Prognostic irrelevance of CD34 expression in childhood B-precursor acute lymphoblastic leukemia

Sir,

Phenotypic subclassification within B-precursor acute lymphoblastic leukemia (ALL) has been shown to have prognostic significance in children. Common ALL antigen (CALLA) expression in B- precursor ALL has been associated in some, but not all, studies with a favorable outcome. According to the notion that acute leukemia is a clonal expression with maturation arrest, CD34 expression on leukemic cells might define particular characteristics of immaturity.[1]

Several studies in childhood B-lineage leukemia ALL have reported a strong association between CD34 expression and favorable prognosis,[2-4] but other studies have not confirmed this association.[5] In order to evaluate the prevalence of CD34 expression and to investigate possible correlations with the presenting clinical-biological features and treatment outcome, we analyzed 52 B-lineage ALL children consecutively admitted to our Service and treated with the AIEOP ALL-91 protocols. The leukemic population was considered CD34 positive if at least 10% of bone marrow blast cells reacted with the HPCA-2 monoclonal antibodies. All subjects expressed CD19. At diagnosis, there was no statistically significant difference in CD20-antigen expression rate between $CD34^+$ and $CD34^-$ patients. Clinical and biological characteristics of the patients are reported in Table 1. The presence of CD34 on blast cells did not correlate with a higher probability of achieving complete response (CR) (p=0.24), nor did it affect the duration of disease free survival (DFS) (p=0.65) or overall survival (OS) (p=0.45) at 63 months of follow-up. There was no significant difference in relapse (REL) (p=0.62) or death rate (p=0.36) between $CD34^+$ and $CD34^-$ patients. After a mean follow-up of 49 months, 17 $CD34^+$ and 19 $CD34^-$ patients are in complete continuous remission (CCR) (p=0.38).

Thus, in a series of 52 *de novo* B-ALL we could not confirm previous reports on the prognostic value of CD34. Differences in clinics and treatment could explain these contrasting results. For instance, in one study[2] patients were enrolled in two successive total therapy studies with different follow-up duration. In another report,[4] at diagnosis $CD34^-$ subjects had significantly more unfavorable prognostic factors, i.e. age > 10 years, WBC count $>10\times10^9$/L and more frequent CNS involvement. These factors could have been responsible for the worse outcome of the $CD34^-$ subjects. Finally, the population studied by Borowitz[3] was randomized to receive two different consolidation regimens. In the study by Wanhaeke,[5] as in ours, the outcome of $CD34^+$ children with B-ALL was no better than the $CD34^-$ children. Some differences between our study and theirs should, however, be kept in mind: their cut-off for CD34 positivity was 30% and no subject with myeloid co-expression or bilineal leukemia was enrolled.

Table 1. Clinical and biological characteristics of 52 children affected by B-ALL, divided according to CD34 antigen expression.

	B-ALL $CD34^+$	*B-ALL $CD34^-$*	*p*
No. of patients	26	26	
Males/Females	20/6	18/8	0.75
Age (mean)	4.39	4.65	0.77
L1/L2 FAB	8/18	20/6	0.001
Mediastinal mass	0 (–)	2 (7,7%)	0.24
Hepatomegaly	20 (77%)	25 (96%)	0.04
Splenomegaly	19 (73%)	25 (96%)	0.02
Lympho-adenomegaly	21 (80.8%)	19 (73%)	0.37
WBC 10×10^9/L	11 (42.3%)	12 (46.1%)	0.50
WBC 10-50$\times10^9$/L	11 (42.3%)	8 (30.7%)	0.28
WBC 50-100$\times10^9$/L	1 (3.8%)	4 (15.3%)	0.17
WBC >100$\times10^9$/L	3 (11.5%)	2 (7.6%)	0.50
CNS involvement	0 (–)	1 (3.5%)	
Early-pre B	9 (34.6%)	14 (38.6%)	0.13
Pre B	4 (15.4%)	2 (7.6%)	0.33
Common	9 (34.6%)	9 (34.6%)	0.61
Bilineal	2 (7.7%)	1 (3.8%)	0.50
Undifferenziated	1 (3.8%)	0	
Not evaluable	1 (3.8%)	0	
My + Antigens	8 (30.8%)	3 (11.5%)	0.09

Long term prognostic value of CD34 has also been analyzed in adult patients with *de novo* acute lymphoblastic or myeloid leukemia. In two studies on adult ALL,[4,9] no statistical differences were seen in DFS or OS between $CD34^+$ and $CD34^-$ cases, although CD34 expression was associated with major adverse prognostic factors. Similarly, a number of studies on adult AML blasts could not confirm the former results and failed to demonstrate an adverse effect of CD34 expression on the outcome of induction therapy, remission duration or event free survival.[6-9]

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Key words

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May-Grünwald Giemsa-fluorescence *in situ* hybridization technique applied to a plasma cell leukemia

Sir,

Plasma cell leukemia (PCL) is a rare malignant plasma cell disorder which is characterized by the presence of more than 2×10^9 plasma cells/L in the peripheral blood.[1,2] Cytogenetic studies performed on plasma cell dyscrasias are scarce and difficult because of the low proliferation rate of plasma cells. Whereas an abnormal karyotype is found in 40% of multiple myeloma (MM) patients, recent reports demonstrate the presence of numerical abnormalities in nearly 90% of patients analyzing interphase nuclei by the fluorescence *in situ* hybridization (FISH) technique.[3,4] Interphase cytogenetic analysis is also possible, on previously stained slides, using the May-Grünwald-Giemsa-FISH (MGG-FISH) technique.[5]

We recently cared for a 75-year-old woman because of a duodenal ulcer. On admission her hemoglobin was 10.3×10^9 gr/L, platelet count 83×10^9/L and leukocyte count 10.7×10^9/L with 26% atypical plasma cells. Serum protein electrophoresis showed a type IgGλ monoclonal component. The bone marrow aspirate revealed an 80% atypical plasmacytosis.

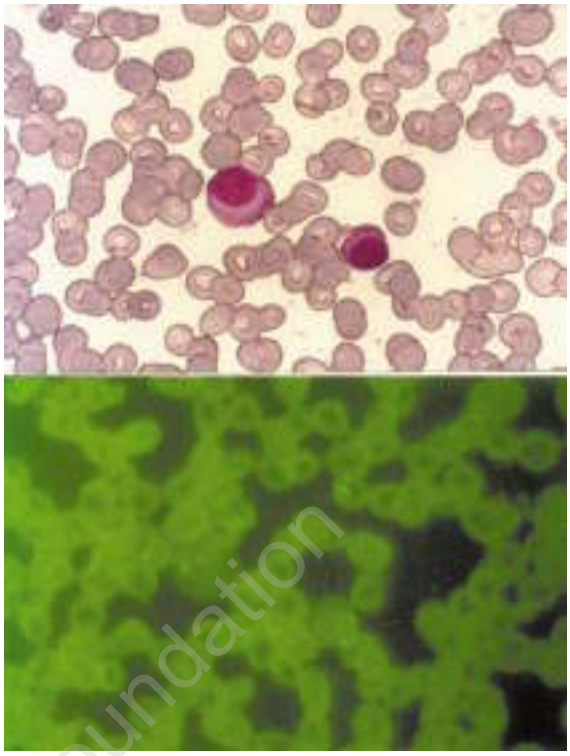

Figure 1. Cytomorphology and interphase FISH of circulating plasma cells from a patient with plasma cell leukemia. In (A), May-Grünwald Giemsa stained plasma cells were identified. In (B), plasma cells were relocated after FISH with spectrum green direct labeled chromosome 18 specific alpha satellite DNA probe. Two hybridization signals are present for chromosome 18.

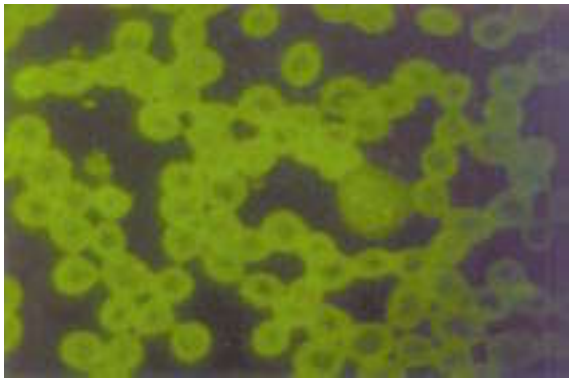

Figure 2. A May-Grünwald Giemsa stained plasma cell was identified and relocated after FISH with a spectrum green direct labeled chromosome 18 specific α-satellite DNA probe. Three hybridization signals are present for chromosome 18.

The patient was diagnosed as having plasma cell leukemia and died 15 days later without receiving any treatment.

Chromosome analysis was performed on a 72-hour culture of peripheral blood with phytohemagglutinin (PHA) and revealed a normal karyotype in 40 mitoses, probably due to stimulation of non-malignant cells.