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ORIGINAL ARTICLE

ROLE OF CD200 IN ADULT PATIENTS WITH ACUTE MYELOID LEUKEMIA

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ABSTRACT

Background: Acute myeloid leukemia (AML) is a complex and heterogeneous hematopoietic tissue neoplasm caused by gene mutations, chromosomal rearrangements and deregulation of gene expression. Some recent studies considered CD200 as a marker of bad prognosis in AML as it is linked to worse overall survival. The present study aimed to assess CD200 expression frequency in patients with AML and evaluate its association with different clinical and laboratory data.

Subjects & Methods: The study was carried on 28 newly diagnosed AML patients and 10 healthy subjects who served as a control group. All patients were subjected to routine laboratory investigations and measurement of CD200 level by flowcytometry.

Results: The 28 de novo AML patients were 15 males and 13 females with age ranging from 32 to 60 years with a mean±SD 48.32±7.88 years, and 10 healthy subjects who served as a control group with age ranged from 24 to 58 years with a mean ± SD 39.20±12.30 years. Cases were classified into CD200 positive (27 cases) and CD200 negative (1 case). Then Positive CD200 cases were classified into CD200 High expression and CD200 Low; patients with CD200<50% were considered as ''low expressing'' and they were 8 (29.6%), while cases with CD200≥50% were considered as ''high expressing'' and they were 19 (70.4%). A significant difference was found in the outcome of the two groups, as poor outcome was more evident with CD200 High expression group (P=0.045).

Conclusion: CD200 is an important prognostic factor for the prediction of the outcome in AML patients.

Key words: acute myeloid leukemia (AML), CD200, prognosis.

INTRODUCTION

Acute myeloid leukemia (AML) is a group of cytogenetically and molecularly heterogeneous hematological malignant disease of the blood cell formation marked by the blockage of myeloid differentiation and uncontrolled proliferation of myeloid progenitor cells, resulting in hematopoietic insufficiency. It is the most common acute leukemia among adults leading to most death events caused by leukemias **[1].**

Cytogenetics and mutation testing remains a critical prognostic tool for treatment strategy. Over the years there have been several different classification systems for AML based on etiology, morphology, immune-phenotyping (IPT) and genetics **[2].**

CD200, also known as aka MOX-2 or OX-2, is normally expressed on many different cell types including T and B lymphocytes and dendritic cells **[3].** Elevated CD200 expression has been observed in a variety of cancers, including leukemia, multiple myeloma, hairy cell leukemia, malignant melanoma, ovarian, head and neck carcinoma,

breast, prostate and colon cancers which are all associated with a poor prognosis for patients **[4].**
The aim of our study is to assess CD200 expression frequency in patients with AML, and also to evaluate its association with different clinical and laboratory data.

SUBJECTS AND METHODS

Patients: This case control study was carried out at clinical pathology and medical Oncology departments in Zagazig University Hospitals in the duration between December 2017 and November 2018. A written informed consent was obtained from all participants. The study was done according to The Code of Ethics of The World Medical Assosiation (Declaration of Helsinki) for studies involving humans. Approval of the study was obtained from Zagazig University Institutional Review Board (IRB). It was conducted on 38 cases; 28 newly diagnosed AML patients; 53.6% were males, and 46.4% were females with male to female ratio of 1.15:1. The control group included 10 apparently healthy subjects. Evaluation of patients were carried out on the day 28 after induction therapy to detect their response to treatment and follow up was carried out for 6 months to assess disease outcome.

Protocol of Treatment: All of the patients were treated with anthracyclin and Ara-c as induction chemotherapy schedules. Visinoid was added in M3 cases.

Assessment of remission achieved after induction therapy (at day 28) through CBC and BM aspiration to evaluate morphological remission. Patients were followed once after 6 months with clinical examination and complete blood cell counts. Marrow examination was done if there was any doubt of a relapse on clinical examination or blood smear. The patients were followed up for 6 months to evaluate disease free survival (DFS).

Samples: Peripheral blood (PB) and bone marrow (BM) samples were collected from all patients; samples were collected at the time of presentation, before therapy was initiated.

Seven mL of peripheral blood were aseptically collected from each patient; 1 mL was dispensed into a tube containing K-EDTA at a concentration of 1.2mg/ml, to be used for CBC and preparation of Leishman stained smears PB smears**.**

Two mL of venous blood were delivered into plain vacutainer tube with stopper, left to clot at 37°C for 10 minutes, then centrifuged at 3000 rpm for 10 minutes. Serum was used for liver, kidney functions, uric acid and LDH estimation. The remaining 3.5 mL of blood were delivered in Na citrate vacutainer tube to be used for PT, PTT.

One ml of PB (from control group) or BM (from case group) was added to EDTA coated sterile vacutainer tubes, for IPT and CD200 measurement. One ml of BM aspirate sample was withdrawn and collected into a lithium heparin coated sterile vacutainer tube for cytogenetic analysis.

Methods: Subjects enrolled in the study were submitted to the following: full history taking, clinical examination (pallor, fever, bleeding tendancy, hepatomegaly, splenomegaly and lymphadenopathy), CBC, BM aspiration and examination, IPT by flowcytometry: using Becton Dickenson FacsCalibar device to detect the following markers (MPO, CD13, CD33, HLA-DR, TDT, CD14, CD64, CD34, CD3, CD20 and CD22) and conventional cytogenetic analysis were performed by G banding technique and karyotyping was done according to International System for Human Chromosome, Nomenclature (ISCN). A minimum of 20 metaphases was required to be examined for a patient to be classified and evaluated.

Specific laboratory investigations:

Measurement of CD200 level by CD200 Monoclonal Antibody (OX104), PE, using FACS Calibur flowcytometry (Becton Dickinson, San Jose, CA) surface staining was done by adding 10 µl of each mAbs to 100 µl of blood in the same tube, incubated for 30 min in the dark at 4ºC, then, washed twice with FACS washing buffer. Finally, 0.5 ml of Phosphate buffer saline (PBS) was added on the washed cells and samples were ready for measurement.

Interpretation: Sample considered positive for CD200 expression when ≥ 24% of cells were expressing it (according to ROC curve), and the other studied markers when ≥ 20% of cells were expressing it, except for CD34 and MPO where their expression by 10% of cells was sufficient to confirm positivity.

CD200 +ve cases were classified into CD200 High expression and CD200 Low expression according to the percentage of expression of CD200: patients with CD200<50% were considered as ‘’ low expressing’’ , while cases with CD200≥50% were considered as ‘’ high expressing’’ .

Statistical analysis: Analysis of data was performed using SPSS computer program (version 22; SPSS Inc. Chicago, Illinois, USA). Chi square test, independent sample t-test, Correlation coefficient (r) and Mann Whitney test were used for statistical analysis. Disease free survival (DFS) was estimated by the Kaplan Meier method and compared using the log-rank test. A P-value < 0.05 was considered statistically significant

RESULTS

Table (1) shows that there were high statistically significant differences between cases and control as regards all laboratory parameters.

Table (2) shows that the expression level of CD200 was significantly higher in AML patients than in controls (P <0.01). The Mean ± SD in patient group was 59.46±19.34 while in the control group was 7.57±4.01.

Table (3) shows CD200 expression (%) in patient group: According to ROC curve, cases were classified into either CD200 +ve case if CD200 expression ≥24% (N=27) **or** CD200 –ve case if CD200 expression <24% (N=1).

Then, CD200 +ve cases were classified into CD200 High expression and CD200 Low expression **according to the percentage of expression of CD200:** patients with CD200<50% are considered as '' low expressing'' and they were 8 (29.6%), while cases with CD200≥50% are considered as '' high expressing'' and they were 19 (70.4%) ***(Atfy et al., 2015).***

Table (4) shows that out of the 27 CD200 +ve cases, 4 cases were found to have favorable cytogenetics (Mean ± SD= 66.66±21.29), 22 were found to have intermediate risk cytogenetics (Mean ± SD= 60.17±15.63) and 1 case has unfavorable cytogenetic.

Table (5) shows that there was a statistically significant difference between CD200 Low and CD200 High expression groups as regard to outcome:

Seven patients (46.7%) out of eight patients with CD200 Low expression have achieved CR (Good outcome), while only 8 patients (53.3%) out of 18 patients with CD200 High expression have achieved good outcome.On another side, only 1 patient (10%) with CD200 Low expression has failed to achieve complete remission (Poor outcome), while 9 patients (90%) with CD200 High expression have had poor outcome (Failure of remission or induction death).

Note: Two patients have leaved Zagazig University before follow up and were missed.

Table (6) shows that there was a statistically significant difference between cases that maintained CR for 6 months and those who relapsed after achieving CR as regard to level of HB and CD200 expression according to its percentage < or ≥ 50% (P value= 0.008 and 0.026 respectively). Note: One CD200 –ve case has maintained CR for 6 months.

Fig. (1) shows that out of 16 patients who achieved complete remission, 4 patients presented with relapse and 2 patients died (death was due to causes other than AML; accident and acute myocardial infarction).

Table 1: Hematological laboratory data among the two studied groups:

Variable	Cases (n=28)	Control (n=10)	Test	P
TLC: ($x10^3/mm^3$) Median ± SD Range	49.59(2.33-207.60) 2.33-207.60	7.75(5.80-10.60) 5.80-10.60	-4.276***	**<0.001***
HB: (gm/dl) Mean ± SD Range	7.8±1.8 4.7-10.7	13.7±1.3 11.0-15.7	-9.716**	**<0.001***
Platelets: ($x10^3/mm^3$) Median ± SD Range	35.0 (7.0-123.0) 7.0-123.0	242.5(225.0-350.0) 225.0-350.0	-4.641***	**<0.001***
Peripheral Blasts (%) Mean ± SD Range	43.9±27.7 5.0-92.0	–	–	–
BM blasts (%) Mean ± SD Range	50.0±19.6 25.0-95.0	–	–	–
ESR (mm/min.) Mean ± SD Range	77.0±34.1 22.0-140.0	11.3±5.6 3.0-20.0	6.023**	**<0.001***
LDH: (U/L) Median ± SD Range	480.5(142.0-2948.0) 142.0-2948.0	175.0 (137.0-220.0) 137.0-220.0	-3.945***	**<0.001***

(*)Highly significant (P<0.001)
(**) independent sample t test (***) Mann Whitney test
SD = standard deviation
BM = bone marrow

Table 2: Comparison of CD200 among the two studied groups:

Variable	Patients (n=28)	Control (n=10)	T	P
CD200			**8.347**	**<0.001****
Mean ± SD	59.46±19.34	7.57±4.012.96-		
Range	2.53-85.03	14.07		

SD = standard deviation
T = independent sample t test
****=highly significant

Table 3: CD200 expression in patient group:

		Frequency	Percent %
CD200	**-ve(<24%)**	1	3.6
	+ve(≥24%)	27	96.4
CD 200 Expression (%):			
- **Low**	**CD200<50%**	8	29.6
- **High**	**CD200≥50%**	19	70.4

Table 4: Relation between CD200 positive patients (27 cases) and cytogenetics:

Variable	Favorable (N=4)	Intermediate (N=22)	Adverse (N=1)	*	P value
CD200+ve Mean ± SD	66.66±21.29	60.17±15.63	71.81± -	0.465	0.634 (NS)

SD = standard deviation
NS= not significant
(-) no Standard deviation calculated as it is one case (*) Anova test

Table 5: Relation between CD 200 expression and outcome of the patients:

	CD 200 positive expression					
	CD 200 Low Expression(<50%)		CD 200 High Expression(≥50%)			P value
Outcome	**N =8**	**%**	**N =17**	**%**	**Test***	
Good outcome (CR) (N=15)	7	46.7%	8	53.3%	3.707	**0.045 (S)**
Poor outcome (FR & Died) (N=10)	1	10%	9	90%		

(*) Chi square test
CR= complete remission
S= significant
FR= failure of remission

Table 6: Comparison between cases that maintained complete remission for 6 months and those who relapsed after complete remission:

Variable	CR for 6 month (n=10) %	Relapse after CR (n=4) %	Test	P
TLC: (x10^3/mm^3) Mean ± SD	21.98±19.06	53.11±29.27	-1.697**	0.090
HB: (gm/dl) Mean ± SD	9.5±1.4	6.7±1.6	-3.150*	**0.008 (S)**
Platelets: (x10^3/mm^3) Mean ± SD	49.3±41.1	41.0±24.7	-0.141**	0.888
Peripheral Blasts (%) Mean ± SD	24.8±23.1	42.3±21.6	-1.557**	0.119
BM blasts (%) Mean ± SD	43.2±8.4	53.5±26.4	-0.283**	0.777
FAB: M2	1 10%	1 25%		1.00
M3	1 10%	0 0.0%	1.595***	
M4	4 40%	1 25%		
M5	4 40%	2 50%		
Cytogenetics:			0.703***	1.00
Favorable	1 10%	0 0.0%		
Intermediate	9 90%	4 100%		
Adverse	0 0.0%	0 0.0%		
CD200 expression:	6 66.7%	0 0.0%	4.952***	**0.026 (S)**
-Low expression (CD200<50%)	3 33.3%	4 100%		
-High expression (CD200≥50%)				
MFI expression:	1 11.1%	0 0.0%	0.772***	1.00
-Low Expression (MFI<11)	8 88.9%	4 100%		
-High Expression (MFI≥11)				

(*) independent sample t test (**) Mann Whitney (***) Chi square test

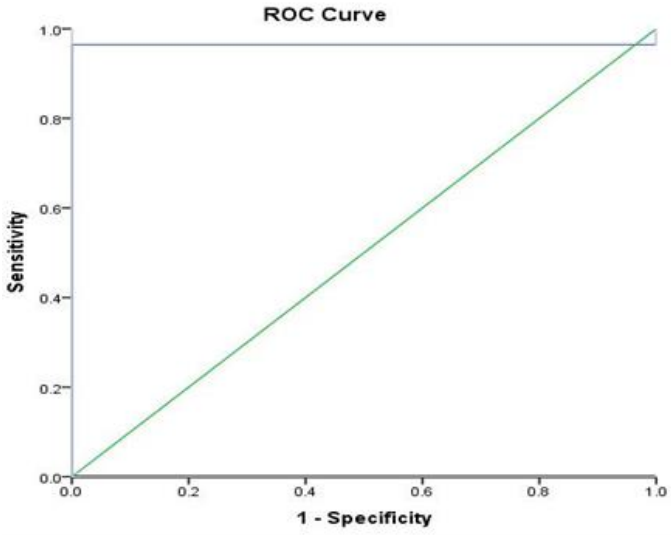

Figure (1): Roc curve for detection of best fit value of CD200.

Table (1): Correlation between CD200 positive patients and other cell markers:

Variables	r	P
CD13	0.272	0.169
CD33	0.126	0.532
MPO	0.008	0.970
HLA-DR	0.088	0.663
CD34	0.425	**0.027***
CD45	0.349	0.074
CD14	0.125	0.534
CD64	0.188	0.348
CD3	0.200	0.317
CD7	0.049	0.807

r : Spearman correlation coefficient

* = significant (P value < 0.05)

This table shows that there was a significant positive correlation between CD200 and CD34 (Figure 13).

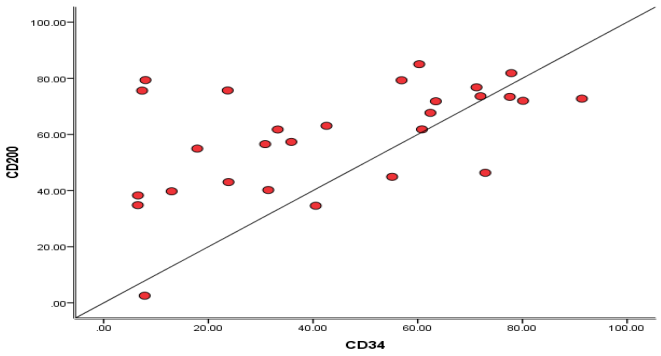

Fig. (2): Correlation between CD200 and CD34.

Table 2: Relation between CD 200 expression and liver and kidney functions:

	CD 200 positive expression			
	CD 200 Low Expression(<50%) Mean± SD	CD 200 High Expression(≥50%) Mean± SD	Test *	P value
TB	0.89±0.69	0.79±0.60	-0.425**	0.671 (NS)
DB	0.58±0.96	0.34±0.28	-0.027**	0.979 (NS)
Total proteins	6.31±0.64	6.52±0.63	-0.972*	0.340 (NS)
Albumin	3.72±0.50	4.15±0.95	-2.215*	0.063 (NS)
SGPT	33.0±27.3	33.0±33.9	-0.478**	0.633 (NS)
SGOT	35.1±25.4	40.4±67.5	-0.584**	0.559 (NS)

	CD 200 positive expression			
	CD 200 Low Expression(<50%) Mean± SD	CD 200 High Expression(≥50%) Mean± SD	Test *	P value
Alkaline phosphatase	83.4±24.2	63.8±21.9	-1.649**	0.099 (NS)
Serum Creatinine	0.85±0.20	1.24±1.62	0.797**	0.425 (NS)
Serum Urea Nitrogen	10.36±2.92	16.36±15.24	-2.204**	0.08 (NS)
Uric acid	4.02±1.29	5.36±1.96	-1.971*	0.060 (NS)

(*) independent sample t test
(**) Mann Whitney
This table shows that there were no statistically significant difference between CD200 Low and CD200 High expression as regards all laboratory data.

Table (3): Cytogenetic risk category of patient group:

Cytogenetic abnormality	Frequency	Percent %
Normal karyotype	13	46.6
t (15;17)	2	7.1
t (8;21)	2	7.1
Trisomy 8	2	7.1
Trisomy 11	2	7.1
Loss of Y chromosome	1	3.6
del 8	2	7.1
del 11	2	7.1
t(1;3)	1	3.6
del 7	1	3.6

According to cytogenetics, 13 cases (46.6%) were of normal karyotype while abnormalities of cytogenetics included 2 (7.1%) with t (15;17), 2 (7.1%) with t (8;21), 2 (7.1%) with Trisomy 8, 2 (7.1%) with Trisomy 11, 2 (7.1%) with del 8, 2 (7.1%) with del 11, 1 (3.6%) with Loss of Y chromosome, 1 (3.6%) with t(1;3) and 1 (3.6%) with del 7.
The –ve CD200 case was with t(1;3) abnormality.

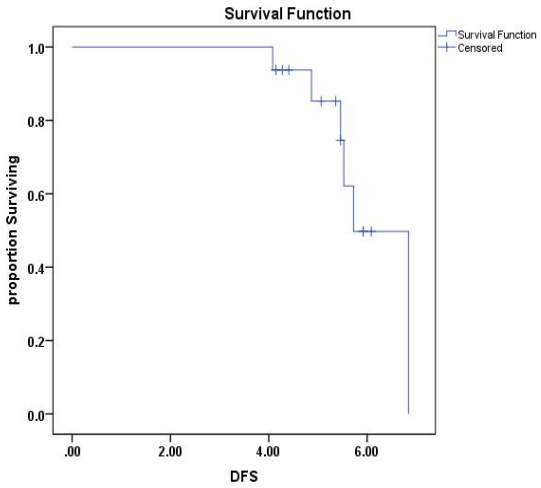

Figure (3): Kaplan Meier curve for Disease free survival (DFS) of patient group:

DISCUSSION

AML represents a heterogeneous group of disorders that are characterized by peripheral blood and bone marrow myeloblast proliferations.

The significance of CD200 expression was investigated in relation to various clinical, laboratories, as well as to treatment response and clinical outcome of patients.

Our patients' age ranged from thirty two to sixty years with mean ± SD 48.32±7.88.

Although occurrence of AML was reported in all age groups, it is well established that AML incidence rises with age, and therefore, accounts for approximately 25% of all leukemias diagnosed in adults **[5].**

Fifteen cases were males (53.6 %) and thirteen were females (46.4 %) with male to female ratio 1.15: 1. Similar higher incidence in men was observed by Maksimovic et al., 2018 **[6].**

Bleeding tendency and pallor were the commonest clinical symptoms in our patients' group (89.3% and 82.1% respectively) followed by splenomegaly (60.7%), fever (42.9%) then hepatomegaly (39.3%) and finally lymphadenopathy (28.6%).

The clinical signs and symptoms of AML are diverse and nonspecific, but they are usually directly attributable to the leukemic infiltration of the bone marrow, with resultant cytopenias. Typically, patients present with signs and symptoms of fatigue, hemorrhage or infections and fever due to decreases in red cells, platelets, or white cells, respectively. Pallor, dyspnea and fatigue on exertion are common. Leukemic infiltration of various tissues, including the liver (hepatomegaly), spleen (splenomegaly), skin (leukemia cutis), lymph nodes (lymphadenopathy), bone (bone pain), gingiva, and central nervous system, can produce a variety of other symptoms **[7].**

Regarding laboratory variables, a clear significant difference was observed between patient and control groups as regarding to: TLC, HB, Platelets, BM blasts, peripheral blasts, LDH and ESR (p value <0.001) **[table 1].**

TLC was significantly increased in patient's group with mean ± SD= 61.91 ± 49.52 (8.05±1.64 in controls) while Platelets and hemoglobin concentration were significantly decreased in patients with mean ± SD of 44±31.5 and 7.8±1.8 respectively versus 265.6±48.4 and 13.7±1.3 in controls and this is in agreement with ***Zahran et al*** **[8]**and ***Atfy et al*** **[9].**

Blasts in BM and in peripheral blood haven't appeared in control samples at all, but the mean of blasts in BM in the case group was 50.0% ±19.6%, and in peripheral blood was 43.9% ± 27.7%. For a diagnosis of AML, a marrow blast count of ≥20 is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16), or t(16;16) **[10].**

No significant difference was present between cases and controls as regards kidney and liver function tests. The two cases of Acute promyelocytic leukemia (APL/M3) showed a clear increase in coagulation profile (PT, PTT and INR) giving a clinical picture of life-threatening hemorrhage, which is caused mainly by enhanced fibrinolytic-type disseminated intravascular coagulation (DIC), the most important clinical feature of APL.

Patients were classified according to FAB classification and immunophenotyping; M4 was the commonest in our study representing 35.7% (10/28). The second most common type was M2 and M5 equally by a percentage of 28.6% (10/28) for each of them while M3 was the least common in our study representing 7.1% (2/28). None of the patients were diagnosed as M0, M1, M6 or M7. In a study done by ***Damiani et al*** **[11],** M5 was the commonest (38%) then M4 (20%), M1 (18%), M2 (16%) M0 (6%) and finally M6 was 2%.

According to the cytogenetic analysis, the 28 patients in our study were classified into three groups: favorable group which included 4 cases (14.3%), intermediate group 23 cases (82.1%) and only 1 case in adverse group (3.6%). There was no significant relation between CD200 expression and the three cytogenetic prognostic groups but it was noticed that the only case with adverse cytogenetic has had failure of remission, and that 48.1% of CD200+ cases were found in the cytogenetically intermediate-risk AML (with normal karyotype).

About half of the patients with AML were found to have ''normal'' cytogenetic analysis by standard culture techniques. These patients were considered as an intermediate risk group. Cytogenetically normal AML (CN-AML) is the largest cytogenetic risk group, and the variation in clinical outcome of patients in this group is greater than in any other cytogenetic group **[12].**

Each of the studied patients was divided into either CD200 positive or CD200 negative case according to receiver operator curve (ROC), according to which, the cut off value for CD200 expression was ≥ 24%. The sensitivity was 96.4%, specificity 100% and total accuracy 97.4% Positive predictive value = 100% and Negative predictive value = 90.9%, (P=<0.001). CD200 is expressed in the control group by a percentage ranged between 2.96-14.07% with a mean value of 7.57±4.01, which is considered –ve.

The frequency of positive CD200 expression was 96.4% (27/28 cases) among AML patients. However, in a study by ***Tonks et al*** **[13],** the

frequency of positive CD200 expression was 43% among AML patients, and 56% (136/244) in another study done by ***Damiani et al*** **[11]** and 76% (78/102) in a study done by ***Atfy et al*.[9].**

In another study on cytogenetically normal AML, CD200 was found positive in 48% (67/ 139) of cases ***(Tiribelli et al)*** **[14],** and 65% (26/40) in another study by ***Zahran et al.*** **[8].** This can be explained by the small sample size of our study. One important notable finding was that the only CD200 –ve case in our study not only had achieved complete remission, but it has also maintained this remission for 6 months. This supports that CD200 negativity is a good prognostic marker in AML.

Regarding IPT markers, there was no statistically significant correlation between their expression and CD200 positive patients' group except for **CD34 (P value= 0.027)** which showed positive good correlation. There may be some relation between existence of CD200 and this primitive marker, CD34 which is known as a bad prognostic marker in many malignancies.

This agreed with ***Tiribelli et al*.** **[14]** and ***Damiani et al.*** **[11]** who found a higher frequency of CD200 expression in CD34 positive cases. It was also reported that CD34 positivity has been significantly correlated with a lower rate of complete remission.

Regarding cytogenetics, although 22 cases of the CD200 +ve cases have belonged to the intermediate risk group, 4 belonged to the favorable group and only 1 case belonged to the high risk group, there was no statistically significant difference between CD200 +ve cases and the three cytogenetic groups. But two important findings were noticed; the only one case which had an adverse cytogenetics (del 7) has not responded to treatment and had failure of remission, and a worse outcome was observed in patients with favorable cytogenetic and high CD200 expression compared to those CD200-Low. ***Tonks et al.*** **[13]** previously reported that in AML, there is a correlation between CD200 expression and the presence of the core binding factor (CBF) associated abnormalities, t (8;21) and inv (16). There is a high frequency of CD200 positive patients in t (8;21) leukemia, these patients also significantly overexpressed CD200 by 1.8-fold when compared to FAB-M2 patients without this cytogenetic aberrations (P=0.03). Furthermore, patients expressing an inv (16) mutation (generally associated with FAB-M4) also significantly overexpressed CD200 when compared to M4 patients without an inv (16) mutation (1.3-fold; P=0.02). Despite the association of CD200 expression with these good risk subtypes, analyses of survival stratified for CBF abnormalities showed that CD200 was associated with worse survival.

Also, it was found that CD200 has an additive negative impact on survival in patients with unfavorable cytogenetic and in secondary leukemia; moreover, it exerted a worsening effect on prognosis of AML patients with favorable biological markers, such as mutated NPM, wild-type Flt3 and CD34 negativity **[15].**

Then CD200 +ve AML patients' group were classified according to their CD200 expression into CD200 High expression (CD200≥50%) and CD200 Low expression (CD200<50%) and the results were as follows: There was no statistically significant difference between both groups as regard to age and sex. This agreed with ***Atfy et al*.** **[9].**

By comparing between both groups as regarding to clinical symptoms, only hepatomegaly and splenomegaly had a significant difference, being more frequent in CD200 High group (10/19 '' 52.6%'' and 14/19 ''73.3%'' respectively.) According to laboratory data, no significant difference was observed between CD200 High and Low subgroups as regard to TLC, Hb level and platelet count (P value= 0.710, 0.130 and 0.791 respectively). This agreed with ***Atfy et al.*** **[9].**

There was no statistically significant difference between CD200 High and Low subgroups as regard serum LDH; (584.4 ± 620.5 and 487.1 ± 107.0.) respectively. This disagreed with ***Atfy et al*.[9]** who reported a significant difference between both subgroups regarding serum LDH which ranged in its value from 164- 3151, with a median of 1025 in CD200 High expression group and from 178- 1575, with a median of 654 in CD200 Low expression group.

According to FAB classification, 8 cases were classified as M2 (1 CD200 Low and 7 CD200 High expressing), 2 cases as M3 (1 CD200 Low and 1 CD200 High), 9 cases as M4 (3 CD200 Low and 6 CD200 High expressing) and 8 cases as M5 (3 CD200 Low and 5 CD200 High) with no significant difference between the two groups.

According to cytogenetics, 4 cases have fallen into the favorable cytogenetic group; 3 of them with High CD200 expression (79.38%, 76.8% and 75.67% with t (15;17) and 2 cases with t (8;21) respectively) and all of the three cases have had worse outcome. The fourth case was with t (15;17) and Low CD200 expression (34.8%) and has achieved complete remission for 6 months.

The only 1 case with adverse cytogenetic and High CD200 expression (71.81%) had failure of remission. Twenty two cases had intermediate cytogenetic risk; 7 of them with Low CD200 expression and 15 with High CD200 expression.

There was a significant difference between both subgroups regarding outcome. The Low CD200 expressing group had showed better outcome as 6 cases out of 7 had achieved CR; 5 of them had maintained this CR for 6 months. In the second group, Eight out of 15 have achieved CR; and only 3 of them had maintained CR for 6 months. These results are in agreement with ***Damiani et al.*** **[11]** who observed a worse survival in patients with favorable cytogenetic and high CD200 expression (33%) compared to those CD200-low (79%).

While taking a look at the outcome and survival of our patient group (N= 28), we found that: The only case with –ve CD200 has achieved CR and maintained this remission for 6 months. Seven out of 8 cases CD200 Low expression have achieved CR and 1 case only has had failure of remission. Also, six cases out of the 7 who achieved CR had maintained this remission for 6 months and only 1 case had died after remission.

On the other hand, only eight cases out of 19 CD200 High expression have achieved CR, 7 cases have died, 2 cases have had failure of remission and 2 cases were missed follow up. Three cases only out of the eight who achieved CR had maintained this remission for 6 months and 1 case had died after remission.

It deserves to mention that four cases in our study had relapsed after achieving CR and all of them were CD200 High expression. From these results, negative and low CD200 cases have better outcome than cases with high CD200 expression, So CD200 expression can be considered as an independent prognostic marker in AML.

The unfavorable prognosis conferred by CD200 expression was consolidated by studying the DFS for the newly diagnosed AML patients, using Kaplan-Meier curve. It was found that the increased expression of this protein was significantly associated with a shorter DFS. This is in concordant with a study performed by ***Damiani and his colleagues*** **[11]** who found that the increased expression of this protein was significantly associated with a shorter DFS time. This comes in concordance with ***Tiribelli and his colleagues*** **[14]** who found that CD200 High patients had a low probability of CR maintenance, and an extremely poor survival, with no patients alive 3 years after diagnosis. A negative impact of CD200 over expression is emerging in myeloid neoplastic disease. A significant correlation was reported between CD200 expression and WHO subtype and the International Prognostic Scoring System (IPSS) risk in a group of patients with myelodysplastic syndrome, and in multivariate analysis CD200 overexpression was found to have a negative prognostic role **[16].**

Therefore, the results of the current study, which are in concordance with those reported by several investigators, confirm that CD200 is an independent prognostic factor for acute myeloid leukemia ***(Tonks et al*** **[13]*; Coles et al*** **[17]** ***; Atfy et al*** **[9]*; Damiani et al ; Tiribelli et al*** **[14]** ***and Zahran et al*** **[8]** ***)***, being associated with a poorer response to treatment and shorter DFS.

CONCLUSION

CD200 is an important prognostic factor for the prediction of the outcome in AML patients

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