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Prognostic Evaluation of Acute Lymphoblastic Leukemia by Immunologic Markers

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=**Abstract**=Leukemic blasts from 128 consecutive patients (68 children and 60 adults) with acute lymphoblastic leukemia(ALL) were tested in each case for the following surface markers: sheep erythrocyte receptor(E-R), T10 antigen(T10), surface membrane immunoglobulin(SmIg) and common ALL antigen(CALLA). A clear distinction of 5 subgroups of patients with ALL was possible: (1) common null-cell or cALL(CALLA+) in 47 patients; (2) intermediate-cell or c/T ALL (CALLA+, T10+) in 29 patients; (3) T-cell or T-ALL(E-R+) in 21 patients; (4) null-cell or null ALL in 29 patients; and (5) B-cell or B-ALL (SmIg+) in 2 patients. Particular emphasis was put on the subgroup with T10 expression together with CALLA. An analysis of clinical data at presentation revealed significant differences for white-cell count, age distribution and organomegaly between cALL and c/T ALL. There were also significant differences in freuqencies of remission induction and survival rate between cALL and c/T ALL. T10 positivity is a poor prognostic factor in common ALL. We evaluated prognostic significance of the markers by univariate and multivariate survival analysis and concluded that a combined use of the markers is essential to reach a precise diagnosis of subgroups of ALL with different biologic and prognostic characteristics.

Key words: ***Acute lymphoblastic leukemia, Prognosis, OKT10, c/T ALL***

INTRODUCTION

Immunologic studies using T- and B-lymphocyte markers have establshed the classification of three groups of acute lymphoblastic leukemia(ALL): one group with T-cell membrane phenotype, one minor group of B-cell origin, and a major group without any conventional markers of lymphoid cells (Borella and Sen 1973). The latter group, which was mostly recognized per exclusionem and called null cell or non-T, non-B ALL, was positively identified by the demonstration of a specific antigen, common ALL antigen(CALLA) which was originally defined by antisera produced in rabbits by immunization with surface membrane immunoglobulin(SmIg)-negative, receptor for sheep erythrocyte(E rosette)-negative ALL cells(Greaves *et al.* 1975). Nevertheless, the origin of the malignant cells in this group, which includes more than 70% of the ALL cases, remained questionable. The demonstration of Ia-like determinants that are expressed by B cells, but also by some cells of the myeloid series and a subset of T cells, left the question as to the true cellular origin of non-T, non-B ALL unsettled. B cell markers identified with monoclonal antibodies and immunoglobulin gene rearrangement have suggested recently that the majority of non-T, non-B ALL are in fact derived from cells at the early stage of B-cell differentiation(Balch *et al.* 1979; Nadler *et al.* 1981; Nadler *et al.* 1983; Pullen *et al.* 1984).

Several findings, however, suggest that in many patients non-T, non-B ALL cells may represent T-cell progenitors, for example, the demonstration of a high content of the leukemic cells for a peculiar DNA polymerase, the terminal deoxynucleotidyl transferase(TdT). Investigation with anti-T cell sera has so far disclosed reactions with non-T, non-B

ALL cells that did not form E rosettes(Kersey *et al.* 1973; Brouet *et al.* 1976; Thiel *et al.* 1979). Thus cells of non-T, non-B ALL may be early ones in T lineage or, more often, in B lineage.

There is a great deal of heterogeneity in this group of diseases in the phenotype of malignant cells, clinical characteristics and response to therapy. The immunologic characteristics of this group and their correlation with prognosis of the disease are less well defined(Sallan *et al.* 1980; Greaves 1981; Greaves *et al.* 1981). Our aim of this study was to find the evidence of early T cell origin in non-T, non-B ALL and to determine whether these markers could define subgroups in accordance with distinctive clinical features and differing responses to standard chemotherapy. Special attention was paid to the recording of the T10 antigen expression, which was reported to be expressed on the early thymocytes, together with the CALLA of non-T, non-B ALL blasts. The presence of T10 antigen in a considerable part of common ALL with lymphoblasts identified by the CALLA disclosed a new subgroup in which a dfferentiation versus the T axis is suggested. The subdivision of common ALL was related to clinical data at presentation, response to chemotherapy and survival rate.

MATERIALS AND METHODS

Patients

This study included 128 patients who were 68 children ranging from 1 to 15 years and 60 adults from 16 to 89 years, previously untreated and first seen between March 1983 and May 1986 in Seoul National University Hospital. All patients had a diagnosis of ALL based on morphological examination of bone-marrow samples at the time of presentation. Cytochemical stains were carried out to exclude cases of acute non-lymphoblastic leukemia.

At the time of diagnosis, information on age, sex, presenting white-cell count, platelet count, hemoglobin concentration, and presence or absence of splenomegaly, lymphadenopathy, hepatomegaly and mediastinal mass was obtained.

Methods

Monoclonal antibody analysis. — The monoclonal antibodies used in this study were J5 detecting CALLA and OKT10 detecting T10 antigen. J5 antibody was supplied in a lyophilized form by UCLA and OKT10 by Ortho Pharmaceutical Corporation. Indirect immunofluorescent studies of ALL cells was done by previously described methods(Cho *et al.* in press). Briefly, cells were incubated with monoclonal antibodies at saturating concentrations on ice for 30 min, washed, then incubated with fluorescein isothiocyanate goat anti-mouse immunoglobulin(Cooper Biomedical) on ice for 30 min; stained cells were washed and examined with a fluorescent microscope equipped with epiillumination. Samples were defined as positive if more than 10% of malignant cells expressed the marker in CALLA and if more than 40% of malignant cells expressed the marker in T10 antigen.

E rosette and SmIg analysis. — Spontaneous rosette formation with sheep erythrocytes and SmIg analysis were studied by previously described methods(Cho *et al.* in press).

Threapy. — Thirty-five adults with ALL received induction therapy of vincristine, prednisolone and L-aspraginase or daunorubicine and CNS prophylaxis followed by maintenance chemotherapy consisting of 6-mercaptopurine and methotrexate(Kim *et al.* 1986), and 45 children with ALL received chemotherapy according to Children's Cancer Study Group Protocols. Remission duration was determined from the time of attainment of less than 5% of lymphoblasts in bone marrow.

Statistical analysis were carried out by standard

Table 1. Subgroups of acute lymphoblastic leukemia(ALL)

Subgroup	Total (n=128)	Children* (n=68)	Adults (n=60)	Phenotypic pattern			
				CALLA	T10	E-R	SmIg
cALL	47(36.7%)	26(38.2%)	21(35.0%)	+	−	−	−
c/T ALL	29(22.7%)	14(20.6%)	15(25.0%)	+	+	−	−
T-ALL	21(16.4%)	13(19.1%)	8(13.3%)	−	+/−	+	−
Null ALL	29(22.7%)	14(20.6%)	15(25.0%)	−	−	−	−
B-ALL	2(1.6%)	1(1.5%)	1(1.7%)	−	−	−	+

*≤15 years

statistical methods including remission induction frequencies and survival analysis of remission duration by the Kaplan-Meier method(Kaplan and Meier 1958). Differences in survival were tested by the log-rank test(Peto *et al.* 1977). Using Vax 11/780 computer and SAS program(SAS User's Guide 1985), multivariate survival analysis was also carried out with constant hazard models of combinations of prognostic factors, comparing them by X^2 likelihood ratio tests(Cox 1972; Bloomfield *et al.* 1979).

RESULTS

Subgroups of ALL

Sixty-eight children and 60 adults with newly diagnosed ALL were examined. We classified each case on the basis of expression of receptors for sheep erythorcytes, early T-cell differentiation antigen(T10), SmIg, and CALLA. The results are given in Table 1. In 47 patients, only CALLA was

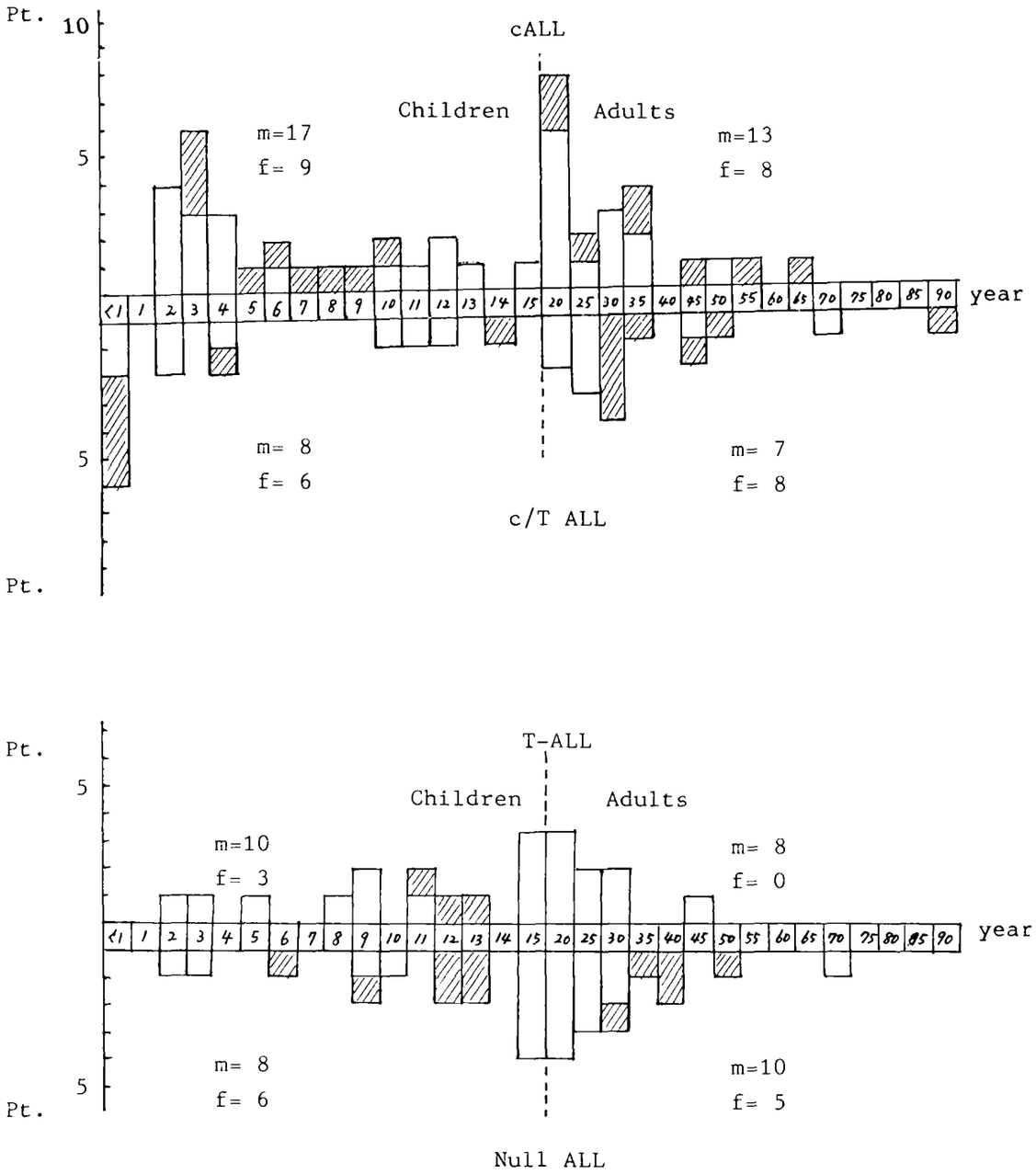

Fig. 1. Age and sex distribution in 126 patients with ALL. A subgrouping according to the immunologic phenotypes of leukemic cells is performed.
Note: □ = male, ▨ = female

demonstrated on the lymphoblasts. This phenotype, which is named cALL, prevailed, being recorded in 38.2% of the children and 35.0% of the adults. In a considerable number of other cases, namely in 29 patients, an additional reaction of the blast cells with OKT10 was recorded. An intermediate phenotype of blast cells expressing both CALLA and T10 antigen was therefore assessed in 29 of 76 patients with CALLA-positive leukemia. This ALL subgroup, named c/T ALL, was found 20.6% of the children and 25.0% of the adults.

E rosette formation of the blast cells was observed in 13 children(19.1%) and 8 adults(13.3%). In only two patients, SmIg were easily detectable on the blast cells. In 29 patients, no marker was demonstrated. Such null ALL occurred in 14 children(20.6%) and 15 adults(25.0%).

Clinical Feautres: Relation to ALL Subgroups

The age and sex distribution of the patients are given in Fig. 1 on the basis of the ALL subgroup. Age distibution is distinctive according to the ALL subgroup in children. A great majority of children with T-, null, and c/T ALL were in under 1 or over 10 years of age, whereas cALL had a peak incidence around 2 to 6 years of age. The male sex predominated in T-ALL.

The relationship between immunologic classification and clinical and hematologic data upon presentation of the disease was investigated in 53 children and 42 adults in the study. The results are given in Table 2 and 3. Four children had a

Table 2. Relationship between immunologic ALL subgroup and clinical signs at diagnosis for children with ALL

Features	Total	cALL	c/T ALL	T-ALL	Null ALL
No. of patients	53	23	12	10	8
Mediastinal enlargement	4	1(4.3)	0(0)	3(30.0)	0(0)
Lymph node enlargement	44	19(82.6)	12(100)	10(100)	3(37.5)
Spleen enlargement	41	17(73.9)	10(83.3)	9(90.0)	5(62.5)
Liver enlargement	50	21(91.3)	12(100)	10(100)	7(87.5)
White-cell count($\times 10^9$/L)					
<50	37	20(87.0)	6(50.0)	5(50.0)	6(75.0)
$\geqslant 50$	16	3(13.0)	6(50.0)	5(50.0)	2(25.0)
Hemoglobin(g/dL)					
<6	15	6(26.1)	4(33.3)	1(10.0)	4(50.0)
Platelet count($\times 10^9$/L)					
<20	3	1(4.3)	2(16.7)	0(0)	0(0)
>100	16	6(26.1)	4(33.3)	1(10.0)	5(62.5)

Table 3. Relationship between immunologic ALL subgroup and cinical signs at diagnosis for adults with ALL

Features	Total	cALL	c/T ALL	T-ALL	Null ALL
No. of patients	42	18	10	7	7
Mediastinal enlargement	3	0(0)	1(10.0)	1(14.3)	1(14.3)
Lymph node enlargement	24	10(55.6)	5(50.0)	6(85.7)	3(42.9)
Spleen enlargement	18	7(38.9)	4(40.0)	4(57.1)	3(42.9)
Liver enlargement	25	11(61.1)	5(50.0)	4(57.1)	5(71.4)
White-cell count($\times 10^9$/L)					
<50	26	13(72.2)	5(50.0)	3(42.9)	5(71.4)
$\geqslant 50$	16	5(27.8)	5(50.0)	4(57.1)	2(28.6)
Hemoglobin(g/dL)					
<6	11	4(22.2)	4(40.0)	2(28.6)	1(14.3)
Platelet count($\times 10^9$/L)					
<20	1	1(5.6)	0(0)	0(0)	0(0)
>100	11	3(16.7)	3(30.0)	2(28.6)	3(42.9)

mediastinal widening on their admission chest X-ray, 3 of those patients being affected by T-ALL and 1 by cALL. Three adults had a mediastinal mass, 1 of those patients being affected by c/T ALL, 1 by T-ALL and 1 by null ALL. Lymph node enlargement was less pronounced both in children and adults with null ALL compared to those with other subgroups. Splenomegaly was evident in most children with T- and c/T ALL and less significant in adult ALL compared to childhood ALL. Liver enlargement was also significantly less often found in adult ALL compared to childhood ALL. Leukocytosis with total white-cell count over 50×10^9/L was evident both in children and adults with T- and c/T ALL. Anemia with hemoglobin less than 6g/dL was less often found in children with T-ALL and in adults with null ALL. Thrombocytopenia with platelet count less than 20×10^9/L was rare.

Outcome of Therapy

Forty children(88.9%) and 23 adults(65.7%) with ALL attained complete remission after induction therapy. The cALL and null ALL had the highest remission rate(100%), followed by c/T ALL(75.%) and T-ALL(62.5%) in children(Table 4). In adults, the cALL also had the highest remission rate(84.6%), followed by T-ALL(66.7%), null ALL(57.1%) and c/T ALL(44.4%)(Table 5). The difference in the remission rate was significant between c and c/T ALL both in children and adults according to the X^2-test.

Table 4. Remission rate in subgroups of childhood ALL

Subgroup	No.	CR (%)	PR (%)	NR (%)
cALL	21	21(100)	0	0(0)
c/T ALL	8	6(75.0)	0	2(25.0)
T-ALL	8	5(62.5)	1(12.5)	2(25.0)
Null ALL	8	8(100)	0	0
Total	45	40(88.9)	1(2.2)	4(8.9)

Note: CR; complete remission, PR; partial remission, NR; no response

Table 5. Remission rate in subgroups of adult ALL

Subgroup	no.	CR (%)	PR (%)	NR (%)
cALL	13	11(84.6)	1(7.7)	1(7.7)
c/T ALL	9	4(44.4)	2(22.2)	3(33.3)
T-ALL	6	4(66.7)	1(16.7)	1(16.7)
Null ALL	7	4(57.1)	2(28.6)	1(14.3)
Total	35	23(65.7)	6(17.1)	6(17.1)

Survival Analysis

The 63 patients who attained complete remission after induction therapy were followed up for 1-36 months and deaths were noted. Survival curves observed in the Kaplan-Meier analysis are plotted in Fig. 2 and 3 according to the immunologic subgroup. The difference in survival between children with cALL and c/T ALL shown in Fig. 2 is statisti-

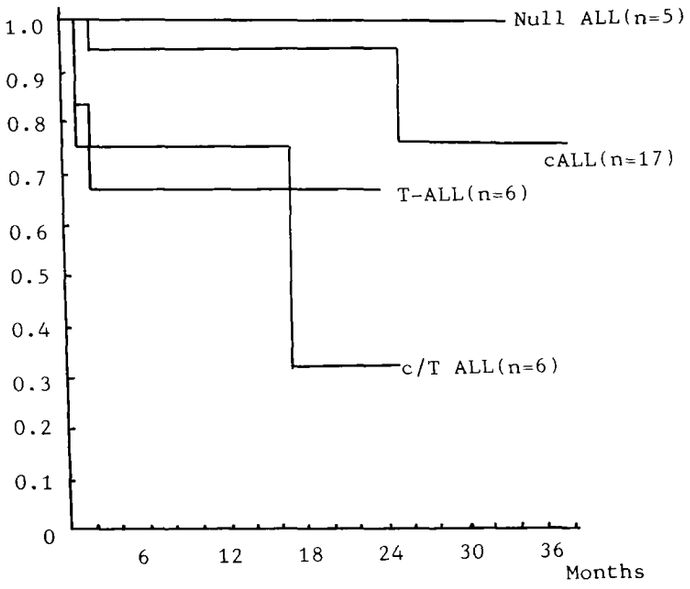

Fig. 2. Survival rate for 34 children with ALL of different immunologic subgroup.

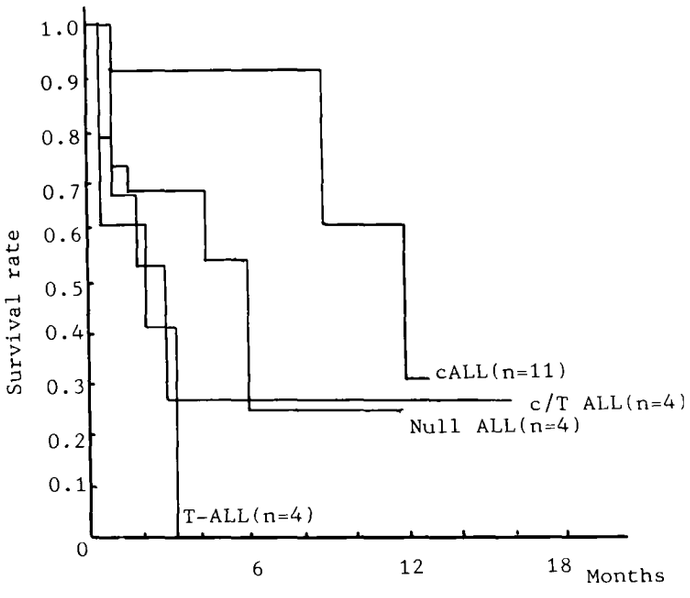

Fig. 3. Survival rate for 23 adults with ALL of different immunologic subgroup.

Table 6. Survival rate in ALL by univariate survival analysis using the Kaplan-Meier method

Variable*	Childhood ALL(n=34)		Adult ALL(n=31)	
	Chi square	p value	Chi square	p value
CALLA	0.257	ns**	0.088	ns
WBC	7.521	<0.01	0.861	ns
ER	3.705	<0.10	4.824	<0.05
T10	0.596	ns	1.125	ns
Age	1.820	ns		

Note: *; variable is defined as follows: CALLA, ER and T10 as positive or negative; WBC as more or less than 50 $\times 10^9$/L; Age as 2 to 6 years of age or not only in childhood ALL
**; not significant

cally significant using log-rank test($p<0.05$). In adults, T-ALL shows the shortest survival and the difference in survival between the cALL and c/T ALL patients shown in Fig. 3 is less significant as that of childhood ALL($p<0.10$).

The prognostic significance of each of the five variables was evaluated by univariate survival analysis(Table 6). The difference in survival between E rosette-positive and -negative group was only significant in adults($p<0.05$) and initial leukocyte count had a prognostic significance only in children($p<0.01$).

Multivariate Survival Analysis of Risk Factors

Since certain cell-marker characteristics(E rosette$^+$ and T10$^+$) and clinical features(high white-cell count and age) appeared to predict poor survival, we carried out multivariate survival analysis with a constant hazard model to find out whether the factors were independant. The results indicated that the two strongest factors were CALLA($X^2=352.093$; $p=0.0001$; 1 degree of freedom(df)) and high white-cell count($X^2=2.75172$; $p=0.0971$; 1 df) in children and the only one strongest factor was E rosette($X^2=3.19077$; $p=0.0741$; 1 df) in adults.

DISCUSSION

Identification of similar cell surface marker on acute lymphoblastic leukemia(ALL) cells by immunologic methods has allowed classification of this maliganacy into T-cell, B-cell, and non-T, non-B(so called null-cell) types(Borella and Sen 1973; Gajl-Peczalska *et al.* 1974; Brouet *et al.* 1976). In addition to disclosing that ALL is a very heterogenous disorder, such an immunologic classification has proved to be of prognostic significan-

Table 7. Multivariate survival analysis in childhood ALL

Variable*	DF**	Estimate	SE***	Chi square	p value
Intercept	1	47.6154	5.55943	73.3558	0.0001
Age	1	−1.653	1.61023	1.05388	0.3046
CALLA	1	−32.173	1.71462	352.093	0.0001
T10	1	−0.464778	1.82263	0.0650268	0.7987
ER	0	−32.981	0	–	–
WBC	1	−2.9838	1.79874	2.75172	0.0971

Note: *; Variable is defined as Table 6.
**; degree of freedom
***; standard error

Table 8. Multivariate survival analysis in adult ALL

Variable	DF	Estimate	SE	Chi square	p value
Intercept	1	8.49698	2.04812	17.2114	0.0001
CALLA	1	−2.0231	1.64295	1.51634	0.2182
T10	1	0.226212	0.963978	0.0550679	0.8145
ER	1	−3.5887	2.00903	3.19077	0.0741
WBC	1	−0.371554	0.9114	0.166198	0.6835

ce(Sen and Borella 1975; Tsukimoto *et al.* 1976; Chessells *et al.* 1977; Greaves *et al.* 1981). The majority of ALL, however, still cannot be clearly allocated to T or B differentiation. Comparative studies have demonstrated that the phenotype of these cells resembles early lymphatic progenitors demonstrable in rare numbers in the bone marrow and fetal organs(Greaves *et al.* 1975). In this way, a pre-B-cell feature of the leukemic cells has been recognized in some of patients belonging to the non-T, non-B cell group(Vogler *et al.* 1978; Brouet *et al.* 1979).

On the other hand, several finding suggest that in many patients, non-T, non-B ALL cells may represent T-cell progenitors. In addition to the biochemical demonstration of the thymic enzyme terminal transferase in ALL(McCaffrey *et al.* 1973; Coleman *et al.* 1974), a reaction of samples that were E rosette-negative with antithymocyte sera favored the assumption of a T differentiation(Kersey *et al.* 1973; Brouet *et al.* 1976; Thiel *et al.* 1978). In this study, we aimed to demonstrate a early T differentiation in non-T, non-B leukemic cells by use of monoclonal antibodies such as J5 detecting CALLA and OKT10 detecting T10 antigen. Our results indicate that a considerable part of common ALL with lymphoblasts identified by the CALLA expressed T10 antigen. We called this new subgroup c/T ALL and the other subgroup cALL with lymphoblasts expressing only CALLA without T10 antigen. For c/T ALL with lymphoblasts expressing both CALLA and T10, a normal counterpart has not been described so far. Recently, however, CALLA-positive cells were detected within the cortex of thymus(Neudorf *et al.* 1984) suggesting that c/T ALL may represent clonal cell population arrested at early stage of maturation versus T.

Comparison with clinical dada provided evidence that the new classification is of biologic relevance. Significant differences in age dstribution(Fig. 1) and in presentation features were found(Table 2 and 3). The most striking clinical features were association of $CALLA^+$ and $T10^+$ phenotypes, and the presence of high initial white-cell count. In other words, a high initial white-cell count was more frequently observed in c/T ALL than in cALL.

A decisive criterion for the evaluation of an ALL classification is its relationship to therapy. We demonstrated significant differences in frequencies of remission induction between cALL and c/T ALL. And patients with c/T ALL had a shorter survival than those with cALL. Our results suggest that T10 antigen expression influences outcome after chemotherapy and survival. Immunologic markers of prognostic value were therefore included in the evaluation of conventional prognostic factors(age, white-cell count). In univariate survival analysis, the demonstration of E rosettes appeared to be associated with a worse response to treatment both in children and adults and high initital white-cell count appeared only in chldren. In this connection it is of interest to note that in the study of Chessells *et al.* (1977), the duration of complete remission was shorter in the group with E rosette than in the group with white-cell count over $100,000/mm^3$. In multivariate survival analysis, the most independent prognostic factor was CALLA in children and E rosette in adults.

Clinical application of immunologic subgroup is important in predicting prognosis. Prognostic grouping may prove to be accomplished by using a combination of traditional risk factors and immunologic phenotyping. Single factor is not enough to predict prognosis and more complex factors are related to prognosis. Laboratory research must endeavor to identify additional biologic characteristics peculiar to each major immunologic subgroup of ALL. These characteristics may dictate therapeutic maneuvers in the future.

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=국문초록=

면역학적 표지에 의한 급성 림프아구성 백혈병의 예후판정

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급성림프아구성백혈병(ALL) 128예(소아 68예, 성인 60예)에서 sheep erythrocyte receptor (ER)와 suface membrane immunoglobulin(SmIg)과 같은 전통적인 림프구표지와 common ALL 항원 (CALLA) 및 T10항원 단세포군항체를 이용하여 그 표현형 분포를 조사하였고, 이들 표지의 표현과 ALL 예후와의 관계를 조사하여 다음과 같은 결론을 얻었다.

1. 면역학적인 림프구표지를 표현한 양상에 따라 ALL은 5개 아형으로 구분할 수 있었다. 제1형은 CALLA만 양성을 보인 common null-cell ALL(cALL)로서 47예였고, 제2형은 CALLA과 T10항원이 동시에 양성인 intermediate-cell ALL(c/T ALL)로서 29예였으며, 제3형은 ER이 양성인 T-cell ALL(T-ALL)로서 21예였고, 제4형은 아무 표지도 나타내지 않은 null-cell ALL(null ALL)로서 29예였고, 제5형은 SmIg가 양성인 B-cell ALL(B-ALL)로서 2예에서 발견되었다.

2. ALL 각 유형별 임상적 특징은 전형적인 T-ALL이 극심한 백혈구증다증을 빈번히 보이고, 10세이상의 소아에서 발생한다는 사실외에 c/T ALL에서도 이와 유사한 양상을 보였다. 즉 소아 c/T ALL은 cALL이 2~6세 사이에 가장 높은 빈도로 발생하는데 비하여 1세 이하나 10세 이상에서 흔히 발견되었고, 소아 및 성인 c/T ALL에서 모두 cALL에 비하여 빈번히 백혈구증다증을 관찰할 수 있었다.

3. ALL 각 유형별 치료효과를 완전관해 유도율로서 비교하였다. 소아 ALL에서는 cALL과 null ALL의 완전관해유도율이 100%로서 가장 높았고, c/T ALL이 75.0% T-ALL이 62.5% 순이었으며, 성인 ALL에서는 cALL이 84.6%, T-ALL이 66.7%, null ALL이 57.1%, c/T ALL이 44.4% 순이었다.

4. ALL 각 유형별 생존율은 소아 ALL에서는 c/T ALL이, 성인 ALL에서는 T-ALL이 가장 낮았고, 생존율에 영향을 주는 인자를 univariate survival analysis로 분석한 결과, 소아에서는 총백혈구수가, 성인에서는 ER만이 생존율에 영향을 주는 단일 인자였다.

5. 면역학적 표지 및 임상적 특징이 모두 생존율에는 영향을 줄 수 있는 바, 이들 중 예후에 독립적으로 영향을 미치는 인자를 찾기 위해 multivariate survival analysis를 실시한 결과, 소아에서는 CALLA과 총백혈구수가, 성인에서는 ER만이 가장 중요한 인자로 발견되었다.

결론적으로 ALL의 예후를 예측하기 위한 가장 중요한 단일인자는 결정하기 어려웠으며 여러가지 면역학적 표지를 함께 사용함으로써 ALL의 아형을 정확히 구분하여 그 생물학적 특성을 밝히는 것이 중요하다고 생각되었다.