

## CD117 Expression and Serum CD117 in Acute Non Lymphoid Leukemia

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### ABSTRACT

**Objective:** The c-kit proto-oncogene encodes a 145 KDa tyrosine kinase transmembrane receptor that binds stem cell factor (SCF). The c-kit has been classified as CD117 and the monoclonal antibody is claimed to be useful in immunophenotyping of acute leukemia. Many studies stated that c-kit is a reliable and specific marker to detect leukemic cells committed to the myeloid lineage regardless of the French-American British (FAB) subtype. Soluble c-kit (sc-kit, kits, s-kit) is produced by proteolytic cleavage of the cell surface receptor.

**Patients & Methods:** In this work, detailed phenotyping and CD117 surface expression were performed on 60 patients with acute myeloid leukemia; 56 newly diagnosed, 2 relapsing AML and 2 biphenotypic leukemia (BAL). The cases comprised 35 males and 25 females with ages ranging from 4 months to 82 years. Assay of serum CD117 was performed by ELISA on 50 of the AML cases and 15 age- and sex-matched healthy subjects as a control.

**Results:** Surface expression of CD117 was detected in 24.1% of AML cases. It was detected in 27.6% of the adults and in 20.7% of the children. There was a significant correlation between CD117 surface expression and CD34 expression ( $p=0.001$ ). Concordance between CD34 and CD117 expression was encountered in 50 cases (86.2%), both positive in 12 (20.68%) and both negative in 38 (65.5%). No significant correlation was encountered between CD117 surface expression and its serum level ( $p=0.823$ ). There was no significant correlation between CD117 and FAB subtypes.

**Conclusion:** CD117/CD34 expression and/or sCD117 may be used for detection and follow up of patients of MRD.

**Key Words:** c-kit - CD117 - sc-kit - AML - MRD.

### INTRODUCTION

The c-kit proto-oncogene encodes a 145 KDa tyrosine kinase transmembrane receptor

that binds stem cell factor (SCF). Thus, it plays a key role in hemopoiesis, melanogenesis and fertility. Both act at multiple levels of hemopoietic hierarchy to promote cell survival, proliferation, differentiation, adhesion and functional activation [1].

The c-kit has been classified as CD117 and the monoclonal antibody is claimed to be useful in immunophenotyping of acute leukemia. Many studies stated that c-kit is a reliable and specific marker to detect leukemic cells committed to the myeloid lineage regardless of the French-American-British (FAB) subtype, and therefore should be included on routine basis for the diagnosis of acute leukemia [11]. Others claimed its discriminative expression on different FAB subtypes [7,11].

Soluble c-kit (sc-kit, kits, s-kit) is produced by proteolytic cleavage of the cell surface receptor [21]. A limited number of studies have investigated serum sc-kit level in acute myeloid leukemia (AML); sc-kit level in AML patients was higher in those with blasts of immature phenotype (FAB M0, M1 & M2) and to be related to leukemic cell burden [17]. However, the significance of serum sc-kit in health and disease remains unclear.

The aim of this work is to evaluate the specificity of CD117 as a tumour marker for AML and to investigate the diagnostic role of the soluble form of c-kit receptor in serum of AML patients and to verify their value in discrimination between FAB subtypes.

## PATIENTS AND METHODS

### *Patients:*

This work was performed on 60 patients with acute myeloid leukemia; 56 newly diagnosed AML cases, 2 relapsing AML and 2 biphenotypic acute leukemia (BAL). They included 35 males and 25 females. Their ages ranged from 4 months to 82 years. All cases presented to the Medical and Pediatric Oncology Departments, National Cancer Institute, Cairo University. All patients were diagnosed according to standard methods including: detailed history, thorough clinical examination, complete blood picture, bone marrow examination & cytochemical stains [12].

Immunophenotyping was carried out on peripheral blood or bone marrow using fluorescent labeled monoclonal antibodies (MoAbs). Double and triple marker labeling were performed, including proper isotype controls. The Mo Abs included: CD1a, CD2, CD3, CD4, CD5, CD7 & CD8 as T markers, CD19, CD20, CD22, CD24, cytoplasmic  $\mu$ , Kappa & lambda as B markers, CD13, CD14, CD33 & myeloperoxidase as myeloid markers, CD16 & CD56 for natural killer & other markers as CD10, CD34 & HLA-DR. Monoclonal antibodies were obtained from Immunotech, Coulter Corporation, Cymbus biotechnology, Becton Dickinson, Dako & IQ products. A whole blood direct staining method was used [16] and cases were assigned to different immunophenotypes as previously described [9]. CD117 (CBL 531F) was obtained from Cymbus biotechnology. The reactivity was detected using flowcytometry (Coulter XL). Assay of Serum CD117 was performed using Quantitative Diaclone ELISA Kit (solid phase sandwich Enzyme Linked Immunosorbent Assay). Fifteen healthy subjects of matched age and sex were included as control for serum c-Kit.

## RESULTS

In this work 58 AML and 2 BAL patients were studied. Clinically, lymphadenopathy and bleeding tendency were the most frequent findings, being found each in 21 patients (35%), followed by splenomegaly in 19 (31.7%) and hepatomegaly in 18 (30%). Other clinical data included fever in 15 patients (25%), hypertrophied gums in 3 (5%) including 1 M0, 1 M3 & 1 M4, proptosis in 3 (5%) including 1 M1, 1 M2 & 1 M5b and disturbed level of consciousness

in only one M1 case (1.67%). The WBC count ranged from 1 to 227 with a mean of  $41.18 \pm 50.23 \times 10^9/L$ . The hemoglobin level ranged from 3.3-12.9 with a mean of  $7.6 \pm 2.09$  g/dL. Hemoglobin levels  $<10$  g/dL were found in 52 patients (86.67%), while 8 patients (13.33%) showed hemoglobin level  $\geq 10$  g/dL. Platelet count ranged from 5.6-337 with a mean of  $60.65 \pm 71.21 \times 10^9/L$ . Platelets were  $< 100$  in 51 patients (85%) PB absolute malignant cell count ranged from 0.8-188.41 with a mean of  $32.84 \pm 45.070 \times 10^9/L$ . The BM malignant cell percentage ranged from 30 to 98% with a mean of  $74.52 \pm 19.94\%$ .

### *Surface Marker Expression:*

Table (1) shows the expression of CD117 and CD34 according to FAB subtypes. CD117 expression was noted in 14/58 cases (24.1%); 8/29 (27.6%) in adults and 6/29 (20.7%) in children. CD117 was coexpressed with CD34 in 12/58 cases (18.3%). The most common FAB subtype which expressed CD117 was M0 in 3/4 cases (75%), followed by M5a in 1 / 3 cases (33.3%), M2 in 3/10 cases (30%), M1 in 6/21 cases (28.57%), M5b in 1/4 cases (25%), M3 in 1/12 cases (8.3%) and no expression was noted in the 4 cases of M4. One of the 2 cases of BAL showed CD117 expression. There was no significant association between CD117 and FAB subtypes ( $p= 0.227$ ).

The association between CD117 expression and FAB subtypes as well as stratification of different combinations of CD117 and CD34 expression are presented in table (1). None of the 4 M4 cases studied expressed CD117, while one case expressed CD34, 2/4 M0 cases showed expression of CD117 without CD34, while 3/21 M1, 2/12 M3 & 1/4 M4 showed CD34 without CD117 expression. Concordance between CD34 and CD117 expression was encountered in 50 cases (86.2%) (Fig.1). Both were positive in 12 (20.68%), while both were negative in 38 (65.5%). Disconcordance was encountered in 8 cases with CD117 +ve CD34 -ve in 2 (3.45%) (Fig. 2) and CD34 +ve CD117 -ve in 6 (10.34%).

The frequency of various marker expression in different cases is presented in table (2). All cases expressed either CD13 or CD33 and 41/60 cases (68.3%) expressed both. CD13 was expressed as a surface marker in 44/58 cases (75.8%) & as a cytoplasmic marker in the re-

maining 7 cases (12%). One of the 2 biphenotypic cases was expressing CD13, CD33, CD34, CD117, CD14, CD19 & CD22. The other one was expressing CD13, CD33, HLA DR, CD19, CD22 & CD10.

No correlation between CD117 expression and any of the surface markers was detected except for CD34 ( $p \leq 0.001$ ) (Table 1 & Fig. 3) & CD7 ( $p = 0.034$ ) (Fig.4).

Table (1): Expression of CD117 & CD34 in 58 AML patients in relation to FAB subtypes.

FAB subtype	Number of cases	CD117 +ve CD34 +ve	CD117 +ve CD34 -ve	CD117 -ve CD34 +ve	CD117 -ve CD34 -ve
M0	4	1 (25%)*	2 (50)	Zero	1 (25%)
M1	21	5 (23.81%)	Zero	3 (14.29%)	13 (61.9%)
M2	10	3 (30%)	Zero	Zero	7 (70%)
M3	12	1 (8.33%)	Zero	2 (16.67%)	9 (75%)
M4	4	Zero	Zero	1 (25%)	3 (75%)
M5a	3	1 (33.33%)	Zero	Zero	2 (66.67%)
M5b	4	1 (25%)	Zero	Zero	3 (75%)
Total	58	12 (20.68%)	2 (3.45%)	6 (10.34%)	38 (65.5%)

\* No. of positive cases (percentage)

Table (2): The frequency of various marker expressions on 58 AML patients.

Marker	Expression No. (%)	Marker	Expression No. (%)	Marker	Expression No. (%)
CD13	51 (87.9%)	Myeloperoxidase	32(55.1%)	CD7	11(18.9%)
CD33	51 (87.9%)	HLA DR	32(55.1%)	CD2	9 (15.5%)
CD14	10 (17.2 %)	CD19	1 (1.7%)	CD5	3 (5.1%)
CD117	14 (24.1%)	CD24	2 (3%)	CD10	—
CD34	17(29.3%)	CD16	4 (6.8%)	CD56	3 (5.1%)

*Serum c-kit:*

Serum level of sCD117 was determined in 50 AML patients as well as 15 healthy controls. sCD117 was elevated in 16/50 patients (32%) ( $p = 0.028$ ). These included 5 M2 (31.25%), 4 M1 (25%), 3 M3 (18.75%), 2 M5b (12.5%), one M5a (6.25%) and one M4 (6.25%). Serum c-kit level ranged from 0.66 to 46.48 with a mean of  $13.22 \pm 14.44$  ng/ml compared to a range from 4.05 to 5.45 with a mean of  $4.79 \pm 0.44$  ng/ml in the control group ( $p$  value < 0.028). No significant correlation was encountered between surface expression of CD117 and its serum level ( $r -0.33, p = 0.823$ ) Fig. (5).

Table (3) shows the expression of surface CD117 and level of sCD117 in serum of studied patients. No statistically significant correlation was observed between both parameters.

Table (3): Expression of CD117 and level of serum CD117 in 45 AML.

FAB subtype	Number of cases	CD117 +ve sCD +ve	CD117 +ve sCD -ve	CD117 -ve sCD +ve	CD117 -ve sCD -ve
M0	4	Zero	3 (75%)	Zero	1 (25%)
M1	12	1 (8.33%)*	4 (33.33%)	2 (16.67%)	5 (41.67%)
M2	9	1 (11.11%)	2 (22.22%)	3 (33.33%)	3 (33.33%)
M3	11	Zero	1 (9.091%)	3 (27.27%)	7 (63.64%)
M4	3	Zero	Zero	1 (33.33%)	2 (66.67%)
M5a	2	1 (50%)	Zero	Zero	1 (50%)
Total		3(6%)	11(22%)	11(22%)	20(40%)

\* Number of cases (percentage)

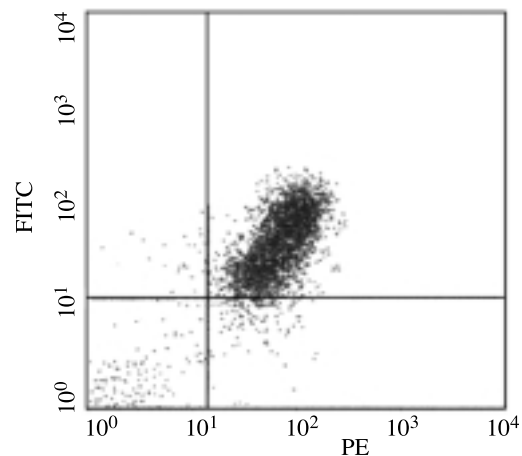


Fig. (1): A case coexpressing CD117 fluorescence isothiocyanate (FITC) and CD34 phycoerythrin (PE).

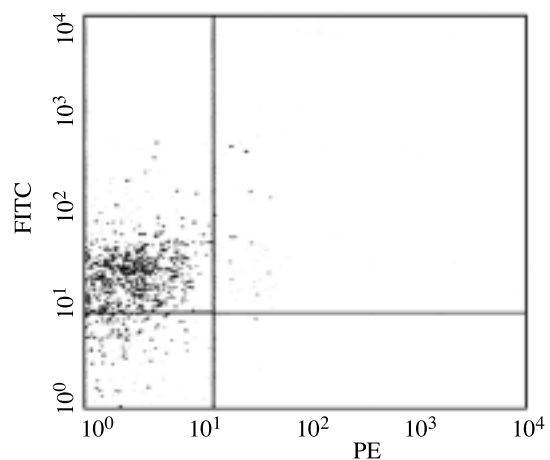


Fig. (2): A case expressing CD117 fluorescence isothiocyanate (FITC) and negative for CD34 phycoerythrin (PE).

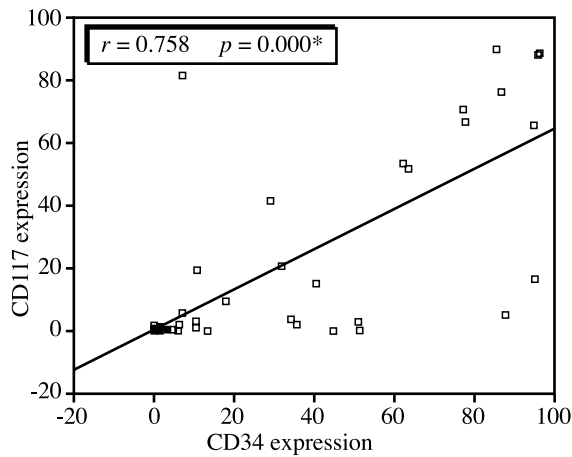


Fig. (3): Correlation between CD117 and CD34 expression in the studied cases, ( $p < 0.05$ ).

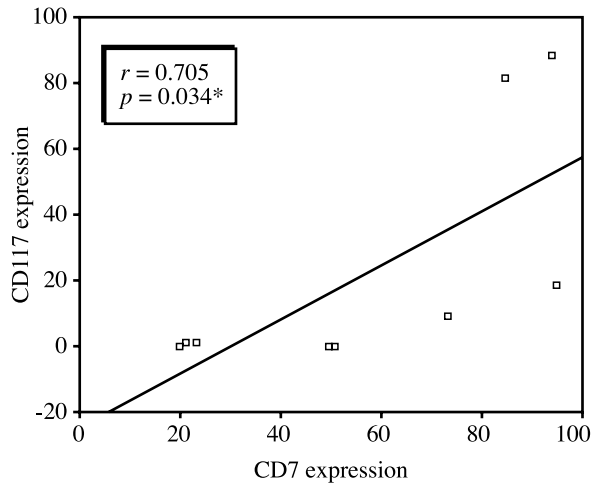


Fig. (4): Correlation between CD117 and CD7 expression in the studied cases, ( $p < 0.05$ ).

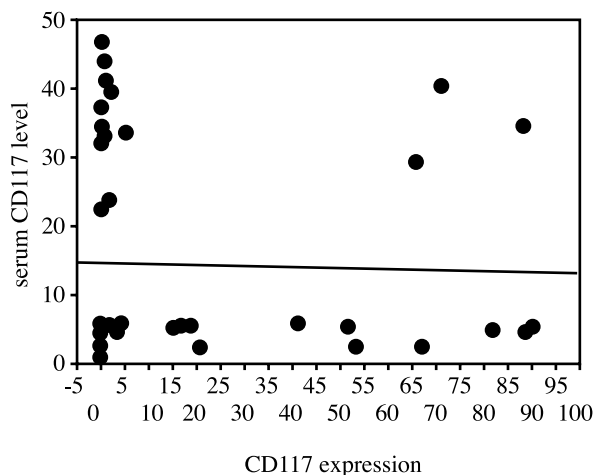


Fig. (5): Correlation of surface CD117 expression and serum CD117 level in AML cases,  $r = -0.03$ ,  $p = 0.82$ .

## DISCUSSION

AML is a disease resulting from the neoplastic proliferation of hemopoietic cells. It can arise in a lineage-restricted cell or in a multipotential stem cell capable of differentiating into cells of erythroid, granulocytic, monocytic and megakaryocytic lineages. A series of genetic alterations rather than a single event may contribute to the malignant transformation. These alterations may occur as inappropriate expression of oncogenes and/or loss of function of tumor suppressing genes. Leukemic cells express certain nuclear, cytoplasmic and cell surface antigens, characterization of which is referred to as immunophenotyping, which is important in diagnosis and classification of AML [3].

The c-kit protooncogene encodes a 145 KDa tyrosine kinase transmembrane receptor, which plays a key role in hemopoiesis, as it is the receptor for the stem cell factor. c-kit is expressed in a minority (< 5%) of bone marrow progenitor cells, half of which expresses CD34 and some appear to be committed to the myeloid lineage [8].

In this work, 58 patients with AML and 2 with BAL were studied. CD117 was encountered in 14/58 cases (24.1%). These results are comparable to what has been reported by Chui et al. [6], who reported 6/20 cases (30%) with CD117 expression among Chinese AML patients of Hong Kong. The percentage of CD117 positivity in the current study (24.1%) is lower than that reported by others where figures varying between 60% & 91% were reported. [2,4,5,10,11,14,18]. The use of different Mo Abs cannot explain the variable results since the same monoclonal antibody (YB5.B8) used by Chui et al. [6] who reported 30% as well as Valverde et al. [18] and Bene et al. [4] who reported a higher frequency (66.6 and 67%, respectively).

Regarding the incidence of c-kit positive cases in pediatric and adult AML patients, no substantial difference was encountered, although the proportion was slightly higher in adult AML (27.6%) than in pediatric AML patients (20.7%). Considering BAL, the CD117 positive case was an adult, while the pediatric one was CD117 negative. The higher incidence in adults is consistent with what has been reported by Bene et al. [4] who detected CD117 positivity in 69% (613/883 patients) in adult AML versus 58% (128/220) in pediatric AML

and 1/5 in pediatric BAL patients and 2/6 adult BAL patients.

In this work, no significant association was encountered between CD117 and FAB subtypes, though a higher percentage of positive cases was encountered in M0 (75%), M2 (30%) and M1 (23.8%) subtypes. The low frequency of CD117 expression in M3 (8.3%) is consistent with what was reported by Knapp et al. [8] and Reuss-Borst et al. [13] who stated that CD117 expression in APL is uncommon. On the other hand, Di Noto et al. [7] detected CD117 expression in 8/16 (50%) of APL patients, thus identifying a subgroup of M3 not associated with a particular phenotypic, morphologic or biomolecular features. This latter finding was confirmed in a large series including 59 M3 cases with c-kit expressed on 62%. The discrepancy between different studies may be due to the small number of cases in some series or true biological differences between different ethnic groups.

In this work, the 4 patients with M4 lacked CD117 and this is contradictory to what has been found by many researchers as Bene et al. [4] who detected CD117 expression in 99/187 (53%) of M4 cases and that of Nomdedéu et al. [11] who detected it in all M4. cases (7/7). The number of cases in our series is too small to make valid comparison but the number in the latter study is also small (only 7); this would again raise the possibility of true biological difference.

In this study, positivity of CD117 in M5 (1/3 in M5a and 1/4 in M5b) is different from what was reported by Nomdedéu et al. [11] who studied 55 AML patients including 5 M5a and 8 M5b; only 5 cases of the 55 were CD117 negative (4 of them were M5b). These authors reported that absence of CD117 expression in AML suggests M5b subtype. Cascavilla et al. [5] also found that 10/11 cases of M5b (91%) lacked CD117 antigen, whereas 100% of M5a cases expressed CD117. In the present study, only 3 cases of M5a and 4 cases of M5b were studied. The small number of the studied cases as well as those of the literature, on account of the frequency of M5, makes it difficult to reach a firm conclusion. The lack of significant correlation between CD117 positivity and FAB subtypes in this study, however, has also been reported by other researchers [4,5,15,16,18].

In this work, CD117 was expressed in 14 / 58 cases (24.1%) of AML patients with significant correlation to CD34 (P 0.001). Both markers were co-expressed in 12 & both were lacking in 39, i.e. a concordance rate (both +ve or both -ve) of 50/60 (86.2%). This is slightly higher than the finding of Bene et al. [4] who reported a concordance rate of 76%. The high concordance is consistent with many studies [4, 5,14,15]. These figures of association between CD117 and CD34 are contradictory to that reported by Wells et al. [19] who stated that although CD117 is a stem cell factor receptor, it did not correlate with CD34 expression. However, these authors worked mainly on relapsed cases. The de novo cases in this series expressed both markers in 4/10 cases (40%).

In the largest series studied [4], 982 AML cases from 5 European institutions (106 M0, 191 M1, 258 M2, 59 M3, 187 M4, 125 M5, 43 M6 and 13 M7) were analyzed. They used 3 different MoAbs: YB5B8, 95C3 and 102B4E1. CD117 was reported in 66% of the cases with concordant CD34 expression in 76% of the cases. Our corresponding figure was 86.2%, but with more double -ve (65.5%) than double +ve (20.68%). Accordingly, the difference between our results and those with high c-kit expression frequency is actually in CD34 expression as well. This difference cannot be attributed to the maturity level as our M0-M2 cases contributed 50.1% compared to 56.6% in Bene-'s cases [4]. Thus, we have a real difference in the frequency of CD34 expression, which might reflect a true biological difference.

A higher concordance rate was also reported in another large series by Schwartz et al. [14] who studied 917 German AML patients; CD117 expression was present in 63% of them. Among these, 67% were CD34+ whereas only 10% of CD34+ cases were negative for CD117. From these results, Schwartz et al. [14] stated that CD117 expression may help to identify phenotypically immature AML, but fails to identify myeloid differentiation of leukemic blasts in approximately one third of patients.

On account of this high incidence of CD117 expression in AML cases in some series, it was claimed to be a better marker for diagnosis of AML [2,4,5,10,11,14]. This is not the case in our hands as CD117 expression was encountered in only 24.1% and we still consider CD13 and/or

CD33 much more sensitive being positive in 87.9%, while 41/60 (68.3%) of our cases expressed both antigens. However, the role of myeloperoxidase is still superior to all markers in the diagnosis of AML whether by cytochemistry or immunophenotyping.

In this work, serum c-kit level was evaluated in 49 patients with AML and one with BAL and was elevated in 15 patients compared to the control group, with no significant correlation between its level and FAB subtype, surface CD117 expression or PB absolute malignant cell count. To the best of our knowledge, only 2 reports [17,20] are available on sc-kit in AML. They reported sc-kit level to be significantly increased in M1&M2 and decreased in M4 & M5 and to be correlated to absolute PB blast count. They concluded that the sc-kit level is related to the stage of differentiation of AML blasts and is useful for assessment of leukemic cell burden. The controversy between their results and that of the present study might be explained by what has been stated by Wypych et al. [20], that the presence of SCF or other binding proteins could potentially influence the c-kit ELISA results. SCF is present in normal human serum in appreciable amounts and may be present in AML patients in variable amounts, thus it might affect the results in different patients to different degrees. However, this would not explain the presence of serum c-kit in the absence of surface expression. This latter situation may arise if there is an abnormality in the c-kit anchoring sequence that prevents, it from attachment to the cell membrane and consequently get immediately released in the serum. In all the situations, serum c-kit provides a marker that can be followed up for monitoring of therapy and disease status in positive cases.

In conclusion CD117, a known stem cell factor, is expressed on 24.1% of ANLL; it is not superior to CD13 & CD33 in diagnosis of ANLL. It showed no relation to FAB subtype, but it provides a marker for minimal residual disease detection especially in combination with CD34. C-kit expression showed no correlation to serum c-kit level; the presence of the latter can also be used as a tumor marker for follow up of patients and monitoring of therapy.

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