

Augmented Post-Induction Therapy for Children with High-Risk Acute Lymphoblastic Leukemia and a Slow Response to Initial Therapy

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INTRODUCTION

In children with acute lymphoblastic leukemia (ALL) who bear certain presenting features, such as a white cell count above 50,000 per cubic millimeter an age of 10 years or older, the presence of bulky disease, T-cell-lineage immunophenotype and various chromosomal translocations carry an increased risk of treatment failure.¹⁻⁵ The outcome for most of these children has improved with the use of intensive chemotherapy after the induction of

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.

Objective

To compare the effect 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

Between January 2005 and December 2011, 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. 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 ($P = 0.004$). The toxic effects of augmented therapy were considerable but manageable.

Conclusion

Augmented post-induction chemotherapy results in an excellent outcome for most patients with high-risk ALL and a slow response to initial therapy.

KEY WORDS

Augmented post induction therapy, leukemia

remission, but approximately 30 percent of such high-risk patients eventually relapse.⁵⁻⁸

Numerous studies have demonstrated that a rapid response to initial chemotherapy is an important prognostic factor in childhood ALL.⁶⁻⁹ German investigators observed that patients with fewer than 1000 blasts per cubic millimeter in the peripheral blood after a seven-day

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

Figure 1. The standard therapy and augmented therapy regimen.

course of prednisone had significantly better event free survival than patients with 1000 or more blasts per cubic millimeter.^{10,11} Similarly, it is reported that children with 25% blasts or fewer in the bone marrow on day seven had a better response to initial chemotherapy (three-year event-free survival, 77%) than those with more than 25% blasts

(three-year event-free survival, 48%).¹¹ In an attempt to improve the outcome for children with a slow response to initial therapy, we follow a strategy of augmented, intensive post-induction chemotherapy that was based on previous successful regimens for ALL.^{6,12,13} This approach appeared promising in a nonrandomized pilot study. 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 with newly diagnosed ALL who were one to nine 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 2005 and December 2011. Those with lymphomatous features were excluded. Diagnosis was based on morphologic, biochemical, and immunologic features of leukemic 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. Patients with slow initial responses (more than 25% marrow blasts on day seven) 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, with UK-ALLX1 protocol. The post induction regimens are with Standard therapy and Augmented Berlin Frankfurt Munster therapy given (Fig 1).^{14,15} Therapy was continued for two years for girls and for three years for boys, beginning with the first interim maintenance period (Fig 1). Pre-symptomatic central nervous system therapy consisted of intrathecal methotrexate and cranial radiation. Informed consent was obtained from the patients, their parents, or both, as deemed appropriate, according to rules of the University.

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 that required analysis of results at six month intervals for a maximum of 10 analyses.¹⁶ 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 % to 62 % or more with a two sided log rank test (alpha level, 0.05).

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, which ever 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 last contact with them. Life table estimates were calculated by Kaplan–Meier procedure, and the standard deviation of the life table estimate was obtained with Greenwood’s formula.¹⁷ 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 follow up. Ninety five percent confidence intervals can be approximated as the life table estimates ± 1.96 SD. The log rank statistic was used to compare patterns of event free survival and overall survival in the groups.^{18,19} 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.²⁰ 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.²¹

RESULTS

Patients

A total of 1136 patients were enrolled. Three patients died before day seven, and marrow was not obtained on day seven from 15 patients. Of the remaining 1118 patients, 360 (32%) had slow responses to initial therapy. Of these,

Table 1. Characteristics of the patients at diagnosis.

CHARACTERISTIC	STANDARD THERAPY (N=156) no. (%)	AUGMENTED THERAPY (N=155) no. (%)	P VALUE	CHARACTERISTIC
Age (years)			0.85	Hemoglobin (g/dl)
1-9	50 (32.1)	54 (34.8)		1-7.9
10-15	73 (46.8)	68 (43.9)		8.0-10.9
≥ 16	33 (21.2)	33 (21.3)		≥ 11.0
White cells ($\times 10^{-3}/\text{mm}^3$)			0.53	Platelets ($\times 10^{-3}/\text{mm}^3$)
< 50	79 (50.6)	76 (49.0)		1-49
50-199	59 (37.8)	66 (42.6)		50-149
≥ 200	18 (11.5)	13 (8.4)		≥ 150
Sex			0.61	CNS disease at diagnosis
Male	89 (57.1)	83 (53.5)		Yes
Female				

340 (94%) entered remission after induction therapy, 19 did not enter remission after induction therapy, and one received modified induction therapy and therefore was deemed ineligible. Of the 340 eligible patients, 317 (93%) underwent randomization. A subsequent review revealed that six 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 1. 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. Among 209 patients with immunophenotypic data, 87.6% had ALL of B cell lineage.

Outcome of Treatment

The four year event free survival rate was significantly better among patients in augmented therapy group than among those in standard therapy group (75.4±4.0 vs. 57.2±4.5%, 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). After an additional follow up period of approximately 1.5 years, five 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 2). 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 2). 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±8.4 % in the standard therapy group and 84.6±5.0 % in the augmented therapy group (P<0.001) (Figure 3) and a relative risk of an adverse event in the standard therapy group of 4.6. For patients who

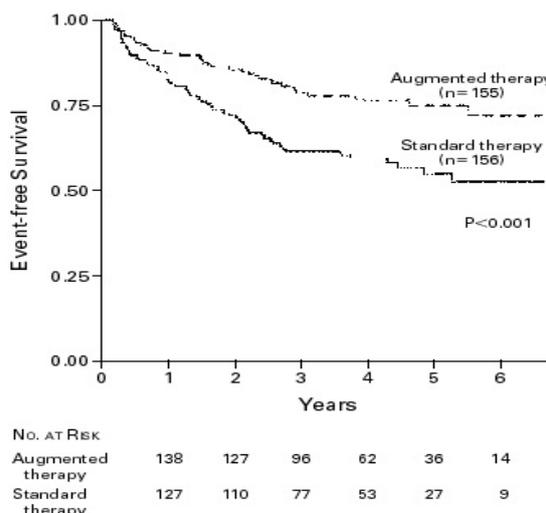


Figure 2. Event free Survival during Five Years of Follow up in Patients with ALL, According to the Type of Post Induction Chemotherapy.

Table 2. Frequency and type of events among patients assigned to standard or augmented therapy.

Event	Standard Therapy (N=156) n (%)	Augmented Therapy (n=155) n (%)
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

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±9.7 vs. 47.9±9.7%) (Figure 3), 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±5.7% in the augmented therapy group and 66.2±5.8% 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 the five year event free survival rate was 73.3±5.7% in the augmented therapy group and 66.2±5.8% 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

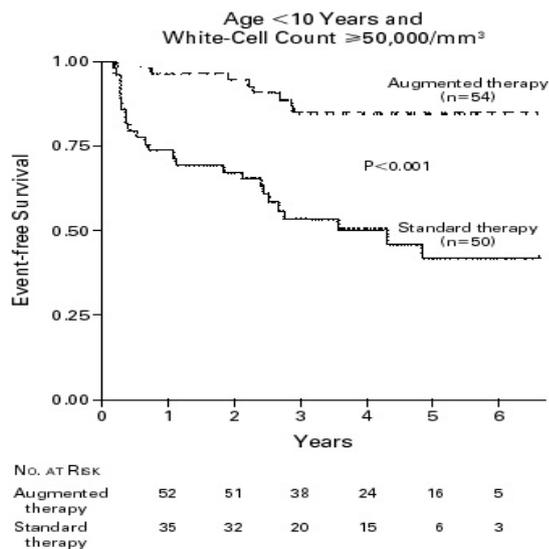


Figure 3. Event free Survival during Five Years of Follow up in Patients with ALL Who Received Standard Therapy or Augmented Therapy, According to Age and White Cell Count at Diagnosis.

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 ± 5.1 percent with augmented therapy and 52.2 ± 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 ± 8.0 percent in the augmented therapy group and 71.4 ± 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 $47.4 \pm 9.1\%$, as compared with $72.4 \pm 2.7\%$ for those with white cell counts below 200,000 per cubic millimeter ($P=0.004$). 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 3. 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). Osteonecrosis developed in 20 patients in the augmented therapy group and in 14 patients in the standard

Table 3. Toxic Effects of standard and augmented therapy.

Toxic Effect	Standard Therapy (N=156) n(%)	Augmented Therapy (N=155) n(%)
Allergic reaction to asparaginase		
<i>Escherichia coli</i> asparaginase	4 (2.6)	64 (41.3)
<i>Erwinia</i> 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* or polyethylene glycol asparaginase.

[†]The causes of death are given in results.

therapy group; only one 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% for the augmented therapy group and 11.9% 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 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.

DISCUSSION

It previously was 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 % 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).^{9,11,22} Other investigators also

reported poor outcomes for patients with a slow response to prednisone or multiagent induction therapy.^{6,10,15,23} 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% vs. 55%). In our nonrandomized pilot study of augmented therapy, the four year event free survival rate (\pm SD) was 70.8 \pm 4.6%.¹⁴ Furthermore, subsequent analysis of the pilot study revealed a six year event free survival rate of 65.4 \pm 4.9%, 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.^{10,15}

Augmented treatment significantly improved event free survival overall (75.0 \pm 3.8%, as compared with 55.0 \pm 4.5% in the standard therapy group). In all subgroups analyzed, augmented therapy resulted in improved event free survival. The difference 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 1995.²⁴ 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.²⁵

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 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.²⁶⁻²⁸

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, suggesting that prolonged therapy was important to the improved outcome with augmented therapy in the current study.²⁸ 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 risks ALL.

CONCLUSION

Augmented post-induction chemotherapy results in an excellent outcome for most patients with high-risk ALL

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