Immunologic Subclassification of Acute Lymphoblastic Leukemia in Childhood and Prognosis (Modified BFM Protocol)*

F. Zintl and R. Häfer

A. Introduction

Acute lymphoblastic leukemias (ALLs) in childhood are clonal proliferations of lymphoid cells. It is now possible precisely to define stages of human lymphocyte differentiation using more traditional cell markers such as surface membrane immunoglobulin (SIg), sheep erythrocyte receptor (E), and cytochemical stains or highly specific monoclonal antibodies. The application of these immunologic methods to the study of ALL has further confirmed the heterogeneous nature of this disease. There appear to be clinical differences among the immunologic subtypes. It is as yet unclear whether T-cell disease is an independent prognostic variable. In the past B-cell ALL was characterized by an extremely poor prognosis. Relatively little information is available regarding the prognosis of the various stages of pre-B-ALL and T-ALL. In a modified Berlin-Frankfurt-Münster (BFM) study, children with non-T-ALL (except B-ALL) and T-ALL were treated according to the ALL VII/81 protocol. Our aim was to determine whether immunologic markers could define subgroups with distinctive clinical features and differing responses to standard chemotherapy.

Universitäts-Kinderklinik Jena, Abt. Hämatologie, Onkologie und Immunologie, Kochstraße 2, 6900 Jena, GDR

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B. Material and Methods

One hundred and forty-three out of 525 untreated patients with childhood ALL were referred for immunophenotype determinations as part of a prospective multicenter study (1981–1987). ALL had been diagnosed in all patients by local and central review of cytologic and cytochemical features according to the French-American-British (FAB) criteria.

All patients were treated with first-line therapy for ALL (modified BFM protocol ALL/VII-81). Before starting cytostatic treatment, the individual risk factor for the patient was determined with the aid of a diagram. Three clinical values were important for the calculation of the risk factor (RF): the initial leukemic cell count and liver and spleen size. Patients with $RF < 1.2$ were considered to have a standard risk; those with $RF > 1.2$ and < 1.7 to have a medium risk; and those with $RF > 1.7$ to have a high risk [1–3]. Patients with confirmed B-cell features were treated completely differently [4]. A panel of monoclonal antibodies (W. Knapp, Vienna) to B-cell, T-cell, and myeloid antigens as well as E-rosetting, surface immunoglobulin, and acid phosphatase were used for phenotype determination.

C. Results

I. Immunologic Subgroups

In a modified BFM study (ALL VII/81) with a total number of 525 children with acute lymphoblastic leukemia, evaluation of 143 consecutively studied patients identified four major immunopheno-

Table 1. Major phenotypes of childhood ALL

		No. patients	%
Early Pre-B-ALL	(HLA-DR$^+$, SIg$^-$, E$^-$, pT$^-$, CD24$^+$, CD10$^-$)	22	15.4
C-ALL	(HLA-DR$^+$, SIg$^-$, E$^-$, pT$^-$, CD24$^+$, CD10$^+$)	82	57.3
B-ALL	(HLA-DR$^+$, SIg$^+$, E$^-$, pT$^-$, CD24$^+$, CD10$^-$)	5	3.5
T-ALL	(HLA-DR$^-$, SIg$^-$, E$^{+/-}$, acP$^{+/-}$, CD1$^{+/-}$, CD3$^{+/-}$, CD10$^{+/-}$)	34	23.8
Total		143	100.0

types of childhood ALL (Table 1). ALL of B-cell lineage (Ia$^+$, CD24$^+$, CD10$^+$, SIg$^{+/-}$) was observed in 109 patients (76.2%); T-cell lineage marker profiles (E$^{+/-}$, acP$^{+/-}$, CD1$^{+/-}$, CD3$^{+/-}$) were identified in 34 children (23.8%). The high proportion of T-ALL is caused by the fact that some centers included only patients with a high WBC in the immunophenotyping study. Four subgroups of B-cell lineage were defined (Fig. 1):

1. The first subgroup was Ia antigen positive, representing 6.4% of non-T-ALL.
2. Another subgroup expressed the Ia and CD24 antigen, representing 13.8% of cases.
3. The third subgroup expressed the Ia, CD24, and CALLA antigens, comprising 75.2% of the cases.
4. The final and most differentiated group represents SIg-positive B-ALL (3.5%).

The leukemic cells from 34 children with ALL expressed T-cell markers, including receptors for sheep erythrocytes, acid phosphatase and/or cell surface differentiation antigens specific for T cells.

Three subgroups of T-ALL could be identified (Fig. 1):

1. The early-T subgroup was CD1 and CD3 negative, representing 26.5% of T-ALL.
2. The second subgroup expressed CD1$^+$ and CD3$^{+/-}$ antigen, representing 53.0% of the cases (intermediate-T).
3. T-ALL cells of the mature-T subgroup (20.5%) lost the CD1 antigen and segregated into cells that had the phenotype of mature thymocytes and T-lymphocytes (CD3$^+$).

II. Immunologic Subgroups and Disease-Free-Survival

Results are reported as conventional product limit estimates by the Kaplan-Meier method [5]. The initial response to chemotherapy of patients with T-ALL

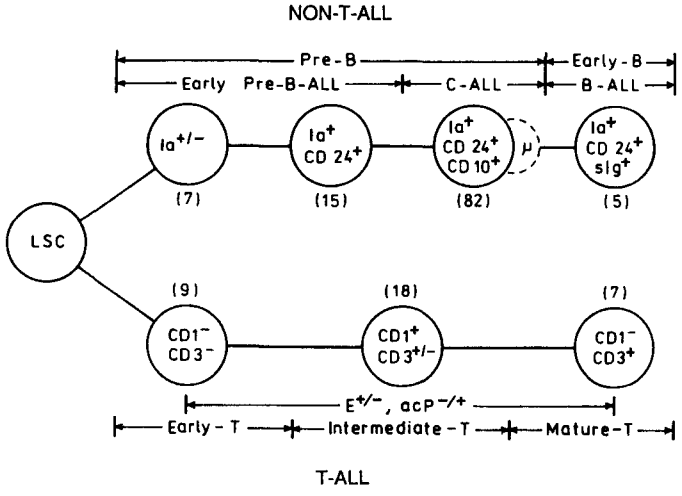

Fig. 1. Immunologic characteristics and subclassification of non-T- and T-ALL

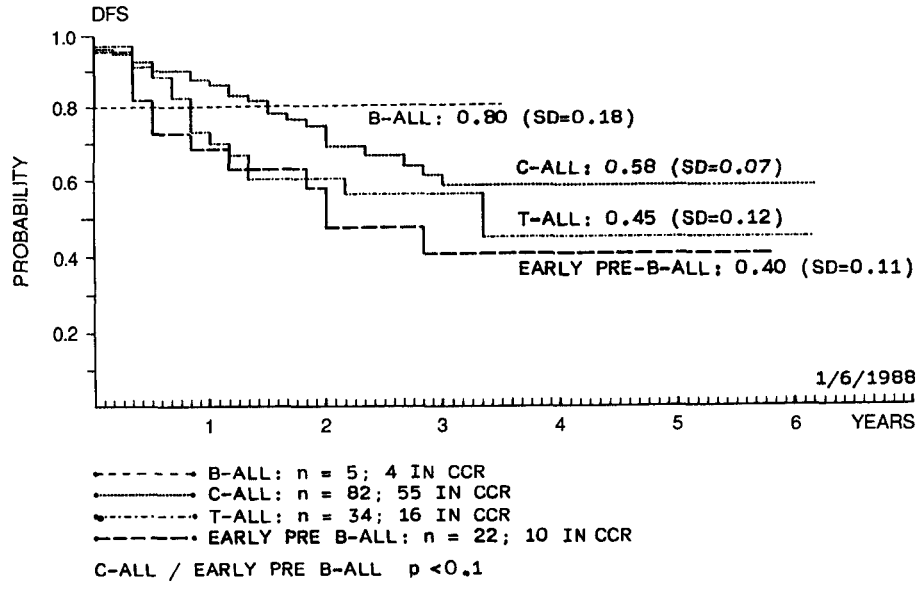

Fig. 2. Kaplan-Meier estimates for probability of disease-free survival for patients with C-ALL, T-ALL, early pre-B-ALL, and B-ALL

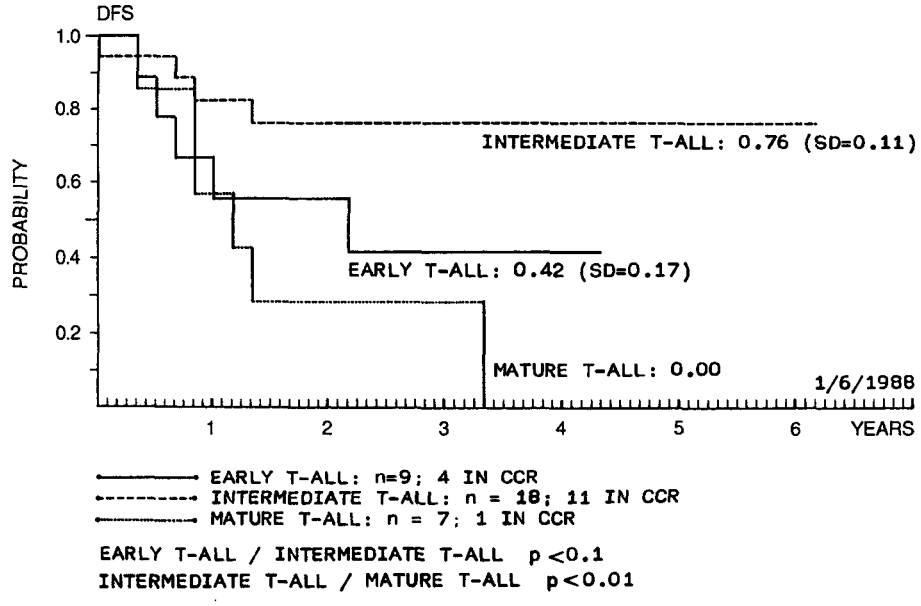

Fig. 3. Kaplan-Meier estimates for probability of disease-free survival for patients with T-ALL

did not differ from those with non-T-ALL.

The probability of disease-free survival (DFS) for 143 children was (Fig. 2):

1. C-ALL group, 0.58 ± 0.07
2. Early-pre-B-ALL group, 0.40 ± 0.11
3. T-ALL group, 0.45 ± 0.12
4. B-ALL, 0.80 ± 0.18

Although the immunologic subgroups of T-ALL were small, intermediate T-ALL patients fared significantly better than those with early T-ALL and mature T-ALL (Fig. 3).

B. Conclusions

Clinical studies have been performed using several series of monoclonal antibodies [6, 7]. In assessing the prognostic usefulness of antiboides in ALL, it is important to consider the influence of traditional unfavorable clinical factors (WBC, age, risk group, thymus tumor) on the patient's outcome:

1. Children with T-ALL had a poorer prognosis with a modified BFM therapy than those with C-ALL.
2. Patients with T-ALL were older and had higher white blood cell counts and organomegaly (Table 2).

Table 2. Comparative features of ALL subclasses

Characteristic	Early pre-B-ALL ($n=22$)	C-ALL ($n=82$)	T-ALL ($n=34$)	B-ALL ($n=5$)
Age (median in years)	$7^4/_{12}$	$4^4/_{12}$	$7^2/_{12}$	$6^5/_{12}$
WBC (median $\times 10^3$)	33.0	20.9	126.5	20.0
Risk group				
Standard	10 (45%)	45 (55%)	10 (29%)	2/4 (50%)
Medium	10 (45%)	34 (41%)	15 (44%)	1/4 (25%)
High	2 (10%)	3 (4%)	9 (27%)	1/4 (25%)
Mediastinal mass	3 (14%)	1 (1%)	17 (50%)	0 (0%)
HLA-DR positive	18 (82%)	79/80 (99%)	0 (0%)	5 (100%)
CALLA positive	0 (0%)	82 (100%)	4 (12%)	1 (20%)

3. Twenty-nine percent of children with T-ALL had standard risk characteristics versus 55% of those with C-ALL.
4. Early pre-B-ALL patients showed clinical factors like T-ALL patients (age, WBC, organomegaly) and had a poorer prognosis than C-ALL patients.
5. Children with intermediate T-ALL had a significantly better prognosis than those with early T-ALL and mature T-ALL.
6. The worse outcome of T-ALL was correlated with being older, higher white blood cell counts, and organomegaly but not with the "T" nature of leukemic cells.
7. B-ALL patients no longer have the worst prognosis of all ALL children when a B-ALL-tailored therapy is used.

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