Zagazig University Medical Journal
www.zumj.journals.ekb.eg

DOI: 10.21608/zumj.2019.10047.1146 Hematology

ORIGINAL ARTICLE

CD34 Expression in Adult Acute Myeloid Leukaemia is an Independent Poor Prognostic Factor

Ayman Fathy Abdelhalim 1, Hossam Eldin Salah 2, Ahmed Amer 1*
1 Hematology unit, Internal Medicine Department, Zagazig University Hospitals, Zagazig, Egypt
2Clinical pathology Department, Zagazig University Hospitals, Zagazig, Egypt;

*** Corresponding author:**
Ahmed Amer
Hematology unit, internal medicine department, Faculty of Medicine, Zagazig University, Postal Code: 44519.
Email:
Dr.ahmedbadwy@hotmail.com

Submit Date: 25-03-2019
Revise Date: 30-06-2019
Accept Date: 01-07-2019

ABSTRACT

Background: CD34 is a marker of hematopoietic stem cells (HSCs) and hematopoietic progenitor cells as well as a marker of several other non-hematopoietic cell types. There is much debate on whether expression of CD34 on malignant acute myelogenous leukemia (AML) blast cells affect the prognosis and response to treatment or not and if it is an independent prognostic factor or affected by other prognostic factors, especially the cytogenetics. Methods: This prospective study had been carried out at Hematology Unit, Zagazig University Hospitals. It included 90 denovo AML patients. CD34 expression was identified by Flow cytometric studies of bone marrow aspirate. It was considered positive if a cut-off level of 10% expression was exceeded. This was then analyzed to detect its impact on outcome and its correlation to other risk factors especially cytogenetics. Results: sixty (66.7%) of the AML patients were CD34 positive and their survival was shorter than patients with negative CD34 expression. CD34 positive AML cases had lower rate of achievement of complete remission. CD34 positivity was significantly linked to less differentiated FAB subtypes (M0, M1, and M2) as well as non-favorable risk cytogenetics. However, multivariate cox regression analysis proved that CD34 positivity confers an independent poor prognostic impact apart from its association with these poor risk factors. Conclusions: CD34 expression may be considered as a poor prognostic biomarker of survival in AML patients, independent from other poor prognostic factors. Its role in AML different subgroups layered by different gene mutations and chromosomal aberrations needs further extensive .studying.

Key words: AML, CD34, Prognosis, cytogenetics

INTRODUCTION

Acute myeloid leukemia (AML) is a malignant disorder of the blood characterized by defective proliferation and differentiation functions of hematopoietic precursor cells, leading to abnormal accumulation of immature precursor cells and impairment of normal growth and maturation of cells involved in normal formation of mature functioning blood cells. 1 AML accounts for about 80% of acute leukemia in adults and 20% of acute leukemia in pediatrics. 2

The prognosis for AML patients varies greatly, ranging from very short survival even for a few days to complete cure. Clinical outcome can be in part predicted by age, performance status, and cytogenetic findings. 3 However, the prognosis of an individual AML patient can't yet be estimated precisely. It is therefore important to find out new biomarkers for the prediction of prognosis, treatment response, detection of relapse, and monitoring for minimal residual disease. 4

CD34 is a cluster of differentiation that was described for the first time by Civin and colleagues. as a cell surface glycoprotein. 5 It works as a cell-to-cell adhesion promotor molecule 6.. It may play a role to mediate the attachment of bone marrow stem cells to BM

extracellular matrix or directly to stromal cells. 7 8

There is still much debate among researchers and clinicians on whether expression of CD34 on malignant myeloid leukemia cell affect the prognosis and response to treatment or not and whether it is an independent prognostic factor or affected by other prognostic factors, especially the cytogenetics. 9

CD34 was extensively studied for its prognostic role in late eighties and nineties. Because of contradictory data, CD34 expression was considered not to be of value as prognostic marker by Kanda and colleagues , 2000 who conducted a meta-analysis of data of 2483 Patients from 22 Studies 10. Nucleophosmin1 (NPM1) and fms like tyrosine kinase 3- internal tandem duplication (FLT3-ITD). 11

This study aimed to evaluate the prognostic impact of expression of CD34 in adult patients with AML and its relation to other prognostic factors, especially cytogenetics.

METHODS

This prospective cohort study was carried out at Hematology Unit, Internal Medicine Department, Zagazig University Hospital. It included 90 denovo AML patients. Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University on 8/1/2017, IRB #: 3319/8-1-17. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. All adult AML patients of both sexes above 18 years of age with normal liver and renal functions and good PS were included. All patients had given their informed consent. All patients having severe cardiac, pulmonary, hepatic, renal, neurological, metabolic disease, or concomitant malignancies were excluded from the study. All patients were subjected to thorough history and physical examination, basic laboratory investigations including: Complete blood counts, Liver & kidney functions, Serum electrolytes, coagulation profile, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), tests for hepatitis B virus(HBV), hepatitis c virus (HCV), human immunodeficiency virus (HIV), pelvi-abdominal ultrasound, and Bone Marrow Aspiration. Immunophenotyping of EDTA bone marrow sample was performed on Becton Dickinson BD, San Diego, USA, FAC scan flow cytometer using acute leukemia panel (CD33, CD34, MPO, CD5, CD3, TDT, CD10, CD13, CD14, CD7, CD19, CD20, CD22, CD64, CD79a, HLA-DR) using a panel of fluorescein (FITC) and phycoerythrin (PE) conjugated MoAbs reactive with these antigens. Detection of CD34 expression by Flow cytometry on malignant myeloid cells of bone marrow aspirate used FITC florescent monoclonal antibody and it was considered positive if a cut-off level of 10% expression was exceeded. Conventional Cytogenetic study was done for all patients.

All these patients were treated by induction 3&7 chemotherapy protocol i.e. 3 days of adriamycine 25mg/m2 and 7 days of continuous infusion of cytarabine 100mg/m2. BM aspirate evaluation was carried out at day 14 of end of induction protocol. Response was assessed according to standardized international response criteria.

After achievement of remission patients with favorable cytogenetics were challenged for consolidation high dose cytarabine regimens. However those with unfavorable cytogenetics or intermediate were referred for arrangement for stem cell transplantation in Cairo.

Patients were followed up 3 monthly after end of the treatment for a median follow up period of 20 months. Follow-up included Physical examination, complete blood picture, and bone marrow examination done every 3 to 6 months unless a suspicious full blood count result or clinical data warranted earlier assessment.

Statistical Analysis

The collected data were computerized and statistically analyzed using SPSS program, version 24 (IBM, New York, USA). Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data compared by independent t test. All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 indicates statistical

significance. Kaplan Meier method was used to estimate overall and disease free survival and log rank test compared survival curves (P value was considered significant at ≤ 0.05 levels). Multivariate cox regression model was used to assess the hazard ratio for events (death or relapse) in different subgroups layered by different variable

RESULTS

Clinic-demographic characteristics of study individuals are summarized in table (1).

CD34 was positive in in 60 cases (66.7%) while it was negative in only 30 cases (33.3%) of the study group.

There was no significant difference between CD34 positive and CD34 negative cases as regards mean value of age, TLC, Hemoglobin, platelets count, ESR, or LDH (table 2).

Chi square test ($\chi 2$) test was applied to test if there were any significant relation between sex, FAB subtype, cytogenetic risk, karyptype, FLT3-ITD mutation and response to treatment and CD34 expression status. Results are shown in Table (3)

It shows clearly that CD34 positivity is significantly associated with unfavorable cytogenetics, lower CR achievement. APL is mainly CD34 negative while AML M0,M1,M2 are mainly CD34 positive

Table 4 shows the distribution of studied cases in respect of detected karyotypes and its correlation with CD34 reactivity. APL with t (15; 17) is mainly CD34 negative, while t (8l21) is mainly CD34 positive. Poor karyotypes as chromosome 7, 5 aberrations or complex karyotypes are all associated with CD34 positivity.

Kaplan-Meier method was used to estimate two years disease free and overall survival of patients of the study using log survival function. The mean overall survival in patients with positive CD34 (10.2 ±1.2 months) was significantly lower than those with negative CD34 (15.7 ±1.7) (P=0.01). DFS was significantly higher in patients with negative CD34 than positive CD34 (12.3 ±1.6 vs 5.9±1.09 respectively, p value = 0.002) (figure 1)

Multivariate Cox regression model examined the impact of CD34 on overall survival with other prognostic factors to test its independent prognostic effect. It showed quite clearly that CD34 positivity is associated with higher mortality rates and poorer outcome independent on all other risk factors (HR = 1.3 and P value = 0.027 CI 1.1-2.9) (Table 5)

Table 1. Clinico-demographic data of the studied group

Character	No.	%
Age(in years): Range(18-77) Median (37) Mean (39) SD (16)	90	100
Sex: Male Female	 44 46	 48.8 51.2
Clinical presentation: CNS infiltration Pallor,weakness,fatigue Fever Gum hypertrophy Purpura, bleeding Lymphadenopathy Spleenomegaly Hepatomegaly Chloroma	 2 39 45 6 30 2 2 6 4	 2 43 50 7 34 2 2 7 4

Tumour lysis, renal impairment	2	2
Virology: Hcv Ab +ve HBsAg +ve Hcv/Hbv –ve	 19 0 71	 21 0 79
Bone Marrow (B.M) Blasts (%): Range (22-95) mean ±SD(70.55±20.85)	 90	 100
FAB classification: M0 M1 M2 M3 M4 M5	 ٤ ١٤ ٣٢ ١٠ ٢٠ 10	 ٤.٤ ١٥.٦ ٣٥.٦ ١١.١ ٢٢.٢ 11.1
Cytogenetic study: favorable intermediate unfavorable	 32 38 20	 35.6 42.2 22.2

FAB: French-American-British

Table 2. Comparison between CD34+ and CD34- AML cases as regards TLC, HgB, platelets count, ESR, LDH.

	CD34 status	N	Mean ± Std. Deviation	T	P value
Age	Negative	30	40.7 ± 15.7	-1.4	0.164
	Positive	60	35.6 ± 16.7		
TLC	Negative	30	40.8200 ± 39.05606	-0.8	0.422843
	Positive	60	48.1083 ± 41.15761		
Hb	Negative	30	7.4733 ± 1.78228	2.1	0.040988
	Positive	60	6.8000 ±1.25792		
PLT	Negative	30	42.0667 ± 52.88695	0.336	0.737586
	Positive	60	38.3167 ± 48.35725		
	Positive	60	63.1833 ± 91.25054		
LDH	Negative	30	1033.8000 ± 416.84036	1.3	0.199819
	Positive	60	905.5000 ± 457.01461		
ESR	Negative	30	107.7667 ± 23.64053	-0.4	0.676319
	Positive	60	110.1833 ± 26.79900		

TLC: Total leukocyte count, Hb: hemoglobin, PLT: platelets, LDH: lactate dehydrogenase, ESR: erythrocyte sedimentation rate.

Table 3. Comparison between CD34 expression status with sex, FAB classification, cytogenetic risk, FLT-ITD mutation and response to treatment

	CD34 positive No. %	CD34 negative No. %	X2	P
Male Female	29 32 31 34.5	15 16.7 15 16.7	0.022	1.0
FAB: M0 M1 M2 M3 M4 M5	 4 13.9 9 10 28 31.1 1 1.1 14 15.5 6 6.7	 0 0 5 5.5 6 6.7 9 10 6 6.7 4 4.4	19.8	0.001*
Cytogenetic: Unfavorable Intermediate Favorable	 14 15.5 35 38.8 11 12.2	 6 6.6 3 3.33 21 23.3	26.181	0.0.001*
Response: Complete remission Non response	 20 22.2 40 44.4	 24 26.6 6 6.7	17.41	0.001*

FAB: French-American-British, CR: Complete remission, NR: No response

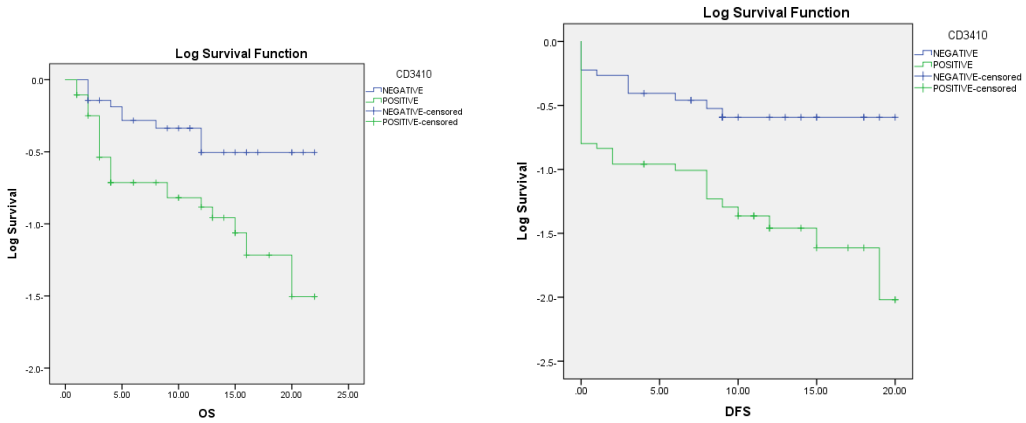
Table 4. frequencies of karyotypes detected in terms of CD34 expression status

		CD34		Total
		NEGATIVE	POSITIVE	
KARYOTYPE	-7	0	2 (2.2%)	2 (2.2%)
	-Y	0	2(2.2%)	2(2.2%)
	del 3, -7	2(2.2%)	0	2(2.2%)
	del 7q31	0	1(1.1%)	1(1.1%)
	Inv (16)	2(2.2%)	2(2.2%)	4(4.4%)
	Normal	14(15.6%)	41(45.6%)	55((61.1)
	t(15;17)	9(9.9%)	1(1.1%)	10(11.1%)
	t(16;16)	1(1.1%)	0	1(1.1%)
	t(8;21)	2(2.2%)	6(6.67%)	8(8.89)
	t(9;22)	0	2(2.2%)	2(2.2%)
	trisomy 8	0	3(3.3%)	3(3.3%)
Total		30(33.33%)	60(66.67%)	90

Table 5. Univariate and multivariate Cox regression analyses of different prognostic factors for Overall survival (OS)

Variable	Univariate			Multivariate (stepwise)		
	HR	95.0% CI	P-value	HR	95.0% CI	P-value
Age	1.02	1.001-1.039	0.044*	1.022	0.992-1.053	0.145
TLC	0.729	0.41-0.73	0.288	0.990	0.975-1.007	0.247
PS	2.564	1.8-3.6	<0.001*	1.6	1.08-2.3	0.019*
IPT (M3)	0.14	0.27-0.7	0.018*	0.159	0.03-0.68	0.014*
CYTOGENETICS	1.89	1.3-2.7	0.001*	2.36	1.76-7.35	0.0137*
CD34+	2.34	1.16-4.77	0.018*	1.3	1.1-2.9	0.027*

TLC: Total leukocyte count, PS: performance status, IPT: immunophenotype



(a) (b)

Figure 1. survival analysis of study cases according to CD34 expression status. (a) Correlation between overall survival and CD34 expression (b) correlation between DFS and CD34 expression

DISCUSSION

AML is a malignant hematopoietic neoplasm characterized by clonal proliferation of the hematopoietic stem/progenitor cell population within the bone marrow. The prognosis for AML patients varies greatly, ranging from very short survival even for a few days to complete cure. CD34 prognostic value has been tested before with much debate between researchers about its role. This study aimed to evaluate the prognostic significance of expression of CD34 in adult patients with AML and its relation to other prognostic factors, especially cytogenetics. Our findings support the hypothesis that CD34 positivity might have an independent poor prognostic effect in AML.

The incidence of AML increases with age, and is most frequently observed in older adults. The median age at diagnosis is 67 years of age1. However, in our study, the patient median age was 37 years and the range was 18-77 years. The difference may be related to higher incidence of AML in the younger age group in Egypt compared to western countries, possible early death of AML patients in older age group before diagnosis, as well as relatively small size of the study group. There was no significant correlation between age and CD34 positivity. This is consistent with results from most studies that investigated CD34 in AML. 9

In our study, males were 46.5% of patients and females were 53.5% with female to male ratio of 1.15:1. There was no significant correlation between sex and CD34 expression (p value = 1) which is exactly consistent with what Zeijlemaker and colleagues has reached. 9

M2 was the most common in our study (35.6%) followed by M4 (22.2%), followed by M1 (15.6%). APL was mostly CD34 negative. CD34 positivity was significantly correlated with M0, M1, M2 and M4. (P value

< 0.001) which is exactly consistent with what Zeijlemaker and colleagues has reached. 9

In our study, Cytogenetic analysis of patients revealed that 22.2% of them were with unfavorable cytogenetics, 42.2% were with intermediate cytogenetics, 35.6% were with favorable cytogenetics. According to Cheson and colleagues, Cytogenetic analysis of patients reveals that 34% of them were with unfavorable cytogenetics, 29% were with intermediate cytogenetics, 8% were with favorable cytogenetics and 29 % were unknown 12. Difference may be related to inability to do NPM1 and FLT3 mutation testing to all intermediate risk group patients for further risk categorization into favorable or unfavorable risk. CD34 was significantly associated with cytogenetic risk groups with p value = 0.001. This is in line with data from Zeijlemaker and collegues 9 but contradicts what Zhu and colleagues has identified. 13. This discrepancy in results may be related to unstandardized methodology of CD34 detection and cut-off value of CD34 positivity.

In our work we defined Cd34 positivity by a cut-off value of 10% of examined cellular population by Flow cytometry. Most of previous studies used 20% cut-off. However Schuurhuis GJ and colleagues used a cut-off value of 1%. Using this cut-off for defining truly CD34 negative AML, it was associated with significantly better outcome. They claim that excluding such cases from analysis leaves no prognostic value for CD34. 11

Zeijlemaker and colleagues used a new definition, without using prior cut-off. This definition used presence or absence of neoplastic CD34 positive cells, which appears to be a powerful predictor for EFS and OS in the entire group of AML patients. Therefore, this new definition not only explains conflicting results published in the past, but also indicates that this independent prognostic marker should be incorporated into AML risk stratification. 9

60 (66.7%) of AML patients had a positive CD34 while only 30 cases (33.3%) were CD34 negative. According to Raspadori D and colleagues 14, (47%) of the AML patients were CD34 negative. However, according to Schuurhuis and colleagues . 2010 (26), (23.6%) of the AML patients were CD34 negative. In Zeijlemaker W 11, CD34 negative cases were 22.3% of examined AML cases, which is very close to our results. The difference is mostly related to the different defining criteria of CD34 positivity in addition to the difference in sample size.

In our study, patients with CD34 positivity were indistinguishable from patients with negative CD34 with respect to age, sex, mean levels of total leukocyte count (TLC), Hemoglobin, platelets count, ESR, and LDH. This indicates that there is no significant correlation between CD34 expression and these risk factors in AML. This typically matches results of most studies 9,10,13,14

Regarding cytogenetic aberrations, 61% of our patients had normal karyotype, followed by t(15;17), t(8;21), inv 16, triosomy 8. These results are very near to those published by Grimwade and colleagues 15. APL with t(15;17) was mainly negative for CD34 expression (>90%) however t(8;21) was mainly CD34 positive. These are nearly similar to results from Civin and colleagues16

In our study, 44/90 patients (48%) achieved remission. Those with negative CD34 had significantly higher CR rate than CD34 positive cases (80% and 50% respectively) p value <0.001. These were nearly the same as results from Civin and colleagues 16 (87% and 59% respectively). However according to Zeijlemaker and colleagues 9 this was 67% and 58% respectively.

Survival analysis for our patients showed that those with positive CD34 had significantly lower overall survival compared to CD34 negative cases (10.2 months versus 15.7 months with p value = 0.01). Same results were identified for disease free survival (5.9 versus 12.3 months with p value 0.002). These results are consistent with data from many studies 14,17–20. However, it contradicts results from other studies 21–27. Reasons for these discrepancies include specimen analyzed (bone marrow or peripheral blood), erythrocyte-lysed whole blood versus gradient density mononuclear cell fractions, use of cryopreserved versus fresh samples, detection systems employed (flow cytometry, immunofluorescence

microscope, immune-enzymatic technique), use of different CD34 antibodies recognizing distinct CD34 epitopes (class I, II, III), degree of intensity for CD34 antigen, cut-off levels for the discrimination of positive and negative cases (5-20%, percentage of leukemic cells present in the sample examined, Patients analyzed (de novo or secondary AML; childhood or adult ALL), biologic characteristics of acute leukemic cells (chromosome or gene abnormalities), and lastly type of chemotherapy regimen employed. 28

Finally multivariate cox regression model examined the impact of CD34 on overall survival with other prognostic factors to test its independent prognostic effect. It showed quite clearly that CD34 positivity is associated with higher mortality rates and poorer outcome independent on all other risk factors (HR = 1.3 and P value = 0.027 CI 1.1-2.9).

In summary, there is lack of standardized definition of CD34 positivity as well as lack of standardized testing technique. We have examined association of CD34 with cytogenetic abnormalities and some gene mutations; especially FLT3 mutation but the number of enrolled patients was not enough to give a high power for the results. We believe that further bigger studies are needed to solidify the evidence and resolve the dispute.

CONCLUSION

CD34 expression might be a marker for predicting outcome and survival in AML leukemia patients. Positive CD34 is a marker for less differentiated AML FAB subtypes. Positive CD34 may be a marker for less CR achievement. CD34 positivity is linked to unfavorable cytogenetic risk group. It might be associated with worse outcome in all cytogenetic risk subgroups.

Standardization of techniques used to detect CD34 and other cell surface markers is highly recommended to overcome the great heterogeneity in research methodology on this marker and help unify the research outcome for more solid evidence.

Conflict of Interest: Nothing to declare.
Financial Disclosures: Nothing to declare.

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How to cite

Amer, A., Abdelhaleim, A., Salah, H. CD34 Expression in Adult Acute Myeloid Leukemia is an Independent Poor Prognostic Factor. *Zagazig University Medical Journal*, 2020; (823-831): -. doi: 10.21608/zumj.2019.10047.1146