Journal of Korean Medical Science
Vol 6, No. 4, 348-354 December 1991

Therapeutic Results and Prognostic Predictors of Childhood Acute Lymphoblastic Leukemia: Cox Regression Analysis

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Determining the current status of therapeutic results of acute lymphoblastic leukemia (ALL), and identifying the important clinical predictors of survival and relapse are essential for establishing therapeutic strategies. Sixty-two children with ALL who were admitted to Chonnam University Hospital from January 1983 to June 1991 were studied. With a mean follow-up period of 53.7 months, the overall 5-year survival rate (5YSR) was 46.1%. The overall rate of 5-year event-free survival (EFS) was 25.4% and significantly differed between risk groups: 48.7% for standard, 16.3% for high, and 12.5% for very high ($p<.05$). Overall 4-year survival after initial relapse was 34.2% and there was no significant difference in survival between those who relapsed during maintenance therapy and those who relapsed after completing maintenance. The Cox proportional hazards model identified central nervous system (CNS) irradiation ($P<0.001$) as having the most important influence upon EFS, followed by serum alanine aminotransferase level, platelet level, and age. On the other hand, CNS leukemia at diagnosis, followed by mediastinal mass, and hemoglobin level were found to be the most important prognostic predictors for relapse. On the basis that present results differ from those of developed countries, we suggest the necessity of a nation-wide cohort study to delineate the characteristics of Korean ALL in children, to make our own protocols, and ultimately to improve the therapeutic outcome.

Key Words: *ALL, Survival, Relapse, Prognostic predictor, Korea, Cox proportional hazards model*

INTRODUCTION

More than 50% of children with acute lymphoblastic leukemia (ALL) in developed countries now achieve prolonged event-free survival (EFS: >5 years from diagnosis) because of the advancement in modern clinical oncology (Eden et al, 1991; Poplack, 1989). In Korea, however, because of numerous disadvantages including: lack of insurance coverage, poor supportive systems in blood banks and laboratories, uncooperative social understanding, and a shortage of experienced oncologists, as well as because of possible differences in pharmacokinetics from those of Caucasians in handling chemotherapeutic agents, such a high rate of survival has not been achieved. Moreover, we havy only a few reports evaluating therapeutic outcome in Korea because we don't have an established protocol of our own (Cho and Hwang, 1986). Also, few studies of prognostic factors predicting survival and relapse, especially multivariate analysis incorporating life-table concept, are available yet. Thus, for a better understanding of the characteristics of Korean ALL, this study was designed to determine the current status of therapeutic results and to discover the important clinical predictors of survival and relapse by Cox regression analysis.

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*This study was supported by the clinical research fund of the Ministry of Education (1991)

PATIENTS AND METHODS

During the period of eight and a half years from

January 1983 through June 1991, sixty-two children having ALL who were newly diagnosed and treated at the Department of Pediatrics, Chonnam University Hospital, were enrolled in this study. Table 1 summarizes the characteristics of the patients and the variables of possible prognostic implication. The patients were divided into 3 risk categories according to the evaluation of risk factors suggested by Nishimura (1981) until 1989, or by Oda et al. (1989) since then.

As a mainstay regimen to induce remission, vincristine and prednisolone (VP) were administered in 48 patients with or without addition of daunomycin (VPD) or L-asparaginase (VPL). Either irradiation of 18-24 cGy plus intrathecal methotrexate (MTX), or a combination of intrathecal MTX, ara-C, and hydrocortisone was given for the prophylaxis of the CNS disease. Maintenance with daily 6-mercaptopurine (6-MP) and weekly MTX was superimposed with monthly intensification with VP. For the patients in higher risk groups, modified LSA_2L_2 protocol (n=5) (CCG-123B, 1982), modified BFM (n=5) (CCG-105A, 1983), or addition of aclacinon to the VPL (n=4) (Oda et al., 1989) was administered.

For estimating survival functions the Kaplan-Meier method was used (Kaplan and Meier, 1957). Overall survival and EFS (time until relapse or death) were evaluated as of 30 June 1991. Patients who died during remission induction phase were counted as having an event in month 1. Mean duration of observation was 53.7 months (range 1-101, SE=6.5). The differences in the survival curves among the risk groups were compared.

Sixteen different variables were evaluated by univariate analysis, and multivariate method using stepwise logistic regression as well as the Cox proportional hazards model (Cox, 1972). The Mantel-Cox test was used to detect signficant differences among groups (Mantel, 1966). A statistical analysis was performed using the BMDP statistical package (Dixon et al., 1988).

RESULTS

Sixty-two patients with childhood ALL were classified into 3 risk groups (standard, 18; high, 18; very high, 26). Eight failed to achieve remission, making the overall remission rate 87.1% whereas it was higher in the standard risk group with 94.4%, and 84.1% for the rest.

Fig. 1 shows the Kaplan-Meier curves indicating the overall 5-year survival rate (5YSR) of 46.1%, and 5YEFS of 25.4%. Fig. 2 compares the 5YSR of the three groups, revealing 64.9% for the standard, 31.6% for the high, and 46.0% for the very high risk group. Fig. 3 shows 5YEFS of 48.7% for the standard, 16.3% for the high, and 12.5% for the very high risk group, indicating significant differences between them ($p<.05$).

Twenty-three patients (42.6%) out of fifty-four who

Table 1. Patients Characteristics and Suggested Prognostic Variables

1. Sex	:	39 males; 23 females
2. Age	:	<2yr, 4; 2-10yr, 38; >10yr, 20
3. WBC ($\times 10^3/mm^3$)	:	<5, 18; 5-10, 9; 10-50, 20; 50-100, 6; >100, 9
4. Blast % in PB smear	:	0, 13; 0-50, 23; >50, 26
5. Hemoglobin (g/dl)	:	<8, 45; >8, 17
6. Platelet ($\times 10^4/mm^3$)	:	<4, 25; 4-10, 27; >10, 10
7. FAB blast morphology	:	L1, 44; L2 or L3, 18
8. Serum ALT level	:	normal, 49; abnormal, 13
9. Serum LDH (U/ml)	:	<500, 24; 500-1000, 17; >1000, 21
10. CNS leukemia at Dx	:	(+), 5; (−), 57
11. CNS irradiation	:	done 46; not done, 16
12. Mediastinal mass	:	(+), 5; (−), 57
13. Liver (cm palpable)	:	0, 7; 0-5, 42; 5-10, 11; >10, 0
14. Spleen (cm palpable)	:	0, 27; 0-5, 25; 5-10, 7; >10, 3
15. Node enlargement	:	<2cm, 52; >=2cm, 10
16. Location	:	urban, 38; rural, 24

Numbers following the colon indicate the number of cases

WBC: white blood cell count; PB: peripheral blood; Dx: diagnosis

FAB: French-American-British; ALT: alanine aminotransferase;

LDH: lactate dehydrogenase; CNS: central nervous system

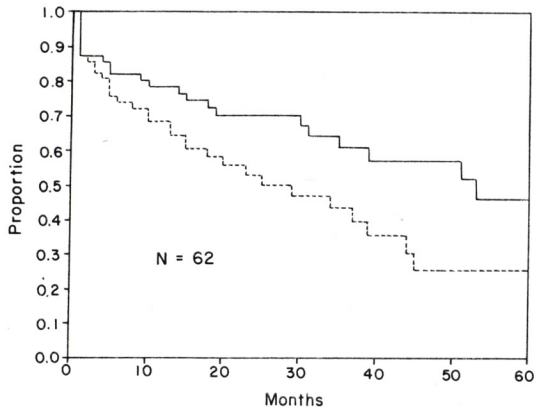

Fig. 1. Kaplan-Meier curves for overall survival (——) and event-free survival (------) in children with acute lymphoblastic leukemia.

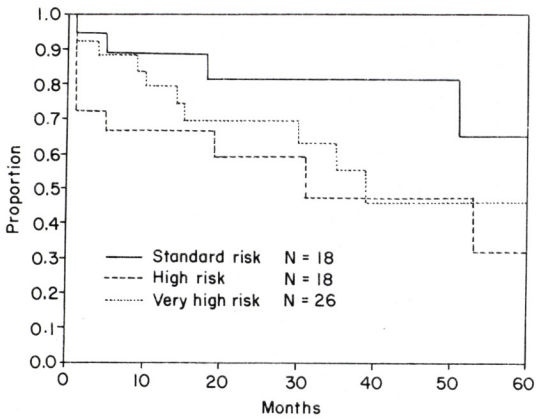

Fig. 2. Survival curves stratified into three risk groups.

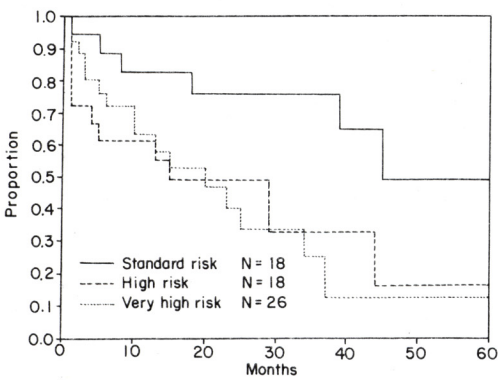

Fig. 3. Event-free survival curves according to three risk groups. ($p < .05$ by Mantel Cox test)

achieved remission had one or more relapses in bone marrow, CNS, testis, or combined sites. Relapses occuring at different sites within 30 days of each other were considered to be combined. The overall survival curve after initial relapse as well as survival after relapse according to whether relapse occurred during maintenance chemotherapy (on therapy) or after its discontinuation (off therapy) was plotted in Fig. 4. The mean duration of observation after initial relapse was 2.8 months (SE = 4.9 mo). The 4YSR was 34.2% and showed no difference between those relapsed on therapy and off therapy. Survival distributions after relapse at each site did not differ (Fig. 5).

To find out the factors affecting EFS, various statistical

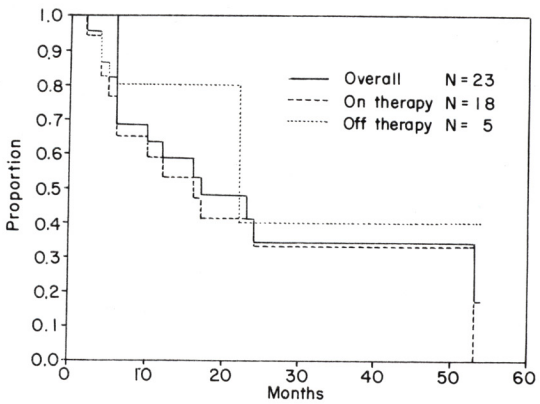

Fig. 4. Overall survival curve after relapse (——). Comparison of survival curves of patient with relapse on maintenance chemotherapy (- - - -) and patient with relapse after cessation of maintenance (------).

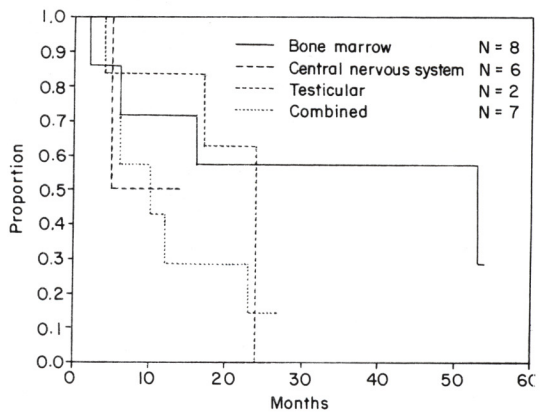

Fig. 5. Comparison of survival curves after relapse according to sites of relapse.

analyses were applied and the results were presented in Table 2. The range of α error were expanded as less than 0.1 because this study was designed to define the relative importance of prognostic factors. Serum alanine aminotransferase (ALT) level and location (urban area had a more favorable prognosis) were identified as having prognostic value in univariate analysis. The logistic regression analysis regarded the same two variables in univariate analysis as the most important independent factors. However, Cox regression analysis ranked CNS irradiation (χ^2, 11.0; $P<.001$) first in relative importance in predicting EFS, followed by serum ALT level, platelet level, and age in that order.

Table 3 summarizes the variables predicting relapse. By univariate analysis, sex (girls had a more favorable prognosis) ranked fourth after location, CNS irradiation, and serum ALT level. Initial WBC count (χ^2, 12.2; $P<.05$) and the percentage of blasts in peripheral blood were identified as the most significant factors by logistic regression analysis. Using the Cox model, CNS leukemia at diagnosis, followed by mediastinal mass, and hemoglobin level were found to have unfavorable influences upon relapse.

Table 2. Relative Importance of Factors Predicting Event-Free Survival

Prognostic Variable	Regression Coefficient (β)	Improvement χ^2 Value	Significance Level (P)
Univariate analysis			
Serum ALT level	—	10.339	<.001
Location	—	4.045	.044
CNS irradiation	—	3,539	.060
Logistic regression analysis			
Serum ALT level	—	10.944	<.001
Location	—	3.726	.054
Cox proportional hazards model			
CNS irradiation	−1.7048	11.010	<.001
Serum ALT level	−1.3265	3.482	.062
Platelet level	−0.4621	3.220	.073
Age	0.6701	3.142	.076

Enter limit: $p<.1$; Remove limit: $p>.15$
β values are shown only for Cox model

Table 3. Relative Importance of Factors Predicting Relapse

Prognostic Variable	Regression Coefficient (β)	Improvement χ^2 Value	Significance Level (P)
Univariate analysis			
Location	—	8.004	.005
CNS irradiation	—	7.242	.007
Serum ALT level	—	4.251	.039
Sex	—	3.079	.079
Logistic regression analysis			
WBC	—	12.227	.016
Blast percent in PB smear	—	8.258	.016
Cox proportional hazards model			
CNS leukemia at diagnosis	2.4923	3.923	.048
Mediastinal mass	1.1820	2.898	.089
Hemoglobin level	−0.7945	2.715	.099

Enter limit: $p<.1$; Remove limit: $p>.15$
β values are shown only for Cox model

DISCUSSION

Although the aim of treatment is the complete cure of all children with ALL, a significant proportion of patients especially those who relapse or who do not achieve remission succumb, in spite of dramatic advances in treatment. Moreover, the current status of outcome in developing countries lags far behind the results in developed countries.

Achievement of complete remission is a sine qua non for a chance of survival. The rate of remission induction was improved to approximately 95% with VP, and L-asparaginase or anthracyclines, but patients with increased risk gained remission less frequently than those with standard risk (88% vs 94%) (Aur et al., 1978; Freeman et al., 1983). The induction rate of 84.1% for increased risk patients found in this study was comparable to others, but remains to be improved by more intensive treatment and better supportive care. The long-term overall EFS has been reported to be about 60%, but those patients with increased risks, especially those with a very high initial leukocyte count, less than 1 year of age, L_2 or L_3 morphology, or lymphomatous features have only a 20-40 percent chance of EFS (Bleyer et al., 1986; Hammond et al., 1987; Miller et al., 1981; Poplack, 1989). Not only the poor facilities and economic support, but also the relatively high proportion of increased risk patients (44/62 = 70.9%) and possibly the relatively small number studied may have contributed to the poor outcome of 25.4% of EFS in this study.

Relapses in marrow and other sites portend poor prognosis for most patients. For bone marrow relapse, one of the important predictors affecting the eventual outcome for children who achieve a second remission is the length of previous remission (Butturine et al., 1987). Also, patients relapsing after completion of maintenance chemotherapy have a better chance both of achieving and maintaining a prolonged second remission than do those relapsing while receiving chemotherapy (Bleyer et al., 1986). Thus, approximately 10-25% of patients who relapse on therapy and up to one-third of patients who relapse after elective cessation of therapy can be expected to go into prolonged second remission by aggressive chemotherapy (Bleyer et al., 1986; Butturine et al., 1987). But in this study, we had too small number of patients to confirm these results.

Certain clinical and laboratory features exhibited at diagnosis are known to have prognostic value for inducing remission or survival (Henderson et al., 1990; Miller et al., 1983; Poplack, 1989). We used the Cox proportional hazards model for assessing prognostic factors. This multivariate analysis method is superior to stepwise logistic regression in assessing biomedical data, because it incorporates the function of time. Hammond et al. (1987) in the Childrens Cancer Study Group reviewed prognostic factors for EFS by multivariate analysis, revealing that the initial leukocyte count, sex, presence of mediastinal mass, day-14 marrow response, age, platelet count, hepatomegaly, and FAB morphologic subtype had great prognostic importance in decreasing order of significance. Sullivan et al. (1982) reported that CNS irradiation plus intrathecal MTX as a method of CNS prophylaxis demonstrated no difference in the overall complete remission rate or incidence of CNS relapse from the repetitive use of intrathecal drug combinations (MTX, ara-C, and hydrocortisone). On the contrary, our present study ranked CNS irradiation first in predicting EFS, although it is not a "front-end" factor. Further study may be needed to clarify this discrepancy. The poor outcome of patients living in rural area could be partly explained by the delay of access to medical services, as well as by relatively poor economic conditions and nutrition. CNS leukemia at diagnosis, and factors reflecting high leukemic cell burden such as high initial WBC count and mediastinal mass were significant variables in predicting relapse.

Though unavailable in this study, immunophenotype, cytogenetics, and day-14 marrow response were known to have significant prognostic importance (Henderson et al., 1990; Miller et al., 1989; Poplack, 1989). Because the predictive value of most prognostic factors except male sex and possibly older age lose their significance in patients in complete remission for 2 years (Sather et alk., 1981), more aggressive combination chemotherapy or bone marrow transplantation (BMT) at first complete remission for patients with very unfavorable prognostic factors should be considered to reduce early relapse associated treatment failure (Butturine et al., 1987). Also, for those who relapse, improved therapeutic modality, including intensive chemotherapy, BMT, and recently developed peripheral blood stem cell auto transplantation should be available before the aim of a complete cure for leukemia can come true (Kessinger and Armitage, 1991; Rivera et al., 1986; Watanabe et al., 1989).

Having the present results showing a relatively poor survival rate and a high proportion of patients with increased risk, along with different prognostic predictors from other studies from developed countries, we suggest the necessity of a nation-wide collaborative cohort study with a much larger sample size comprising other important variables such as cytogenetics, immunophenotype, and day-14 marrow response and

other factors like pharmacokinetics, and side effects of chemotherapeutics, to help us understand the biology and characteristics of Korean ALL. This may contribute to the establishment of a Korean protocol and, of strategies of tailoring therapy according to "risk" factors in order to ultimately obtain a better survival rate of childhood ALL in Korea.

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