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PROGNOSTIC VALUE OF MYELOID ANTIGEN EXPRESSION IN ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Expression of cell surface molecules associated with lymphoid and myeloid lineage differentiation on the blasts of 53 patients with acute lymphoblastic leukemia (ALL) was investigated. 1.9% of cases were only HLA-DR+; 7.6% were HLA-DR+, CD19+; 22.6% were HLA-DR+, CD19+, CD10+; 30.2% were HLA-DR+, CD19+, CD10±, CD20+; and 37.7% were HLA-DR±, CD7+, CD5±. Aberrant expression of one or more myeloid antigens including CD13, CD15, CD33 and CD34 was found in 30.2% of cases. The relationship of myeloid positive (MY+ ALL) and negative cases (MY- ALL) with patient characteristics were studied. No significant differences in clinical features, response to therapy or survival was found between the two groups. Study of each marker separately indicated an association between expression of CD5 and CD10 with age and expression of CD20 and CD33 with decrease in hemoglobin ($p<0.03$). No correlation between expression of markers and survival was found except for CD13 and CD15 antigens ($p<0.03$). CD15+ cases showed longer survival than negative cases (541±72 vs. 364±34 days) whereas CD13+ cases showed shorter survival than negative ones (378±32 vs. 616±106).
showed a trend towards a longer or shorter survival.
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INTRODUCTION

In recent years study of the aberrant expression of lineage-associated antigens in acute leukemias, particularly in acute lymphoblastic leukemia (ALL), has been an attractive subject for investigators. Coexpression of myeloid antigens on lymphoblasts of patients with ALL has already been emphasized in previous reports.[1-8] This coexpression has been explained as reflecting aberrant gene expression, malignant transformation of pluripotent progenitor cells capable of both lymphoid and myeloid differentiation, or immortalization of rare progenitor cells coexpressing features of both lineages.[9-11] The clinical and prognostic value of such coexpression remains uncertain. Data from several reports indicate that the presence of myeloid antigens on lymphoblasts of ALL patients is predictive of a poor response to therapy.[12-14] Contrary to this are reports that show no prognostic value for expression of myeloid markers in these patients.[15-16] In this study we examined the immunophenotypes of blasts from 53 patients with ALL and evaluated the prognostic significance of lymphoid and myeloid differentiation markers present on the blasts of these patients.

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MATERIALS AND METHODS

Patients

53 patients, morphologically and cytochemically diag-

nosed as ALL entered this study from June 1995 to August 1998. There were 23 females and 30 males with a mean age of 25.7 years (range 3-79). Treatment of patients included vincristine, daunorubicin and prednisone for 4 weeks and intrathecal therapy by methotrexate once weekly for 6 times.

Immunophenotypic analysis

Cell surface marker analysis was performed on isolated blood or marrow mononuclear cells by an indirect immunofluorescence technique using a panel of monoclonal antibodies (mAbs) against lymphoid and myeloid markers. MAbs used in this study, including CD7, CD10, CD13, CD15, CD19, CD20, CD33, CD34 and HLA-DR were obtained from DAKO, Denmark. CD5 mAb was produced in our laboratory.[17] Cells were treated with appropriate dilutions of mAbs. After 1-hr incubation, a fluorescein conjugated goat anti-mouse Ig (Sigma, St. Louis, MI) was added. Finally the cells were analyzed by a Ziess fluorescence microscope. Samples were considered positive when more than 30% of the cells stained with a particular antibody.

Statistical analysis

Statistical analysis was performed using SPSS program. Survival times and remission duration were plotted using Kaplan-Meier method.[18] Remission and survival rates and duration were determined from the date of diagnosis to the relapse and death dates, or date last known alive. Relationship between the expression of markers and age, number of blasts, leukocyte and platelet counts and hemoglobin was analyzed by Student's t-test. Relationship to survival rate, sex and presentation with extramedullary involvement was calculated using chi-square or Fisher's exact tests.

RESULTS

Expression of lymphoid antigens

According to the reactivity of mAbs, the ALL cases were classified in five groups; I- HLA-DR+ (n=1). II- HLA-DR+, CD19+ (n= 4). III- HLA-DR+, CD19+, CD10+ (n= 12). IV- HLA-DR+, CD19+, CD10±, CD20+ (N= 16). V- HLA-DR+, CD7+, CD5± (n=20). Group I to IV are assigned as B lineage ALL and group V as T ALL. All patients of group I and V had L2 morphology. A significant correlation between CD7 expression and L2 subclass (p= 0.01), CD10 and L1 subclass (p= 0.02) and lack of CD10 in L3 subclass (p= 0.03) was observed. 47.2% of all patients were CD10 positive.

Expression of myeloid antigens

Blast cells from 16 patients (30.2%) with ALL expressed one or more myeloid antigens (MY+ ALL). Frequency of expression of myeloid antigens was as follows: CD13, 9.4%; CD15, 21%; CD33, 9.4%; CD34, 1.9%; The incidence of myeloid positivity was 7 of 20 patients in T ALL and 4 of 25 in CD10 positive patients. Most MY+ patients had L2 morphology (p= 0.02). No significant correlation between expression of myeloid markers and immunological groups was found.

Relationship between expression of markers and clinical and biological characteristics of patients

A significant association between patient age at time of diagnosis and expression of CD10 and CD5 markers was found. CD10 positive patients were younger than CD10 negative cases (19 ± 13 vs. 32 ± 22 years, p= 0.004) whereas CD5 positive cases were older than negative ones (38 ± 26 vs. 21±16, p= 0.009). A relationship between lack of expression of CD7 and expression of CD20 and CD33 and decreased concentration of hemoglobin was found (p<0.03). Number of marrow blasts was higher in CD20 positive than negative cases (p= 0.027). No significant differences were found in MY+ ALL and MY- ALL patients in relation to organomegaly, hemoglobin, leukocyte and platelet count, age, sex and number of marrow blasts (Table I). Correlation between complete remission (CR) duration and survival and expression of markers is presented in Table II. The difference between MY+ and MY- groups in CR duration and survival was not significant (Fig. 1). A significant association between mean survival of patients and expression of CD13 and CD15 molecules was found. The mean sur-

Table I. Clinical and laboratory characteristics of patients with ALL.

Variable	Total	MY+ALL	MY- ALL	*P* value
No. of patients	53	16 (30.2%)	37 (69.8%)	
M: F ratio	30: 23	6: 10	24: 13	0.1
Age (range)	26 (3-79)	29 (5-79)	23 (3-78)	0.3
Leucocyte count (×10⁹/L)	32 (0.7-300)	52.6 (0.9-167)	25 (0.7-300)	0.2
Platelet count (×10⁹/L)	70 (16-560)	100 (20-560)	57 (16-250)	0.5
Extramedullary involvement	37 (69.8%)	10 (65.5%)	27 (73%)	0.5
Hemoglobin(g/dL)	9.2 (3.6-25)	9.5 (5.3-13.3)	9.1 (6.9-13.3)	0.6
FAB classification				
L1	5	—	5	
L2	44	13	31	
L3	4	3	1	
CR duration(days)	300 ± 398	249 ± 144	322 ± 467	0.1
Survival(days)	558 ± 517	550 ± 213	558 ± 606	0.09
Survival rate	66%	81.3%	61.1%	0.3

FAB: French-American-British; CR: Complete remission.
Values are mean ± SD.

Table II. Remission duration and survival of patients with ALL.

Antigen		No. of Patients	Complete remission (days)	*P* value	Survival (days)	*P* value
CD10	-	28	307±79	0.9	428±45	0.4
	+	25	292±77		370±44	
CD13	-	48	311±60	0.5	616±106	0.03
	+	5	198±65		378±32	
CD15	-	42	316±68	0.6	364±34	0.02
	+	11	238±45		541±72	
CD20	-	37	297±63	0.9	398±40	0.9
	+	16	307±110		406±51	
CD19	-	30	213±35	0.7	414±46	0.6
	+	23	413±115		383±43	
CD5	-	42	332±67	0.3	410±36	0.6
	+	11	180±47		336±67	
CD7	-	33	356±84	0.2	399±37	0.9
	+	20	208±39		403±58	
CD33	-	48	340±83	0.9	440±81	0.7
	+	5	330±123		530±103	
HLA-DR	-	2	69±69	0.4	132±125	0.09
	+	51	309±56		411±32	

Values are mean ± SE.

vival time for CD13 positive cases was 378 ± 32 days versus 616 ± 106 for negative cases (p= 0.03). These data for CD15 were 541± 72 and 364 ± 34 (p= 0.02), respectively. Analysis of remission and survival curves failed to show any prognostic significance for expression of these two markers. The presence or absence of CD10 and other markers did not change survival parameters.

DISCUSSION

In this study the presence of lymphoid and myeloid antigens in 53 patients with ALL was investigated. According to the expression of markers, patients were divided into two groups of T-ALL and B lineage ALL with frequencies of 37.7% and 62.3%, respectively. T-ALL patients were older than non-T-ALL cases and presented with lower hemoglobin levels. Patients with CD10 positivity were significantly younger and CD20 positivity was associated with a higher number of marrow blasts and decreased hemoglobin levels.

Study of myeloid marker expression in our patients indicated a frequency of 30.2% for MY+ ALL groups. Although the incidence of MY+ cases has been reported to vary with age and a range of 7% to 25% in childhood ALL and up to 40% in adult ALL has been suggested,[19] the small number of patients in our study has not allowed us to separate patients according to age.

In a recent large-scale study, expression of myeloid antigens including CD13, CD14 and CD33 has been found to be an independent predictor of a poor outcome among 236 children with ALL.[12] In previous reports Wiener and Sobol had reported that myeloid-associated-antigen expression in

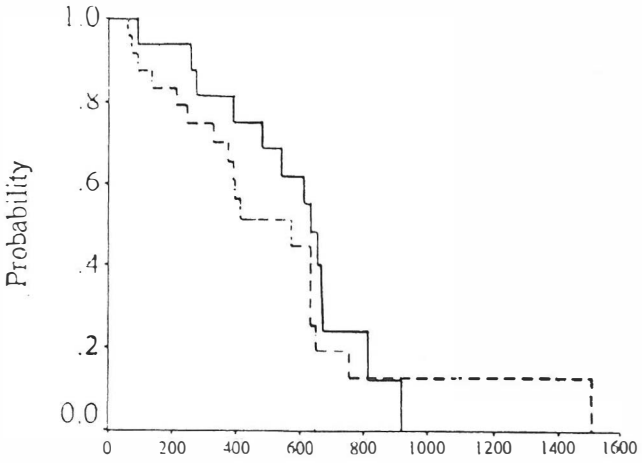

Fig. 1. Survival curve for ALL patients according to the presence or absence of myeloid antigens. MY+ ALL(-) vs. MY- ALL(--). Probability is estimated by the method of Kaplan and Meier. Survival of patients showed no significant difference between MY+ and MY- ALL (p= 0.49).

ALL was associated with a low remission induction rate and, among adults with B-lineage ALL, shorter survival.[13,20] Similarly, Ipizua reviewed 62 adult ALL cases and found 13% coexpressing myeloid markers.[21] These patients had shorter remission duration and survival. In our study no significant differences were observed among MY+ and MY- patients in regard to CR duration and survival and despite longer mean survival for CD15+ cases and shorter mean survival for CD13+ patients. Survival curves plotted according to standard methods did not show any significant differences. This result is similar to other reports in which no prognostic value was found for the presence of myeloid-associated antigens on ALL blasts.[19,22,23] In more recent studies reported by Boucheix and Preti, the presence of CD13 and CD33 antigens was observed on less than 10% of ALL patients and no clinical correlation was seen.[16,19] As explained, the clinical and biological significance of myeloid-positive ALL is a subject of considerable interest and controversy. Differences in definitions of myeloid-antigen expression, immunophenotyping methods, study populations, treatment regimens or a combination of these features may explain the discordant results.

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