

## AUGMENTED POST-INDUCTION THERAPY FOR CHILDREN WITH HIGH-RISK ACUTE LYMPHOBLASTIC LEUKEMIA AND A SLOW RESPONSE TO INITIAL THERAPY

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### ABSTRACT

**Background** Children with high-risk acute lymphoblastic leukemia (ALL) who have a slow response to initial chemotherapy (more than 25 percent blasts in the bone marrow on day 7) have a poor outcome despite intensive therapy. We conducted a randomized trial in which such patients were treated with either an augmented intensive regimen of post-induction chemotherapy or a standard regimen of intensive post-induction chemotherapy.

**Methods** Between January 1991 and June 1995, 311 children with newly diagnosed ALL who were either 1 to 9 years of age with white-cell counts of at least 50,000 per cubic millimeter or 10 years of age or older, had a slow response to initial therapy, and entered remission at the end of induction chemotherapy were randomly assigned to receive standard therapy (156 children) or augmented therapy (155). Those with lymphomatous features were excluded. Event-free survival and overall survival were assessed from the end of induction treatment.

**Results** The outcome at five years was significantly better in the augmented-therapy group than in the standard-therapy group (Kaplan–Meier estimate of event-free survival [ $\pm$ SD]:  $75.0 \pm 3.8$  vs.  $55.0 \pm 4.5$  percent,  $P < 0.001$ ; overall survival:  $78.4 \pm 3.7$  vs.  $66.7 \pm 4.2$  percent,  $P = 0.02$ ). The difference between treatments was most pronounced among patients one to nine years of age, all of whom had white-cell counts of at least 50,000 per cubic millimeter ( $P < 0.001$ ). Risk factors for an adverse event in the entire cohort included a white-cell count of 200,000 per cubic millimeter or higher ( $P = 0.004$ ), race other than black or white ( $P < 0.001$ ), and the presence of a t(9;22) translocation ( $P = 0.007$ ). The toxic effects of augmented therapy were considerable but manageable.

**Conclusions** Augmented post-induction chemotherapy results in an excellent outcome for most patients with high-risk ALL and a slow response to initial therapy. (N Engl J Med 1998;338:1663–71.)

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**I**N children with acute lymphoblastic leukemia (ALL) who are older than one year of age, certain presenting features, such as a white-cell count above 50,000 per cubic millimeter,<sup>1–3</sup> an age of 10 years or older,<sup>4,5</sup> the presence of bulky disease,<sup>1,3,6</sup> T-cell–lineage immunophenotype,<sup>7–9</sup> and various chromosomal translocations,<sup>10–16</sup> carry an increased risk of treatment failure. The outcome for most of these children has improved with the use of

intensive chemotherapy after the induction of remission,<sup>17–22</sup> but approximately 30 percent of such high-risk patients eventually relapse.

Numerous studies have demonstrated that a rapid response to initial chemotherapy is an important prognostic factor in childhood ALL.<sup>17,18,23–28</sup> German investigators observed that patients with fewer than 1000 blasts per cubic millimeter in the peripheral blood after a seven-day course of prednisone had significantly better event-free survival than patients with 1000 or more blasts per cubic millimeter.<sup>17,28,29</sup> Similarly, we reported that children with 25 percent blasts or fewer in the bone marrow on day 7 had a better response to initial chemotherapy (three-year event-free survival, 77 percent) than those with more than 25 percent blasts (three-year event-free survival, 48 percent).<sup>26</sup> In an attempt to improve the outcome for children with a slow response to initial therapy, we developed a strategy of augmented, intensive post-induction chemotherapy that was based on previous successful regimens for ALL.<sup>30–32</sup> This approach appeared promising in a nonrandomized pilot study.<sup>33</sup> We now report on a randomized comparison of augmented therapy with standard intensive post-induction therapy in children with high-risk ALL who entered remission after a slow response to initial therapy.

### METHODS

#### Patients

Children and adolescents with newly diagnosed ALL who were 1 to 9 years of age and had white-cell counts of at least 50,000 per cubic millimeter or who were 10 years of age or older were enrolled between January 1991 and June 1995. Those with lymphomatous features<sup>6</sup> were excluded. Diagnosis was based on morphologic, biochemical, and immunologic features of leukemic

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cells, including lymphoblast morphology as determined by Wright–Giemsa staining, negative staining for myeloperoxidase, and reactivity with monoclonal antibodies to lymphoid differentiation antigens associated with B-cell or T-cell lineage, as described previously.<sup>34</sup> Patients with slow initial responses (>25 percent marrow blasts on day 7) who had entered remission by day 28 were randomly assigned at the end of induction therapy to receive standard or augmented therapy.

#### Treatment Protocol

All patients received identical five-week courses of induction chemotherapy, as previously described.<sup>33</sup> The post-induction regimens are given in Table 1. During the first year of post-induction therapy, the augmented regimen included more vincristine, asparaginase, methotrexate, and dexamethasone than the standard regimen, although the standard regimen included more oral methotrexate, prednisone, and mercaptopurine. Therapy was continued for two years for girls and for three years for boys, beginning with the first interim maintenance period (Table 1)<sup>35</sup> (and unpublished data). Presymptomatic central nervous system therapy consisted of intrathecal methotrexate and cranial radiation. This protocol was approved by the National Cancer Institute and the institutional review boards of the participating institutions. Informed consent was obtained from the patients, their parents, or both, as deemed appropriate, according to Department of Health and Human Services guidelines.

#### Study Design and Statistical Analysis

Balanced block randomization was used to ensure that approximately equal numbers of patients were randomly assigned to each regimen. The study was monitored by an independent data-monitoring committee and followed a monitoring plan that was based on group sequential monitoring boundaries<sup>36</sup> that required analysis of results at six-month intervals for a maximum of 10 analyses. With a target enrollment of 296 randomized patients, we estimated that the study had a power of approximately 81 percent at the final analysis to detect a change in five-year event-free survival from 45 percent to 62 percent or more with a two-sided log-rank test (alpha level, 0.05). The monitoring boundary was crossed in July 1996 (the ninth planned data analysis), and at that time study results were released.

This analysis was performed in December 1997. Similarities between patients in the two groups were assessed with chi-square tests for homogeneity of proportions. Outcome analyses used life-table methods and associated statistics. The primary end point examined was event-free survival from the time of randomization. The events considered were relapse at any site, death during remission, or a second malignant neoplasm, whichever occurred first. Data on patients who had not had an event at the time of the analysis were censored in the analysis of event-free survival at the time of the last contact with them. Life-table estimates were calculated by the Kaplan–Meier procedure, and the standard deviation of the life-table estimate was obtained with Greenwood's formula.<sup>37</sup> The Kaplan–Meier estimates ( $\pm$ SD) are presented for either the first five years or the first three years after randomization, depending on the number of patients in the follow-up. Ninety-five percent confidence intervals can be approximated as the life-table estimates  $\pm 1.96$  SD. The log-rank statistic was used to compare patterns of event-free survival and overall survival in the groups.<sup>38,39</sup> Comparisons of randomized treatment regimens were performed according to the intention-to-treat method. Stratified log-rank tests were also used to adjust for the possible modifying effect of other factors on the comparison of interest.<sup>40</sup> An adjusted Cox regression analysis was used to determine the influence of prognostic factors on the primary treatment effect. Life-table analyses of the effect of isolated central nervous system and marrow relapses on the results with each regimen were compared with the log-rank statistic. Life-table analysis of the relative risk of an adverse event was calculated with the log-rank ratio of observed events to expected events.<sup>41</sup>

## RESULTS

#### Patients

A total of 1136 patients were enrolled. Three patients died before day 7, and marrow was not obtained on day 7 from 15 patients. Of the remaining 1118 patients, 360 (32 percent) had slow responses to initial therapy. Of these, 340 (94 percent) entered remission after induction therapy, 19 did not enter remission after induction therapy, and 1 received modified induction therapy and therefore was deemed ineligible. Of the 340 eligible patients, 317 (93 percent) underwent randomization. A subsequent review revealed that 6 of these patients did not have a slow response; thus, 311 patients were eligible for the study. Of these, 156 were assigned to standard therapy and 155 were assigned to augmented therapy.

The characteristics of the patients in the two groups are shown in Table 2. There were no significant differences between the groups. Most patients were at least 10 years of age, and approximately half had white-cell counts of at least 50,000 per cubic millimeter. Centrally reviewed cytogenetic data on translocations associated with a high risk of an adverse event were available for 91 of the patients: 3 patients had the t(4;11) translocation, 4 had t(1;19), and 7 had t(9;22). Among 209 patients with immunophenotypic data, 87.6 percent had ALL of B-cell lineage.

#### Study Violations

Thirteen patients (seven in the standard-therapy group and six in the augmented-therapy group) received a bone marrow transplant during their first remission but were included in the intention-to-treat analysis. Indications for transplantation included the presence of a t(9;22) translocation (four patients), a white-cell count of more than 200,000 per cubic millimeter (three patients), virus-associated hemophagocytic syndrome (one patient), the presence of myeloid antigen (two patients), and other reasons (three patients). Two patients in the standard-therapy group and one patient in the augmented-therapy group refused cranial radiotherapy. Five patients assigned to augmented therapy did not receive the second cycle of delayed intensification therapy. Major changes in treatment were required for three patients assigned to standard therapy (two patients had fungal infections, and one had an elevation in aminotransferases) and five patients assigned to augmented therapy (three patients had elevations in aminotransferases, one had leukoencephalopathy, and one was not compliant with oral therapy).

#### Outcome of Treatment

At the time the study data were released in July 1996, the four-year event-free survival rate was significantly better among patients in the augmented-therapy group than among those in the standard-therapy

TABLE 1. THE STANDARD-THERAPY AND AUGMENTED-THERAPY REGIMENS.\*

STANDARD THERAPY			AUGMENTED THERAPY		
PHASE	TREATMENT	DOSE	PHASE	TREATMENT	DOSE
<b>Consolidation (5 wk)</b>	Prednisone	7.5 mg/m <sup>2</sup> /day 0; 3.75 mg/m <sup>2</sup> /day days 1, 2	<b>Consolidation (9 wk)</b>	Cyclophosphamide	1000 mg/m <sup>2</sup> /day IV days 0, 28
	Cyclophosphamide	1000 mg/m <sup>2</sup> /day IV days 0, 14		Cytarabine	75 mg/m <sup>2</sup> /day SQ or IV days 1-4, 8-11, 29-32, 36-39
	Mercaptopurine	60 mg/m <sup>2</sup> /day PO days 0-27		Mercaptopurine	60 mg/m <sup>2</sup> /day PO days 0-13, 28-41
	Vincristine	1.5 mg/m <sup>2</sup> /day IV days 14, 21, 42, 49		Vincristine	1.5 mg/m <sup>2</sup> /day IV days 14, 21, 42, 49
	Cytarabine	75 mg/m <sup>2</sup> /day IV days 1-4, 8-11, 15-18, 22-25		Asparaginase	6000 U/m <sup>2</sup> /day IM days 14, 16, 18, 21, 23, 25, 42, 44, 46, 49, 51, 53
	Methotrexate† Radiotherapy‡	IT days 1, 8, 15, 22 Cranial, 1800 cGy Cranial, 2400 cGy, and spinal, 600 cGy		Methotrexate† Radiotherapy‡	IT days 1, 8, 15, 22 Cranial, 1800 cGy Cranial, 2400 cGy, and spinal, 600 cGy Testicular, 2400 cGy
<b>Interim maintenance (8 wk)</b>	Mercaptopurine	60 mg/m <sup>2</sup> /day PO days 0-41	<b>Interim maintenance I (8 wk)</b>	Vincristine	1.5 mg/m <sup>2</sup> /day IV days 0, 10, 20, 30, 40
	Methotrexate	15 mg/m <sup>2</sup> /day PO days 0, 7, 14, 21, 28, 35		Methotrexate	100 mg/m <sup>2</sup> /day IV days 0, 10, 20, 30, 40 (escalate by 50 mg/m <sup>2</sup> /dose)
				Asparaginase	15,000 U/m <sup>2</sup> /day IM days 1, 11, 21, 31, 41
<b>Delayed intensification (7 wk)</b>			<b>Delayed intensification I (8 wk)</b>		
Reinduction (4 wk)	Dexamethasone	10 mg/m <sup>2</sup> /day PO days 0-20, then taper for 7 days	Reinduction (4 wk)	Dexamethasone	10 mg/m <sup>2</sup> /day PO days 0-20, then taper for 7 days
	Vincristine	1.5 mg/m <sup>2</sup> /day IV days 0, 14, 21		Vincristine	1.5 mg/m <sup>2</sup> /day IV days 0, 14, 21
	Doxorubicin	25 mg/m <sup>2</sup> /day IV days 0, 7, 14		Doxorubicin	25 mg/m <sup>2</sup> /day IV days 0, 7, 14
	Asparaginase	6000 U/m <sup>2</sup> /day IM days 3, 5, 7, 10, 12, 14		Asparaginase	6000 U/m <sup>2</sup> /day IM days 3, 5, 7, 10, 12, 14
Reconsolidation (3 wk)	Vincristine	1.5 mg/m <sup>2</sup> /day IV days 42, 49	Reconsolidation (4 wk)	Vincristine	1.5 mg/m <sup>2</sup> /day IV days 42, 49
	Cyclophosphamide	1000 mg/m <sup>2</sup> IV day 28		Cyclophosphamide	1000 mg/m <sup>2</sup> IV day 28
	Thioguanine	60 mg/m <sup>2</sup> /day PO days 28-41		Thioguanine	60 mg/m <sup>2</sup> /day PO days 28-41
	Cytarabine	75 mg/m <sup>2</sup> /day SQ or IV days 29-32, 36-39		Cytarabine	75 mg/m <sup>2</sup> /day SQ or IV days 29-32, 36-39
	Methotrexate†	IT days 29, 36		Methotrexate‡ Asparaginase	IT days 29, 36 6000 U/m <sup>2</sup> /day IM days 42, 44, 46, 49, 51, 53
<b>Maintenance (12 wk)§</b>	Vincristine	1.5 mg/m <sup>2</sup> /day IV days 0, 28, 56	<b>Interim maintenance II (8 wk)</b>	Vincristine	1.5 mg/m <sup>2</sup> /day IV days 0, 10, 20, 30, 40
	Prednisone	40 mg/m <sup>2</sup> /day PO days 0-4, 28-32, 56-60		Methotrexate	100 mg/m <sup>2</sup> /day IV days 0, 10, 20, 30, 40 (escalate by 50 mg/m <sup>2</sup> /dose)
	Mercaptopurine	75 mg/m <sup>2</sup> /day PO days 0-83		Asparaginase	15,000 U/m <sup>2</sup> /day IM days 1, 11, 21, 31, 41
	Methotrexate	20 mg/m <sup>2</sup> /day PO days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77	Methotrexate†	IT days 0, 20, 40	
	Methotrexate†	IT day 0	<b>Delayed intensification II (8 wk)</b>	Same as for delayed intensification I	
		<b>Maintenance (12 wk)§</b>	Vincristine	1.5 mg/m <sup>2</sup> /day IV days 0, 28, 56	
			Prednisone	60 mg/m <sup>2</sup> /day PO days 0-4, 28-32, 56-60	
			Mercaptopurine	75 mg/m <sup>2</sup> /day PO days 0-83	
			Methotrexate	20 mg/m <sup>2</sup> /day PO days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77	
			Methotrexate†	IT day 0	

\*IV denotes intravenously, PO orally, IT intrathecally, SQ subcutaneously, and IM intramuscularly.

†The doses were age-adjusted as follows: age 1 to 1.9 years, 8 mg; age 2 to 2.9 years, 10 mg; age ≥3 years, 12 mg. Patients with central nervous system disease at diagnosis did not receive intrathecal methotrexate on days 15 and 22 of consolidation therapy.

‡During the first two weeks of consolidation therapy, patients without central nervous system disease at diagnosis received 1800 cGy of cranial radiotherapy in 10 fractions; patients with central nervous system disease at diagnosis received 2400 cGy to the cranial midplane in 12 fractions and 600 cGy to the spinal cord in 3 fractions. In the augmented-therapy group, patients with testiculomegaly at diagnosis received 2400 cGy bilateral testicular radiation in 8 fractions.

§The cycles of maintenance therapy were repeated until the total duration of therapy, beginning with the first interim maintenance period, reached two years for girls and three years for boys.

TABLE 2. CHARACTERISTICS OF THE PATIENTS AT DIAGNOSIS.

CHARACTERISTIC*	STANDARD THERAPY (N=156)	AUGMENTED THERAPY (N=155)	P VALUE†	CHARACTERISTIC*	STANDARD THERAPY (N=156)	AUGMENTED THERAPY (N=155)	P VALUE†
	no. (%)				no. (%)		
Age (yr)			0.85	Hemoglobin (g/dl)			0.94
1-9	50 (32.1)	54 (34.8)		1-7.9	82 (52.9)	78 (52.7)	
10-15	73 (46.8)	68 (43.9)		8.0-10.9	52 (33.5)	48 (32.4)	
≥16	33 (21.2)	33 (21.3)		≥11.0	21 (13.5)	22 (14.9)	
White cells (×10 <sup>-3</sup> /mm <sup>3</sup> )			0.53	Platelets (×10 <sup>-3</sup> /mm <sup>3</sup> )			0.23
<50	79 (50.6)	76 (49.0)		1-49	83 (54.2)	81 (54.0)	
50-199	59 (37.8)	66 (42.6)		50-149	41 (26.8)	50 (33.3)	
≥200	18 (11.5)	13 (8.4)		≥150	29 (19.0)	19 (12.7)	
Sex			0.61	CNS disease at diagnosis			0.69
Male	89 (57.1)	83 (53.5)		Yes	3 (1.9)	3 (2.0)	
Female	67 (42.9)	72 (46.5)		No	151 (98.1)	150 (98.0)	
Race			0.55	Morphology§			0.12
White	106 (67.9)	111 (71.6)		L1	121 (77.6)	105 (67.7)	
Black	7 (4.5)	9 (5.8)		Mixed L1/L2 or L2/L1	23 (14.7)	29 (18.7)	
Other	43 (27.6)	35 (22.6)		L2	12 (7.7)	21 (13.5)	
Down's syndrome			0.99	Immunophenotype¶			0.98
Yes	3 (1.9)	4 (2.6)		B-cell lineage	94 (87.0)	89 (88.1)	
No	153 (98.1)	151 (97.4)		T-cell lineage	14 (13.0)	12 (11.9)	
Liver‡			0.25	Karyotypic features			0.32
Normal	97 (62.2)	82 (52.9)		Number			
Moderately enlarged	56 (35.9)	70 (45.2)		Diploid (46)	18 (42.9)	11 (22.4)	
Markedly enlarged	3 (1.9)	3 (1.9)		Pseudodiploid (46)	3 (7.1)	4 (8.2)	
Spleen			0.49	Hypodiploid (<46)	12 (28.6)	19 (38.8)	
Normal	72 (46.2)	62 (40.0)		Hyperdiploid (47-50)	4 (9.5)	5 (10.2)	
Moderately enlarged	83 (53.2)	91 (58.7)		Hyperdiploid (>50)	5 (11.9)	10 (20.4)	
Markedly enlarged	1 (0.6)	2 (1.3)		Translocations			0.66**
Lymph nodes			0.17	t(4;11) present	1 (2.4)	2 (4.1)	
Normal	96 (61.5)	82 (52.9)		t(4;11) absent	41 (97.6)	47 (95.9)	
Moderately enlarged	56 (35.9)	71 (45.8)		t(1;19) present	3 (7.1)	1 (2.0)	
Markedly enlarged	4 (2.6)	2 (1.3)		t(1;19) absent	39 (92.9)	48 (98.0)	
Mediastinal mass			0.78	t(9;22) present	3 (7.1)	4 (8.2)	
Absent	150 (96.2)	149 (96.8)		t(9;22) absent	39 (92.9)	45 (91.8)	
Present	6 (3.8)	5 (3.2)					

\*Because of rounding not all percentages total 100. Percentages were based on the number of patients for whom there were data on the various characteristics. CNS denotes central nervous system.

†The global chi-square test for homogeneity was used.

‡The degree of organomegaly was determined as described by Steinherz et al.<sup>6</sup>

§The French-American-British system of classification was used.

¶Data on the immunophenotype were available for a subgroup of 108 patients in the standard-therapy group and 101 patients in the augmented-therapy group.

||Centrally reviewed and accepted cytogenetic data were available for a subgroup of 91 patients.

\*\*The P value is for the overall comparison for the three translocations.

group (75.4±4.0 vs. 57.2±4.5 percent, P=0.009, adjusted for multiple evaluations of the data). At that time the median follow-up for patients with event-free survival was 31 months (range, 1 to 63). When we reanalyzed the data in December 1997 after an additional follow-up period of approximately 1.5 years, 5-year event-free survival remained significantly better in the augmented-therapy group than in the standard-therapy group (75.0±3.8 vs. 55.0±4.5 percent, P<0.001) (Fig. 1). The median follow-up for patients with event-free survival was 49 months (range, 2 to 82 months). The difference in event-free survival was maintained (P<0.001) when patients who received a bone marrow transplant were censored at the time

of transplantation. Overall survival at five years was also better in the augmented-therapy group than in the standard-therapy group (78.4±3.7 vs. 66.7±4.2 percent, P=0.02).

There were 65 events in the standard-therapy group and 36 events in the augmented-therapy group (Table 3). Isolated marrow relapse was the main cause of treatment failure for both regimens, occurring in 43 patients in the standard-therapy group and 30 patients in the augmented-therapy group (P=0.004 by the log-rank test), whereas central nervous system relapses were more common among patients in the standard-therapy group (8 vs. 0, P=0.002 by the log-rank test). Seven patients in the standard-

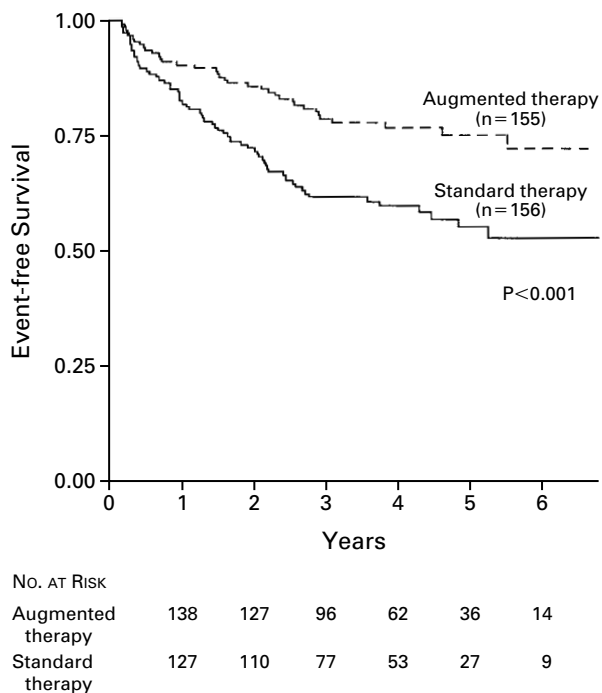
therapy group and four patients in the augmented-therapy group died while in remission.

In all subgroups analyzed, the results were better among patients who received augmented therapy than among those who received standard therapy. The difference in outcome between groups was most pronounced for patients who were one to nine years of age, all of whom had high white-cell counts as dictated by the eligibility criteria, with five-year event-free survival of  $41.7 \pm 8.4$  percent in the standard-therapy group and  $84.6 \pm 5.0$  percent in the augmented-therapy group ( $P < 0.001$ ) (Fig. 2A) and a relative risk of an adverse event in the standard-therapy group of 4.6. For patients who were 10 or more years old with white-cell counts of at least 50,000 per cubic millimeter, the outcome was better after augmented therapy than after standard therapy (three-year event-free survival,  $66.7 \pm 9.7$  vs.  $47.9 \pm 9.7$  percent) (Fig. 2B), with a relative risk of an adverse event of 1.7 in the standard-therapy group ( $P = 0.21$ ). Among patients who were 10 or more years old with white-cell counts below 50,000 per cubic millimeter, the five-year event-free survival rate was  $73.3 \pm 5.7$  percent in the augmented-therapy group and  $66.2 \pm 5.8$  percent in the standard-therapy group (relative risk of an adverse event, 1.26;  $P = 0.45$ ). Among 31 patients with white-cell counts of 200,000 per cubic millimeter or higher, event-free survival was better for those in the augmented-therapy group (relative risk of an adverse event in the standard-therapy group, 2.2;  $P = 0.14$ ).

Augmented therapy improved the outcome for patients with ALL of either B-cell lineage or T-cell lineage. Estimates of five-year event-free survival for patients with B-cell-lineage ALL were  $74.7 \pm 5.1$  percent with augmented therapy and  $52.2 \pm 5.9$  percent with standard therapy ( $P = 0.002$ ). For patients with T-cell-lineage ALL, event-free survival at three years was  $91.7 \pm 8.0$  percent in the augmented-therapy group and  $71.4 \pm 12.1$  percent in the standard-therapy group ( $P = 0.25$ ). Furthermore, the outcome for patients with ALL of T-cell lineage was similar to that for patients with ALL of B-cell lineage, regardless of regimen.

**Prognostic Factors**

An analysis of prognostic factors for the entire cohort of patients indicated that most base-line characteristics did not influence event-free survival. However, a white-cell count of 200,000 per cubic millimeter or higher, race other than black or white, and the presence of a t(9;22) translocation were prognostically important. For patients with white-cell counts of at least 200,000 per cubic millimeter, three-year event-free survival was  $47.4 \pm 9.1$  percent, as compared with  $72.4 \pm 2.7$  percent for those with white-cell counts below 200,000 per cubic millimeter ( $P = 0.004$ ). Patients who were neither black nor white had a significantly increased risk of an adverse

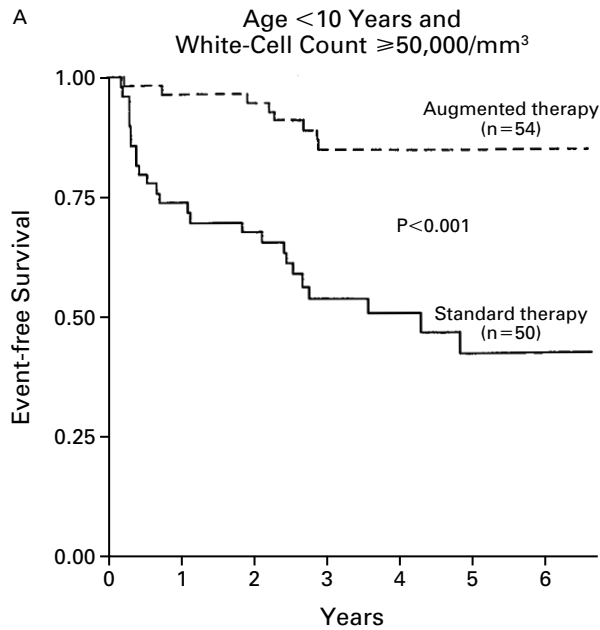


**Figure 1.** Event-free Survival during Five Years of Follow-up in Patients with ALL, According to the Type of Post-Induction Chemotherapy.

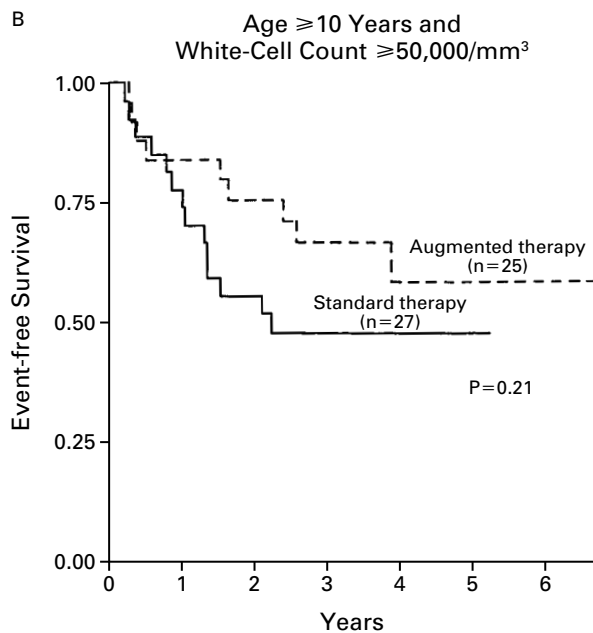
**TABLE 3.** FREQUENCY AND TYPE OF EVENTS AMONG PATIENTS ASSIGNED TO STANDARD OR AUGMENTED THERAPY.

EVENT	STANDARD THERAPY (N=156)	AUGMENTED THERAPY (N=155)
	no. (%)	
Isolated marrow relapse	43 (27.6)	30 (19.4)
Central nervous system relapse	8 (5.1)	0
Marrow and central nervous system relapse	3 (1.9)	1 (0.6)
Testicular relapse	2 (1.3)	0
Marrow and testicular relapse	1 (0.6)	0
Relapse at other sites	1 (0.6)	0
Second cancer	0	1 (0.6)
Death in remission*	7 (4.5)	4 (2.6)
Total	65 (41.7)	36 (23.2)

\*All but two deaths were related to the toxicity of treatment.



No. AT RISK	0	1	2	3	4	5	6
Augmented therapy	52	51	38	24	16	5	
Standard therapy	35	32	20	15	6	3	



No. AT RISK	0	1	2	3	4	5	6
Augmented therapy	21	17	13	6	4	2	
Standard therapy	20	15	9	5	1	0	

**Figure 2.** Event-free Survival during Five Years of Follow-up in Patients with ALL Who Received Standard Therapy or Augmented Therapy, According to Age and White-Cell Count at Diagnosis.

event, as compared with whites or blacks (five-year event-free survival,  $51.2 \pm 6.0$  percent vs.  $69.4 \pm 3.4$  percent;  $P < 0.001$ ). Patients with a  $t(9;22)$  translocation had a significantly increased risk of an adverse event, as compared with those without this translocation (three-year event-free survival,  $28.6 \pm 17.1$  percent vs.  $73.6 \pm 4.8$  percent;  $P = 0.007$ ).

Notably, of the seven patients with the Philadelphia chromosome, two of the three in the standard-therapy group and three of the four in the augmented-therapy group had events. Both patients with the Philadelphia chromosome who survived without an event (one in each group) received a bone marrow transplant while in first remission. A Cox regression analysis with adjustment for these and other common prognostic factors revealed no attenuation of the effect of treatment on the difference in outcome between the augmented-therapy and the standard-therapy groups ( $P = 0.001$ ).

#### Toxic Effects

The toxic effects of the two types of therapy are shown in Table 4. There was a higher frequency of allergic reactions to *Escherichia coli* asparaginase in the augmented-therapy group than in the standard-therapy group (64 vs. 4 reactions). The majority of the patients with allergic reactions (49 and 4, respectively) successfully continued asparaginase therapy after they were switched to erwinia asparaginase or polyethylene glycol asparaginase. Osteonecrosis developed in 20 patients in the augmented-therapy group and in 14 patients in the standard-therapy group; only 1 of these patients was under 10 years of age at the time of diagnosis. Life-table estimates for the occurrence of osteonecrosis at three years were 15.1 percent for the augmented-therapy group and 11.9 percent for the standard-therapy group ( $P = 0.44$ ). No cases had developed after three years of follow-up. The mean total duration of hospitalization was slightly longer for patients in the augmented-therapy group than in the standard-therapy group, primarily because of the additional time needed for the second cycles of interim maintenance and delayed intensification therapy (data not shown).

Three patients in the augmented-therapy group died in remission as a result of toxicity: one died of acute respiratory distress syndrome, one of pulmonary toxicity, and one of *Candida tropicalis* infection; one patient in remission was murdered. Seven patients in the standard-therapy group died in remission. Four of these deaths were due to documented infection: aspergillosis in one patient, clostridium septicemia in one, hepatosplenic candidiasis in one, and infection with an unspecified gram-negative bacteria in one. Of the remaining three deaths, one was due to pulmonary hemorrhage, one was due to acute respiratory distress syndrome after a presumed infection, and one was due to unknown causes.

**TABLE 4.** TOXIC EFFECTS OF STANDARD AND AUGMENTED THERAPY.

TOXIC EFFECT	STANDARD THERAPY (N=156)	AUGMENTED THERAPY (N=155)
	no. (%)	
Allergic reaction to asparaginase		
<i>Escherichia coli</i> asparaginase	4 (2.6)	64 (41.3)
Erwinia asparaginase	0	15 (9.7)*
Polyethylene glycol asparaginase	0	2 (1.3)*
Pancreatitis	2 (1.3)	5 (3.2)
Thrombotic events	0	4 (2.6)
Mucositis	0	38 (24.5)
Seizures	3 (1.9)	5 (3.2)
Leukoencephalopathy	1 (0.6)	2 (1.3)
Osteonecrosis	14 (9.0)	20 (12.9)
Stroke	1 (0.6)	0
Death†	6 (3.8)	3 (1.9)

\*These allergic reactions occurred in patients after they had switched from *E. coli* asparaginase to erwinia asparaginase or polyethylene glycol asparaginase.

†The causes of death are given in the Results section.

## DISCUSSION

We previously reported that among children with high-risk ALL, those with a rapid response to initial therapy (defined as the presence of no more than 25 percent blasts in the marrow on the seventh day of induction chemotherapy) had a better outcome than those with a slow response (more than 25 percent blasts).<sup>24,26,27</sup> Other investigators also reported poor outcomes for patients with a slow response to prednisone or multiagent induction therapy.<sup>17,25,28,29</sup> In this randomized trial of post-induction treatment of patients with a slow response, we found that the outcome with augmented treatment was superior to that with standard treatment (five-year event-free survival, 75 percent vs. 55 percent). In our nonrandomized pilot study of augmented therapy, the four-year event-free survival rate ( $\pm$ SD) was  $70.8 \pm 4.6$  percent.<sup>33</sup> Furthermore, subsequent analysis of the pilot study revealed a six-year event-free survival rate of  $65.4 \pm 4.9$  percent, suggesting that the results of the randomized trial are unlikely to change significantly with longer follow-up. Our results also suggest that the degree of cytoreduction achieved after one to two weeks of induction chemotherapy is a useful indicator of the susceptibility of leukemic cells to chemotherapeutic drugs.

Augmented treatment significantly improved event-free survival overall ( $75.0 \pm 3.8$  percent, as compared with  $55.0 \pm 4.5$  percent in the standard-therapy group). In all subgroups analyzed, augmented therapy resulted in improved event-free survival. The dif-

ference was significant in the subgroup of patients who were one to nine years of age, all of whom had high white-cell counts. There was a trend toward a better outcome among older patients. There was also a trend toward improved outcomes with augmented therapy in patients with ALL of either B-cell lineage or T-cell lineage. This finding is in agreement with our analysis, which demonstrated improved outcome for the entire cohort of children with T-cell-lineage ALL who were treated with Children's Cancer Group protocols between 1989 and 1995.<sup>34</sup> Augmented therapy was ineffective for the seven patients with the Philadelphia chromosome. Five of these seven patients had events, and four of them ultimately died. The two patients who survived without events received a bone marrow transplant while in first remission. These data are consistent with recent data from European studies of children with ALL who have a poor response to initial prednisone therapy.<sup>42</sup>

The toxic effects of augmented therapy have been considerable, but they appear to be manageable. The most common long-term toxic effect was osteonecrosis, which occurred almost exclusively in adolescent patients.

We noted a significantly lower rate of central nervous system relapse in the augmented-therapy group than in the standard-therapy group. Since the patients assigned to each regimen received cranial radiotherapy and intrathecal therapy for presymptomatic treatment of the central nervous system, the benefit observed with augmented therapy may have been due to the use of intensified systemic therapy. Indeed, previous investigators have noted a similar effect with intensive systemic therapy.<sup>43-45</sup>

Although we do not know which components of augmented therapy were responsible for the improved outcome, we surmise that the effect is attributable to the increased dose intensities and prolonged duration of therapy. During the interim maintenance phase in the augmented-therapy regimen, repeated courses of vincristine, intravenous methotrexate, and asparaginase replaced the daily oral mercaptopurine and the weekly oral methotrexate used in the standard-therapy regimen. The augmented regimen also included an additional two weeks of nonmyelosuppressive therapy with vincristine and asparaginase during each consolidation or reconsolidation course and included both a second interim maintenance phase and a second course of delayed intensification.

A recent Children's Cancer Group study of intermediate-risk ALL showed that patients with a slow response had an improved outcome when treated with two courses of delayed intensification rather than one course,<sup>45</sup> suggesting that prolonged therapy was important to the improved outcome with augmented therapy in the current study. We are attempting to distinguish the relative contributions of

early increased dose intensity and a prolonged duration of therapy in a new therapeutic study of children with high-risk ALL.

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## APPENDIX

The following institutions and principal investigators of the Children's Cancer Group participated in the study: Group Operations Center, Arcadia, Calif. — W. Bleyer, A. Khayat, H. Sather, M. Krailo, J. Buckley, D. Stram, R. Sposto; University of Michigan Medical Center, Ann Arbor — R. Hutchinson; University of California Medical Center, San Francisco — K. Matthay; University of Wisconsin Hospital, Madison — P. Gaynon; Children's Hospital and Medical Center, Seattle — R. Chard; Rainbow Babies and Children's Hospital, Cleveland — S. Shurin; Children's National Medical Center, Washington, D.C. — G. Reaman; Children's Hospital of Los Angeles, Los Angeles — J. Ortega; Children's Hospital of Columbus, Columbus, Ohio — F. Ruymann; Columbia Presbyterian College of Physicians and Surgeons, New York — S. Piomelli; Children's Hospital of Pittsburgh, Pittsburgh — J. Mirro; Vanderbilt University School of Medicine, Nashville — J. Lukens; Doernbecher Memorial Hospital for Children, Portland, Oreg. — L. Wolff; University of Minnesota Health Sciences Center, Minneapolis — W. Woods; Children's Hospital of Philadelphia, Philadelphia — A. Meadows; Memorial Sloan-Kettering Cancer Center, New York — P. Steinherz; James Whitcomb Riley Hospital for Children, Indianapolis — P. Breitfeld; University of Utah Medical Center, Salt Lake City — R. O'Brien; University of British Columbia, Vancouver — C. Fryer; Children's Hospital Medical Center, Cincinnati — R. Wells; Harbor-UCLA and Miller Children's Medical Center, Long Beach, Calif. — J. Finklestein; University of California Medical Center, Los Angeles — S. Feig; University of Iowa Hospitals and Clinics, Iowa City — R. Tannous; Children's Hospital of Denver, Denver — L. Odom; Mayo Clinic and Foundation, Rochester, Minn. — G. Gilchrist; Izaak Walton Killam Hospital for Children, Halifax, N.S. — D. Barnard; University of North Carolina, Chapel Hill — J. Wiley; University of Medicine and Dentistry of New Jersey, Camden — M. Donaldson; Children's Mercy Hospital, Kansas City, Mo. — M. Hetherington; University of Nebraska Medical Center, Omaha — P. Coccia; Wyler Children's Hospital, Chicago — J. Nachman; M.D. Anderson Cancer Center, Houston — B. Raney; Princess Margaret Hospital, Perth, Western Australia — D. Baker; New York University Medical Center, New York — A. Rausen; and Children's Hospital of Orange County, Orange, Calif. — M. Cairo.

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