Cd56 in t-cell acute lymphoblastic leukemia: a malignant transformation of an early myeloid-lymphoid progenitor?

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Concerning biological and clinical aspects,T-cell acute lymphoblastic leukemia is now considered to be a heterogeneous disorder. Here we analyze the impact of particular phenotypic patterns on prognosis of 30 cases of T-cell ALL; poor response to induction treatment and short survival were observed in patients who expressed CD56. The antigen profile of these cases suggests a malignant transformation of an early progenitor belonging to both pathways of differentiation, myeloid and lymphoid. We studied 30 consecutive patients diagnosed as having T-lineage ALL between June 1993 and April 2002. Diagnosis was based on FAB morphological criteria by May-Grünwald-Giemsa staining and EGIL[1,2] immunophenotypic criteria by flow cytometry on bone marrow aspirates. Inmunophenotypic analyses were performed according to standard techniques on a FACScan flow cytometer. The expression of the following antigens was evaluated: CD3, CD4, CD5, CD7, CD10, CD15, CD16, CD19 ,CD20, CD34, Tdt, CD1a, CD2, CD8, CD13, C14, CD22, CD33, CD56, CD117,CD19,CD45, HLA-DR, both CD4 and CD8, TCR γδ or αβ. T- lineage was confirmed in keeping with EGIL proposals. Any aberration in surface antigen expression with regard to hypothetical normal T-lineage differentiation scheme was recorded.[3] All patients were given the Spanish PETHEMA 93[4] and PETHEMA 96[5] protocols for ALL. Relapsing patients were included inexperimental protocols. Complete remission (CR) was considered when bone marrow blast cell counts were below 5%. Continous variables were dichotomized according to the more relevant data in medical literature.[6] All statistical analyses were performed using the SPSS software package. Patients clinical and laboratory data are summarized in Table 1. Twenty-four (80%) of 30 patients achieved CR after induction phase;two of them died because of HCST-related toxicity; nine responding patients relapsed and only one of them is alive.The 5-year overall survival (OS) for the entire group was 39.8% (95% CI, 18.7-60.9) and 5-year disease-free survival (DFS) was 39.1% (95% CI, 20.7- 57.5). The median OS duration was 33.8 months (range 13.4- 54.3) and the median DFS duration, 15.2 months (range 6.5-243.9). Concerning response to induction treatment, only leukocyte count higher than 20 x 10^9/L and CD56 expression were found to be significant adverse factors by univariate analysis. In multivariate analysis, CD56 expression was finally the only independent prognostic factor for achieving CR in this group (p=0.02). Of note, all CD56-positive T-cell ALL cases expressed CD34 (p=0.04). In addition, CD56- positive cases of T-ALL showed fewer pan-T markers than did CD56-negative T-ALL cases(3 ± 1.4 vs. 4.9 ± 1.7 respectively, p=0.04).

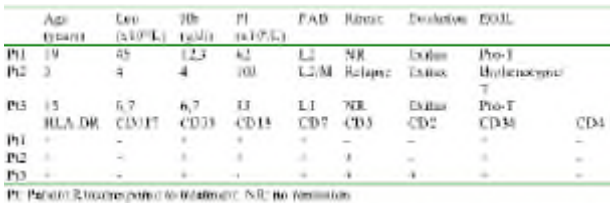
Table 1. Patients' clinical characteristics and laboratory data at diagnosis

Variable	*Media(range); #Number(percentage)	Aberrant antigen	%
Age(years)*	12.9(1-30)	CD117	(16.7%)
WBC(x10⁹/L)*	131.6(2-578)	CD34	(46.7%)
Hb(g/L)	101.4(40-153)	CD13	(16.7%)
Platelets (x10⁹/L)*	116.1(20-424)	CD15	(3.3%)
BM blasts(%)*	85.2(45-98)	CD33	(20%)
Gender(M/F)#	23/7(76.7/23.3)	HLA-DR	(30%)
CNS-i#(y/n)	2/28(6.7/93.3)	CD19	(10%)
MM#(y/n)	9/21(30/70)	CD10	(26.7%)
FAB(L1/L2)#	12/18(40/60)	CD56	(13.3%)

*: Median (range); Number(percentage)
MM: Mediastinal mass; CNS: Central Nervous System involvement

None of the CD56 positive cases coexpressed CD4. EGIL subtype frequency and white cell count were comparable among CD56 positive and negative cases. The clinical and laboratory data of the CD56 group are detailed in Table 2. Here we found CD56 to be a marker associated with a worse outcome. Our T-cell ALL patients expressing surface CD56 are likely to fail to achieve initial CR and accordingly they have poorer survival rates. CD56 T-cell ALL is an infrequent subset(4 of 30 patients). Three of these four CD56-positive cases show a special phenotype: all of them are positive for CD34 and express at least one other aberrant marker, such as CD19 or some myeloid antigen. CD4 coexpression absence excluded dendritic cell neoplasms.[7] Some previous reports suggest of the role of CD56 antigen as an adverse prognostic factor in acute leukemia[8] but, as T-lineage for our CD56 cases is unequivocally confirmed by cytoplasm detection of CD3 together with the absence of cytoplasm CD1a and myeloperoxidase, CD56-positive T-cell ALL may represent an inmature type of T-cell leukemia still expressing markers from several lineages. Suzuki et al. described a hybrid myeloid/ natural killer acute leukemia characterized by a lymphoblastic appearance (namely L2), extramedullary involvement and refractory to therapy.[9] These cases expressed CD34, HLA-DR, CD7, CD33 and CD56 but lacked T-markers other than CD7(only one case showed CD2). Another subtype of myeloid/natural killer acute leukemia, immunophenotypically more mature, was reported by Scott et al.[10] being CD34_ HLA- DR- CD33+ and CD56+. However, our CD56-positive cases displayed CD2 (1 patient) and CD5 (3 patient), so that they seem to be more committed to the T-lineage. It is posible that these entities (ours and those from myeloid/natural killer origin) represent the malignant counterpart to a normal early-progenitor not well defined but with T, NK and myeloid features. Because it has a better initial response if chemotherapy including daunorubicin and cytosine arabinoside is used at the onset of treatment, myeloid/natural killer acute leukemia must be considered at diagnosis in these cases of possible T-ALL with poor phenotypic expression of T-lineage markers.

Table 2. Clinical and phenotypical data of 3 of CD56-positive cases.



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References

1. Uckun FM, Sensel MG, Sun L, et al. Biology and treatment of childhood T-lineage acute lymphoblastic leukemia. Blood 1998; 91:735-46.
2. Kaneko Y, Frizzera G, Shikano T, et al. Chromosomal and immunophenotypic patterns in T cell acute lymphoblastic leukemia (TALL) and lymphoblastic lymphoma (LBL). Leukemia 1989;3: 886-92.
3. Bene MC, Castoldi G, Knapp W, et al. Proposals for the immunological classification of acute leukemias . European Group for the Immunological Characterization of Leukemias (EGIL). Leukemia 1995; 9: 1783-6.
4. Ribera JM, Ortega JJ, Oriol A, et al. PETHEMA Group, Spanish Society of Hematology. Prognostic value of karyotypic analysis in children and adults with high-risk acute lymphoblastic leukemia included in the PETHEMA ALL-93 trial. Haematologica 2002; 87: 154-66.
5. Ortega JJ, Ribera JM, Oriol A, et al. PETHEMA Group, Spanish Society of Hematology. Early and delayed consolidation chemotherapy significantly improves the outcome of children with intermediate risk acute lymphoblastic leukemia. Final results of the prospective randomized PETHEMA 89-ALL trial. Haematologica 2001; 86: 586-95.
6. Pui CH, Behm FG, Crist WM. Clinical and biologic relevance of immunologic markers studies in childhood acute lymphoblastic leukemia. Blood 1993;82: 343-62.
7. Feuillard J, Jacob MC, Valensi F, et al. Clinical and biologic features of CD4 + CD56 + malignancies. Blood 2002; 99:1556-1563.
8. Raspadori D, Damiani D, Michieli M, et al. CD56 and PGP expression in acute myeloid leukemia: impact on clinical outcome. Haematologica 2002; 87: 1135-40.
9. Suzuki R, Yamamoto K, Seto M, et al. CD7+ and CD56 myeloid/natural killer cell precursor acute leukemia: a distinct hematolymphoid disease entity. Blood 1997;90:2417-28.
10. Scott AA, Head DR, Kopecky KJ, et al. HLA-DR, CD 33+, CD56+, CD16- myeloid/ natural killer cell acute leukemia: a previously unrecognized form of acute leukemia potentially misdiagnosed as French-American-British acute myeloid leukemia-M3. Blood 1994;84:244-55.