.2 ± 6.1	46.2 ± 6.1
Cell lineage				
B	296 (82.7%)	76.4 ± 2.5	74.7 ± 2.5	73.6 ± 2.6
T	62 (17.3%)	50.5 ± 6.3	48.4 ± 6.2	48.4 ± 6.3
CNS leukemia (CNS-3)				
Yes	14 (3.9%)	35.7 ± 11.7	35.7 ± 11.7	35.7 ± 11.7
No	344 (96.1%)	73.3 ± 2.4	71.5 ± 2.4	70.6 ± 2.5
DNA index				
1.16–1.60	66 (18.4%)	87.9 ± 4.0	84.8 ± 4.4	84.8 ± 4.4
Other	292 (81.6%)	68.2 ± 2.7	66.8 ± 2.7	65.8 ± 2.8
t(9;22)				
Present	12 (3.4%)	41.7 ± 13.0	41.7 ± 13.0	41.7 ± 13.0
Absent	346 (96.6%)	72.8 ± 2.4	71.1 ± 2.4	70.2 ± 2.5
t(1;19)				
Present	13 (3.6%)	69.2 ± 12.1	69.2 ± 12.1	69.2 ± 12.8
Absent	345 (96.4%)	71.9 ± 02.4	70.1 ± 2.5	69.3 ± 2.5
Day 15 BMA[b]				
⩾5%	14 (3.9%)	21.4 ± 9.5	21.4 ± 9.5	21.4 ± 9.5
Other	344 (96.1%)	73.8 ± 2.4	72.1 ± 2.4	71.2 ± 2.5

[a]Standard risk group included children 1 to 9 years old with a leukocyte count $<50 \times 10^9$/l.
[b]Bone marrow aspirate.

Table 3 Treatment results according to presenting features in patients treated in study 12 (1988–1991)

Feature	*No. of patients (n = 188)*	*EFS (% ± s.e.)*		
		5 year	*8 year*	*10 year*
Non-T lineage				
NCI risk group[a]				
Standard	99 (52.7%)	78.8 ± 4.1	71.7 ± 5.2	71.7 ± 12.1
High	52 (27.7%)	61.5 ± 6.6	55.1 ± 8.1	55.1 ± 18.5
T lineage				
NCI risk group[a]				
Standard	5 (2.7%)	60.0 ± 19.0	60.0 ± 19.0	60.0 ± 21.9
High	24 (12.8%)	50.0 ± 9.8	45.8 ± 10.7	45.8 ± 16.9
Sex				
Male	102 (54.3%)	62.7 ± 4.8	56.6 ± 5.8	56.6 ± 10.3
Female	86 (45.7%)	73.3 ± 4.7	67.3 ± 5.7	67.3 ± 15.7
Age at diagnosis (years)				
<1	8 (4.3%)	25.0 ± 12.5	25.0 ± 15.3	25.0 ± 21.7
1–9	128 (68.0%)	75.0 ± 3.8	68.6 ± 4.7	68.6 ± 9.9
⩾10	52 (27.7%)	55.8 ± 6.8	49.7 ± 8.1	49.7 ± 17.6
Race				
White	170 (90.4%)	68.8 ± 3.5	62.1 ± 4.3	62.1 ± 9.6
Black	17 (9.1%)	52.9 ± 11.5	52.9 ± 12.1	52.9 ± 21.0
Other	1 (0.5%)	100.0	100.00	100.0
WBC ($\times 10^9$/l)				
<10	88 (46.8%)	75.0 ± 4.6	71.6 ± 5.6	71.6 ± 12.7
10–49	58 (30.9%)	67.2 ± 6.1	56.6 ± 7.3	56.6 ± 15.2
50–99	16 (8.5%)	68.8 ± 11.1	61.9 ± 12.7	61.9 ± 22.1
⩾100	26 (13.8%)	42.3 ± 9.3	38.5 ± 10.1	38.5 ± 17.4
Cell lineage				
B	159 (84.6%)	70.4 ± 3.6	63.9 ± 4.4	63.9 ± 106
T	29 (15.4%)	51.7 ± 9.0	48.3 ± 9.6	48.3 ± 14.2
CNS leukemia (CNS-3)				
Yes	10 (5.3%)	50.0 ± 14.4	50.0 ± 15.8	50.0 ± 35.4
No	178 (94.7%)	68.5 ± 3.5	62.2 ± 4.2	62.2 ± 9.0
DNA index				
1.16–1.60	35 (18.6%)	80.0 ± 6.6	77.0 ± 8.1	77.0 ± 21.3
Other	153 (81.4%)	64.7 ± 3.8	58.8 ± 4.6	58.0 ± 9.4
t(9;22)				
Present	6 (3.2%)	66.7 ± 17.2	66.7 ± 19.2	
Absent	182 (96.8%)	67.6 ± 3.5	61.3 ± 4.2	61.3 ± 9.0
t(1;19)				
Present	7 (3.7%)	71.4 ± 15.6	71.4 ± 15.6	71.4 ± 38.2
Absent	181 (96.3%)	67.4 ± 3.5	61.1 ± 4.2	61.1 ± 9.0
Day 15 BMA[b]				
⩾5%	9 (4.8%)	11.1 ± 7.4	11.1 ± 7.4	11.1 ± 10.5
Other	179 (93.2%)	70.4 ± 3.4	64.0 ± 4.1	64.0 ± 9.3

[a]Standard risk group included children 1 to 9 years old with a leukocyte count $<50 \times 10^9$/l.
[b]Bone marrow aspirate.

overriding importance of treatment as a prognostic factor, it is not surprising that the predictive strength of some factors identified here has either been abolished or reduced in other clinical trials. For example, in studies of the Dana-Farber Cancer Institute/Consortium incorporating extended L-asparaginase therapy, patients with T-lineage ALL fared as well as those with B-lineage leukemia.[18] Similar results have been reported by the Children's Cancer Group,[19] for a study testing augmented therapy that included methotrexate, vincristine and L-asparaginase, and by the Berlin–Frankfurt–Münster group,[20] for a treatment incorporating high-dose methotrexate (5 gm/m^2) into the consolidation phase. The Dana-Farber results for infant ALL also appeared to have been improved by addition of high-dose cytarabine to an already intensive chemotherapy regimen.[21]

In our studies, the 4-year event-free survival rate was 73 ± 19% for patients with Philadelphia chromosome-positive ALL and low presenting leukocyte count who were treated with chemotherapy alone.[12] The treatment modification responsible for this favorable outcome is uncertain, but comparison with other protocols suggests that intensive use of the epipodophyllotoxins played a role. Given this favorable result, one could argue that children with 'good prognosis' Philadelphia chromosome-positive ALL should not receive hematopoietic stem cell transplantation in first remission and instead should be treated only with intensive chemotherapy including epipodophyllotoxins. However, a recent large-scale study show that allogeneic transplantation of bone marrow from an HLA-matched related donor was superior to intensive chemotherapy alone in terms of event-free survival and overall sur-

Table 4 Treatment results according to presenting features in patients treated in study 13A (1991–1994)

Feature	*No. of patients (n = 165)*	*5-year EFS (% ± s.e.)*
Non-T lineage		
NCI risk group[a]		
Standard	84 (50.9%)	88.1 ± 3.6
High	54 (32.7%)	70.4 ± 6.2
T lineage		
NCI risk group[a]		
Standard	2 (1.2%)	50.0 ± 25.0
High	20 (12.1%)	65.0 ± 10.7
Sex		
Male	92 (55.8%)	71.1 ± 4.7
Female	73 (44.2%)	83.5 ± 4.4
Age at diagnosis (years)		
<1	5 (3.0%)	20.0 ± 12.6
1–9	117 (70.9%)	87.1 ± 3.1
⩾10	43 (26.1%)	55.7 ± 7.6
Race		
White	139 (84.3%)	79.1 ± 3.5
Black	23 (13.9%)	69.6 ± 9.3
Other	3 (1.8%)	33.9 ± 19.2
WBC ($\times 10^9$/l)		
<10	71 (43.0%)	78.9 ± 4.8
10–49	50 (30.3%)	77.9 ± 6.0
50–99	20 (12.1%)	90.0 ± 6.7
⩾100	24 (14.5%)	58.3 ± 9.7
Cell lineage		
B	142 (86.1%)	79.5 ± 3.3
T	23 (13.9%)	60.9 ± 10.2
CNS leukemia (CNS-3)		
Yes	6 (3.6%)	50.0 ± 17.7
No	159 (96.4%)	77.9 ± 3.3
DNA index		
1.16–1.60	32 (19.4%)	93.8 ± 4.3
Absent	133 (80.6%)	72.9 ± 3.9
t(9;22)		
Present	6 (3.6%)	33.3 ± 15.7
Absent	159 (96.4%)	78.6 ± 3.3
t(1;19)		
Present	8 (4.8%)	100.0
Absent	157 (95.2%)	75.8 ± 3.8

[a]Standard risk group included children 1 to 9 years old with a leukocyte count $<50 \times 10^9$/l.
The follow-up time has not reached 8 years for many patients on this study.

vival, even among the subset of patients with the best prognosis.[22] Hence, until our result is confirmed, patients with Philadelphia chromosome-positive ALL, regardless of risk status, should be offered the option of allogeneic transplantation if a matched sibling donor is available. It remains to be determined if the clinical potential of the ABL tyrosine kinase inhibitor STI-571 can be extended from chronic myeloid leukemia to ALL with the Philadelphia chromosome.[23] If so, it could revolutionize the management of this genetic variant.

Early treatment response is one of the most important prognostic factors in children with ALL. Most investigators assess this variable by morphologic examination of bone marrow or peripheral blood after 7 or 14 days of remission induction therapy,[24–26] as was done in our studies 11 and 12.[3,27] Recently, we and others have extended the evaluation of early treatment response to the measurement of minimal residual leukemia, using immunologic detection of blast cells with flow cytometry or polymerase chain reaction amplification of clone-specific immunoglobulin and T cell receptor gene rearrangements.[28–30] Patients with high levels of minimal residual leukemia after remission induction or who require extended therapy to attain an 'immunologic' or 'molecular' remission (leukemic involvement of less than 0.01%) were found to have a high risk of relapse, regardless of their presenting features.[31] In study 13A, measurement of the level of minimal residual leukemia was shown to have a significant prognostic impact, even after adjustment for the day-7 treatment response as assessed by the clearance of peripheral blast cells.[32] We have now included measurements of minimal residual leukemia in the risk assignment criteria of our current Total Therapy study. Patients with high levels of residual leukemia after induction therapy will be offered the option of allogeneic hematopoietic stem cell transplantation.

Concern that cranial irradiation can cause neuropsychological deficits, endocrinopathy and occasional brain tumors has led to the reduced use of this treatment modality.[33] Cranial irradiation was administered to two-thirds of the patients in study 11, 30% in study 12 and 17% in study 13A. The isolated CNS relapse rate was high in study 12, especially among patients who were treated with conventional doses of chemotherapy (data not shown). The reason for the increased frequency of CNS relapse in study 12 is not apparent and may be due to the lack of early intensive intrathecal therapy and the relatively low intensity of systemic therapy (eg no pulse therapy with glucocorticord plus vincristine). In studies 11 and 12, the presence of any amount of leukemic cells in the cerebrospinal fluid at diagnosis or iatrogenic introduction of blast cells following a traumatic lumbar puncture was correlated with an increased risk of CNS relapse.[34,35] In study 13A, early intensive intrathecal therapy was administered to these patients as well as those with other presenting features associated with a high risk of CNS relapse (ie leukocyte count of 100×10^9/l or higher, and the presence of the Philadelphia chromosome). Despite the reduced use of cranial irradiation in this study, the CNS relapse rate was negligible, resulting in a higher overall event-free survival rate.[5] Some investigators use craniospinal irradiation to treat patients with CNS leukemia at diagnosis. We suggest that cranial irradiation plus intrathecal chemotherapy, as used in all of our three studies, is sufficient for this group, because none of the 13 patients with CNS leukemia at diagnosis in study 13A has relapsed in the CNS. In fact, in the current Total Therapy study, we are testing the hypothesis that with intensive systemic and intrathecal therapy including the use of dexamethasone, cranial irradiation can be omitted from all (including those with CNS leukemia at diagnosis) but the occasional patient with refractory CNS leukemia.

Results of our randomized treatment aims remain essentially the same with extended follow-up. In study 11, the type or schedule of post-remission therapy did not affect the ultimate outcome of therapy. In study 12, adjusting the dosages of chemotherapy to account for the patient's ability to clear the drugs improved the early treatment outcome in patients with B-lineage ALL, but the long-term result did not attain statistical significance, probably because the small number of patients limited the power of the analysis. In this study, we also found that the dose intensity of 6-mercaptopurine therapy strongly influenced treatment outcome, particularly among patients with a homozygous wild-type thiopurine methyltransferase phenotype.[36] In this regard, increasing dose intensity until neutropenia precludes further chemotherapy may be counterproductive, as this practice lowers overall dose intensity.

Therapy-related second malignancies accounted for a substantial proportion of adverse events in each of the three Total

Therapy studies.[37] In study 11, the frequency of epipodophyllotoxin-induced acute myeloid leukemia was significantly higher in the group of patients randomized to receive weekly doses of etoposide or teniposide than in those receiving the drugs on an every-other-week schedule.[6] The finding of a high frequency of this complication among patients with low thiopurine methyltransferase, and hence high thioguanine nucleotide levels, suggested that antimetabolites could potentiate the leukemogenic effects of the epipodophyllotoxins.[38] In study 12, intensive antimetabolite therapy preceding and during cranial irradiation increased the risk of therapy-induced brain tumors, especially in patients with low activity of thiopurine methyltransferase.[39] These results underscore the importance of pharmacogenetic and pharmacodynamic studies of the leukemic host.[40] Finally, in study 13A, the concomitant use of L-asparaginase appeared to enhance the leukemogenic effects of the epipodophyllotoxins, accounting for a high rate of therapy-induced acute myeloid leukemia.[41] Because patients at high risk of epipodophyllotoxin-induced acute myeloid leukemia cannot be identified with certainty, we now limit the use of these agents to about 10% of the patients with very high risk leukemia who are candidates for allogeneic stem cell transplantation.

Several therapeutic approaches may further advance the cure rate in childhood ALL and are being pursued at this institution and elsewhere. First, therapy is being further intensified in patients who do not attain a molecular remission at the end of remission induction. Until effective specific therapy can be devised, patients at very high risk cases of relapse, including those who fail induction therapy or have a high level of residual leukemia after its completion, as well as those with Philadelphia chromosome-positive ALL, are undergoing allogeneic transplantation following consolidation therapy to maximize reduction of the leukemic cell burden. Ultimately, treatment strategies will probably need to target specific genetic lesions to improve outcome for all children with ALL.

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