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Prognostic Impact of Poliovirus Receptor Expression (PVR) (CD155) in Context to FLT3-ITD and NPM1 Mutation Status at Egyptian Acute Myeloid Leukemia

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Abstract

Background: Acute myeloid leukemia is a heterogeneous hematological malignancy with diversity in molecular, phenotypic and genetic alteration. Accurate assessment of prognosis is mandatory to reduce relapse, changing treatment related mortality, decision making for appropriate therapy protocols. **Aim:** A case control observational analytical study to assess the prognostic value of poliovirus (CD155) in acute myeloid leukemia and its significant in-patient stratification. **Subject & Methods:** 100 newly diagnosed de novo AML selected from oncology center, Mansoura University. Measurement of PVR (CD155) by multiparameter flow cytometry in addition to cytogenetic and molecular stratification. **Results:** Statistical stratification according to median cut off CD155 > 5.35. Higher expression was associated with an increased risk of death and relapse, LDH. While lower expression is associated with longer OS & DFS. Cox regression with univariate analysis revealed that LDH, molecular stratification, CD155 were significant risk factors for shorter OS, while positive expression of CD16, CD56 AML M3 were significantly associated with longer survival. Multivariate analysis revealed that CD155 was a significant risk factor for shorter OS. **Conclusion:** Variability in expression of CD155 in AML patients due to dual costimulatory and inhibitory function, high expression associated with tumor bulk and progression, short OS, increased relapse rate. Cox regression analysis shows its indepen-

dent risk factor. It could be implemented in routine laboratory for risk stratification into low, high risk that needs more therapeutic modalities with new immunotherapy. In future could be targeted therapy such as PDL, CTLA-4 and open more therapeutic hope for those patients.

Keywords

CD155, PVR, FLT3, Nucleophismin, AML

1. Introduction

Acute myeloid leukemia is a heterogeneous disease at both the phenotypic and molecular level with a variety of distinct genetic alterations giving rise to the disease. It is characterized by maturation arrest and subsequent accumulation of blast cells at various stages of incomplete differentiation. In spite of advanced chemotherapy protocols and B.M Transplantation, relapse still occurs in approximately half of the patients with AML and the 5-year overall survival rate is only about 40% [1].

Accurate assessment of prognosis is central to the management of AML through stratifying patients according to their risk of treatment resistance or treatment-related mortality (TRM), the cytogenetic finding was considered the cardinal marker for AML risk stratification. The somatic mutations that have been identified in the following genes (e.g., *NPM*1, *FLT*3, *DNMT*3*A*, *WT*1) are involved in the pathogenesis of AML and affect the prognosis of these patients. Prognostic factors act as guide the physician in deciding between standard or increased treatment intensity, consolidation chemotherapy or allogenic hematopoietic stem cell transplant, or more fundamentally in choosing between established or investigational targeted immunotherapy [2].

Over the past few years, identification of new prognostic factors remains important; especially those potentially refining therapeutic options. The development of prognostic markers is particularly important in AML with normal cytogenetics (CN AML) and currently, three molecular markers NPM1- and CEBPA mutations and FLT3 internal tandem duplication (FLT3-ITD) are used in clinical practice [1].

Poliovirus receptor is the fifth member in the nectin-like molecule family, and functions as the receptor of poliovirus; therefore, CD155 is also referred to as necl-5, or PVR. As an immunoglobulin-like adhesion molecule, As the ligand for both costimulatory receptor DNAX accessory molecule 1 (DNAM-1) CD226 and coinhibitory receptor TIGIT and CD96 on natural killer and T cells [3]., CD155 seems to play a dual role in oncoimmunity with higher affinity for TIGIT than DNAM-1 [4].

CD155 is involved in cell motility, and T cell-mediated immunity and a recognition molecule for natural killer (NK) cells to induce their cytotoxicity [5]. CD155 is barely expressed in various normal human tissues, including in im-

mune, epithelial, and endothelial cells [6] but frequently overexpressed in human malignant tumors [7] [8].

CD155 is upregulated by LPS or inflammatory cytokines from antigen presenting cells and has been shown to regulate the development and function of immune cells in cancer settings [9], may also be used to positively select MHC independent T cells in the thymus [10]. Furthermore, recipient CD155-deficient mice have more severe graft versus host disease (GVHD) than do WT mice [11].

Furthermore, CD155 expression on dendritic cells (DC) can be upregulated by a series of toll-like receptor (TLR) agonists, including LPS. This induction involves TLR adaptor molecules MYD88 and TRIF with activation of NF-kB [12] [13].

To the best of our knowledge, these molecules had increasing clinical value in solid tumor that high levels associated with a poor prognosis [14] [15]. Little studies on its prognostic value in AML and its clinical significance in stratification of those patients is still unclear. Despite invitro observations that CD155 overexpression on tumor cells plays critical role in cell motility during invasion and migration [16] [17], whether CD155 plays a critical tumor cell–intrinsic role upon tumor growth and metastasis in vivo remains unknown, and the relative contributions of it on tumor versus host cells in limiting antitumor immunity or response to therapy have not been previously defined.

The present study was designed to assess the prognostic value of Poliovirus receptor (CD155) in patients with acute myeloid leukemia and its significant in-patient stratification.

2. Method

This study was conducted on 100 patients with de novo acute myeloid leukemia. They were selected from Oncology Center, Mansoura University (OCMU) between Mars 2018 and May 2020. The Mean age of patients was 53.9 ± 14.3 years. They comprised 54 males (54%) and 46 females (46%). In addition, there are 30 apparently healthy individuals. They were 15 males & 15 females were selected to serve as control group. Their Mean age was 52.7 ± 10.54 years.

All patients gave informed consent for both treatment and genetic analysis. All patients received intensive induction therapy (Cytarabine 100 mg/m^2/d for 7 days i.v. continuous infusion and Daunorubicin 90 mg/m^2/d for 3 days i.v.) consolidation therapy (Cytarabine 1 gm/m^2/12 h on the 1st, 3rd and 5th days with Daunorubicin 45 mg/m^2/d for 3 days i.v). The patients who achieved complete remission with poor risk cytogenetic or failed induction or relapsed were prepared of BM transplant.

All patients gave informed consent to their participation in this study, and were diagnosed on the basis of clinical presentation, cytomorphology, cytochemistry as well as immunophenotyping and the Institutional Revision Board (IRB) of Mansoura University approved the study protocol on 6-11-2018, code number: MS.18.10.346.

2.1. Measurement of CD155 (PVR) Expression by Multiparameter Flow Cytometry

The following fluorochrome-conjugated monoclonal antibodies were used: PE antihuman PVR (CD 155) **Clone**: SKII.4 purchased from dako.

Routine immunophenotyping for every cases using CD45-V500 (BD Bioscience) for specific gating strategy on dim CD45 that represents immature blast population, stem cell markers (CD34, HLA-DR) for blasts; (cyt MPO, CD13, CD33, CD117) as a primary panel for myeloid lineage; (CD14, CD36, CD11b, CD11c, CD64) for M4 and M5; (CD61, glycophorin A) for M6; (CD41, CD42) for M7; and (CD19, CD10, CD79a, CD3, cyt CD3) for lymphoid lineage. Erythrocyte lysis solution (were all purchased from Beckman Coulter) was purchased from BD Biosciences. Briefly, 100 µL of whole blood was immune stained for 30 min in the dark, followed by lysis with 500 µL of erythrocyte lysis solution before two washes with 500 µL of PBS. After centrifugation, the supernatants were discarded, and cell pellets were resuspended in 500 µL of PBS for analysis through FACS software. With the intensity of staining directly proportional to the density of CD155 cell surface expression of the poliovirus receptor (CD155) was determined by flow cytometric analysis using 488 nm wave length laser excitation using ADVIA software of analysis interpretation on multiparameter 8 color, 3 laser BD-FACS Canto II, V 33396202133, USA.

2.2. Molecular Assay of FLT3-ITD by Conventual PCR

DNA extraction by DNA was extracted using Thermo scientific Gene JET Whole Blood Genomic DNA Purification Kit according to the protocol of manufacturer's instructions. The extracted DNA was stored frozen at −20˚C. The DNA samples were quantified by NanoDrop instrument, and the samples were measured 17 - 45 ng/µL. Apply 1 µl of extracted DNA with 12.5 µl ready master mix, 0.1 µl of 100 pmol of each primer (Forward: 5' GCA ATT TAG GTA TGA AAG CCA GC 3' and Reverse: 5' CTT TCA GCA TTT TGA CGG CAA CC 3') complete with 11.3 µl water. According to protocol of 95 c for 3 minutes followed with 35 cycles of 95 c for 30 seconds, 66 c for 30 seconds, 72 c for 30 seconds then final extension at 72 c for 7 minutes.

2.3. Molecular Assay of Nucleophismin by Real Time PCR

Using Ipsogen NPM1 Muta Screen Kit (Qiagen, REF 677013, Germany) that depends on detection of wild type and mutant NPM (Mutant A,B,D) by oligonucleotide hydrolysis principle uses specific primers and an internal double dye probe with a reporter and a quencher (FAM™, TAMRA™) for amplification reactions, In addition, a 3'-end modified phosphate oligonucleotide is used that perfectly matches the wild-type NPM gene and does not allow polymerization with amplification thermal cycle protocols 50 c for 2 min, 95 c for 10 min, (95 c for 15 sec, 60 c for 90 min for 40 cycles). Using DT prime 4 /DNA technology (SN: ASD312, USA).

2.4. Cytogenetic and Molecular Genetic Analyses

- Pretreatment blood samples from all patients were studied by chromosome banding analysis to improve the accuracy of cytogenetic diagnosis.
- The specimens were also analyzed by fluorescence in situ hybridization for the presence of t (8; 21) (q22; q22) for M2, t (15; 17) (q22; q12) for M3 inv (16) (p13q22) for M4e or 11q23 for M5.

2.5. Statistical Analysis

Data were analyzed running IBM-SPSS© for windows version 19.0. A two-sided p value of <0.05 was required for statistical significance. The Chi Square Test was used for testing the relation between categorical variables. Mann-Whitney U test or Kruskal-Wallis H test were used for comparison between two or more groups. Survival was determined by the Kaplan-Meier test, the Log Rank test was used for comparison. Independent hazards of different prognostic factors were tested by the Cox's regression model.

Qualitative data were presented as numbers and percentages and analyzed using chi-square test. Test for data normality was done using Kolmogorov-Smirnov test. Parametric data were described as mean ± SD and analyzed using paired sample t test, while non-parametric variables were expressed as median (min-max). Kaplan-Meier was used for survival analysis. Survival comparison was carried out by the log-rank test. Statistical significance was presumed at $p \leq 0.05$.

3. Results

The present study was conducted on 100 AML cases. Mean age was (53.94 ± 14.3), 54.0% of them were males. Hepatomegaly, splenomegaly and lymphadenopathy were positive in 17.0%, 43.0%, and 12.0% respectively. Based on FAB classification, cases were classified into 3 groups; AML M1-M2 (n = 42); AML M3 (n = 17), and AML M4-M5 (n = 41). Cytogenetic analysis, molecular FLT3/ Nucleophismin and positive expression of CD56 and CD16 were presented in Table 1. 44.0% of cases were died. Median CD155 was 5.35 (0.1 - 95.9). According to median CD155 AML cases divided into 2 groups < 5.35 and >5.35.

Patients' characterization was studied depending on those whose statistical stratification revealed insignificant difference regarding age, gender, organomegaly, and FAB classification among studied groups as shown in Table 2 while There was significant elevation of LDH in AML group with CD155 > 5.35 compared to AML group with CD155 < 5.35. High significant increase of positive FLT3 with Higher expression of CD155 while higher nucleophismin is increased with low expression $p < 0.005$, significant association of CD155 with NK cells (CD16/ CD56). Recurrent chromosomal abbreation could be detected in 29/100 while normal karyoptype in 71/100. Otherwise, no other significant could be detected as illustrated in Table 3. There was significant increased risk of death and relapse among AML group with CD155 > 5.35 compared to AML group with CD155 < 5.35 (p 0.001, 0.016 respectively) as demonstrated in Table 4.

Table 1. Individual characteristics of AML patients.

Parameter		Value
Gender	Male	54 (54.0%)
	Female	46 (46.0%)
Mean age		53.94 ± 14.3
Hepatomegaly (positive N/100)		17 (17.0%)
Splenomegaly (positive N/100)		43 (43.0%)
Lymphadenopathy (positive N/100)		12 (12.0%)
CD56 (positive N/100)		56 (56.0%)
CD16 (positive N/100)		54 (54.0%)
FAB classification	AML M1-M2	42 (42.0%)
	AML M3	17 (17.0%)
	AML M4-M5	41 (41.0%)
Cytogenetic	t (8; 21) (positive N/24)	4 (16.7%)
	Inver 16 (positive N/22)	8 (36.4%)
	11q23 rearrangement (positive N/8)	4 (50.0%)
	t (15; 17) (positive N/14)	13 (92.9%)
Response to TTT	Remission (N/100)	78 (78.0%)
	Relapse (N/100)	22 (22.0%)
Survival	Lived (N/100)	56 (56.0%)
	Dead (N/100)	44 (44.0%)
FLT3	Positive 38/100	38%
NPM	Positive 56/100	56%
Groups	AML group (with CD155 < 5.35)	50 (50.0%)
	AML group (with CD155 > 5.35)	50 (50.0%)

Abbreviation: FAB: French-American-British classification, TTT: Time to treat, CD: Cluster differentiation.

Table 2. Patients characteristics among studied groups.

Parameter		AML group (with CD155 < 5.35) (N = 50)		AML group (with CD155 > 5.35) (N = 50)		P
Age*	**Mean ± SD**	52.94 ± 12.84		54.94 ± 15.69		0.487
Sex	**Male**	26	52.0%	28	56.0%	0.688
	Female	24	48.0%	22	44.0%	
Hepatomegaly	**Positive**	10	20.0%	7	14.0%	0.424
Splenomegaly	**Positive**	19	38.0%	24	48.0%	0.313
Lymphadenopathy	**Positive**	6	12.0%	6	12.0%	1.00
FAB	**M1-M2**	19	38.0%	23	46.0%	0.175
	M3	12	24.0%	5	10.0%	
	M4-M5	19	38.0%	22	44.0%	

Chi-Square test, independent T test*. P between two group. **significant (P value < 0.05).

Table 3. Comparison of some laboratory parameters among studied groups.

Parameter		AML group (with CD155 < 5.35) (N = 50)	AML group (with CD155 > 5.35) (N = 50)	P
Hb*	**Mean ± SD**	8.24 ± 2.0	7.94 ± 2.20	0.484
WBCS	**Median**	27.0	21.0	0.492
	Min-Max	1.0 63.0	1.0 95.0	
PLT	**Median**	33.50	33.0	0.753
	Min-Max	14.0 266.0	13.0 266.0	
LDH	**Median**	88.0	770.0	**<0.001**
	Min-Max	60.0 920.0	256.0 970.0	
Blast in BM	**Median**	60.0	80.0	0.076
	Min-Max	20.0 90.0	20.0 90.0	
FLT3	**Positive**	12 31.5%	26 68.5%	**0.002**
NPM	**Positive**	40 71.5%	16 28.5%	**0.001**
CD56	**Positive**	36 72.0%	20 40.0%	**0.001**
CD16	**Positive**	34 68.0%	20 40.0%	**0.005**
t (8; 21) (positive N/24)	**Positive**	3 21.4%	1 10.0%	0.615
Inver 16 (positive N/22)	**Positive**	4 30.8%	4 44.4%	0.662
11q23 rearrangement (positive N/8)	**Positive**	2 66.7%	2 40.0%	1.00
t (15; 17) (positive N/14)	**Positive**	10 90.9%	3 100.0%	1.00

Mann-Whitney test, independent T test*. P between two group. **significant (P value < 0.05).

Table 4. Survival and response to TTT among studied groups.

Parameter		AML group (with CD155 < 5.35) (N = 50)		AML group (with CD155 > 5.35) (N = 50)		P
Survival	**Live**	38	76.0%	18	36.0%	**<0.001**
	Dead	12	24.0%	32	64.0%	
Response to TTT	**Remission**	44	88.0%	34	68.0%	**0.016**
	Relapse	6	12.0%	16	32.0%	

Chi-Square test. P between two group. **significant (P value < 0.05).

Study correlation between different parameters with CD155 among studied AML cases. There was significant positive correlation between CD155 and LDH, molecular p < 0.005 Otherwise, no other significant difference could be detected as presented in Table 5.

COX regression analysis was conducted for prediction of survival within cases, using age, gender, laboratory data, CD155, CD56, CD16, FAB classification and cytogenetic as covariates. Univariate analysis revealed that LDH and CD155 were

Table 5. Correlation between different parameters with CD155 among studied AML cases.

		CD155
Age	R	0.007
	P	0.948
Hb	R	0.001
	P	0.989
WBCS	R	0.155
	P	0.123
PLT	R	−0.128
	P	0.203
Blast	R	0.028
	P	0.783
LDH	R	**0.544**
	P	**<0.001**
Molecular	R	0.456
	P	0.001
Cytogenetics	R	0.029
	p	0.612

Pearson correlation, P significant < 0.05.

significant risk factor for shorter OS among cases and also positive expression of CD16 and CD56 and AML M3 were significantly associated with longer survival. Multivariate analysis revealed that only CD155 was significantly risk factor for shorter OS as show in Table 6.

Survival analysis:

At the end of follow up period (24 months), overall survival (OS) of studied patients estimates 90.0% at 12 months interval. OS of studied patients estimates 56.0% at 24 months interval as illustrated in Figure 1.

As regard CD155, OS estimates 98.0% at 12 months interval and 76.0% at 24 months interval in (CD155 < 5.35) group, also OS estimates 82.0% at 12 months interval and 36.0% at 24 months interval in (CD155 > 5.35) group, significant difference between 2 groups (P < 0.001).

At the end of follow up period (24 months), disease free survival (DFS) of studied patients estimates 88.5% at 12 months interval. DFS of studied patients estimates 67.3% at 21 months interval as presented in Figure 2.

As regard CD155, DFS estimates 100% at 12 months interval and 80.6% at 21 months interval in (CD155 < 5.35) group, also DFS estimates 75.8% at 12 months interval and 50.0% at 21 months interval in (CD155 > 5.35) group, significant difference between 2 groups (P < 0.001).

Table 6. Cox regression analysis for prediction of survival within AML cases.

		Univariate analysis				Multivariate analysis			
		p	HR	95% CI		p	HR	95% CI	
	Age	0.343	1.010	0.989	1.031				
	Gender	0.791	0.923	0.508	1.675				
	Hb	0.143	1.11	0.965	1.278				
	WBCS	0.333	1.008	0.992	1.023				
	PLT	0.778	0.999	0.994	1.006				
	BM blast	0.729	0.998	0.987	1.009				
	LDH	**0.019**	**1.001**	**1.00**	**1.004**	0.892	1.00	0.999	1.001
	CD155	**<0.001**	**1.030**	**1.019**	**1.041**	**0.039**	**1.020**	**1.001**	**1.040**
	CD56	**<0.001**	**0.279**	**0.149**	**0.522**	0.366	0.662	0.271	1.619
	CD16	**<0.001**	**0.312**	**0.167**	**0.584**	0.451	0.719	0.304	1.694
FAB	**M1-M2**	-	R	-	-	-	R	-	-
	M3	**0.038**	**0.279**	**0.084**	**0.933**	0.344	0.527	0.140	1.986
	M4-M5	0.516	0.816	0.441	1.507	-			
Cytogenetic	**Favorable**	-	R	-	-				
	Intermediate	0.700	1.240	0.416	3.693				
	Unfavorable	0.540	1.527	0.395	5.912	-			

HR, hazard ratio; CI, confidence interval; COX regression was used.

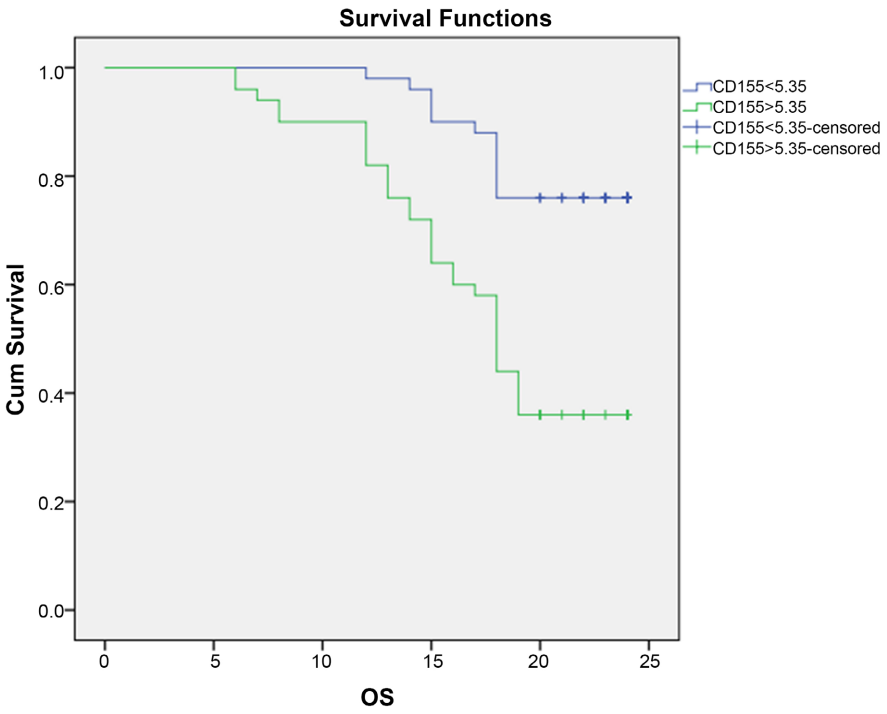

Figure 1. Kaplain meir curve for overall survival among studied groups. Abberviation: OS: overall survival, CD: cluster differntiation.

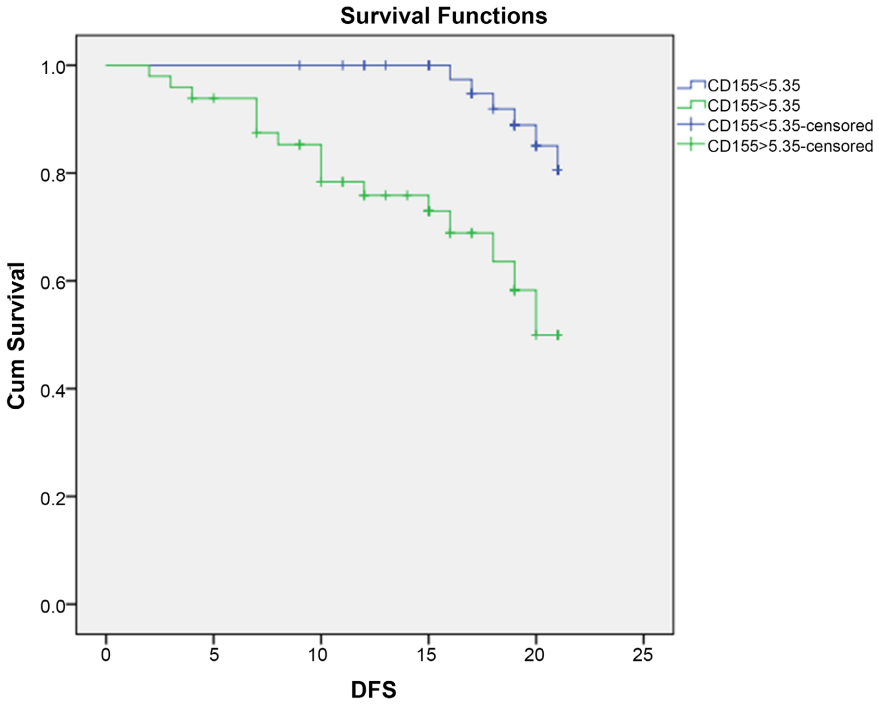

Figure 2. Kaplain meir curve for disease free survival among studied groups. Abberviation: DFS: disease free survival, CD: cluster differntiation.

4. Discussion

Acute myeloid leukemia (AML) is a hematopoietic malignancy characterized by a clonal expansion of low differentiated hematopoietic precursors that infiltrate the bone marrow and limit normal hematopoiesis. Although AML occurs in all ages, it appears predominantly in older people. AML remain a major clinical challenge characterized by a poor prognosis, poor overall survival and management difficulties, which is even more difficult in elderly patients who frequently have other pathologies associated with age [18].

The capacity of the immune system to control tumor growth and metastasis has focused attention in order to develop new strategies to treat cancer directed to stimulate the patient immune system such as checkpoint blockade or using engineered immune cells to attack cancer as it is currently used in CAR-T therapies. Thus, novel cancer immunotherapies have emerged in the last decades that are being analyzed in clinical trials in patients with hematologic and solid cancer [19].

The analysis of the patient immune system represents a central point for the design of personalized immunotherapies. Several alterations have been described in T and NK cells in AML patients that limit tumor control by the immune system [20].

Nectin and nectin-like molecules can represent biomarkers for cancer diagnosis, players in immune responses and targets for cancer immunotherapy. CD112 (Nectin-2) and CD155 (Necl-5) were identified as ligands for the DNAM-1 receptor [21]. DNAM-1 (also known as CD226) was first discovered as a costimu-

latory receptor expressed on cytotoxic T cells. DNAM-1 is also expressed by NK cells and is involved in T cell- and NK cell-mediated cytotoxicity [19].

In the last decade, one of the major advances in cancer immunotherapy was the use of monoclonal antibodies (mAbs) to block inhibitory immune checkpoints. One of these inhibitory receptors is TIGIT (T cell immunoreceptor with Ig and ITIM domains), that is expressed in different immune cells such as T cells, regulatory T cells, follicular T cells and NK cells. TIGIT could bind to CD155 (PVR) on dendritic cells (DCs), macrophages, etc. with high affinity. TIGIT shares the same ligands, CD155 and CD112, with the activating/co-stimulatory receptor DNAM-1 and shows higher affinity than DNAM-1 for CD155 [22].

Blockade of TIGIT led to increased cell proliferation, cytokine production, and degranulation of TA-specific CD8+ T cells and TIL (tumor infiltrating lymphocytes) CD8+ T cells [23].

Expression of CD155 among AML patients is heterogenous, according to median cut off CD155 (5.35), stratification of those patients into low and high risk. This matched with increased soluble CD155 in cancer patients by study of [24].

The variability of CD155 expression in AML could be explained by its dual function in oncoimmunity. CD155 may favor proliferative signals and tumor growth along with malignant cell invasion and metastasis. On the other hand, CD155 provides a direct link between cellular responses to stress and immune surveillance because it is a ligand for DNAX associated molecule 1 (DNAM 1) an activating receptor expressed on natural killer cells and cytotoxic T cells [13].

Up regulation of CD155 renders tumor cells more sensitive to elimination by immune cells. Cytotoxic lymphocytes also express inhibitory receptors able to bind to CD155 [25].

Adding additional complexity to the clinical is the significance of CD155 expression on malignant cells. It is likely that the role of CD155 will change during tumor progression in the early phases of tumor progression. In the early phases of tumor formation, CD155 surface expression on tumor cells mainly promotes anti-tumor immune function while in the late phase it supports tumor growth and immune escape.

In the present study, highly significant correlation with LDH as tumor bulk mass, this in agreement with [26], univariate cox regression analysis revealed that CD155 was a significant risk factor for shorter overall survival among AML patients. In contrast, positive expression of CD16 and CD56 and AML (M3) subtype were significantly associated with longer survival while multivariate analysis revealed that only CD155 was significantly associated with shorter overall survival.

Furthermore, survival analysis revealed that OS significantly higher in CD155 < 5.35 compared to CD 155 > 5.35 of patients. Moreover, DFS was non- significantly higher in CD155 < 5.35 compared to CD155 > 5.35.

These finding in agreement with other published data by [27] have demonstrated that high PVR expression correlates with poor outcome in AML.

These findings could be explained by the fact that CD155 can combine with

costimulatory molecule CD226 (DNAM-1), and coinhibitory molecules TIGIT and CD96, having a dual function in oncoimmunity. Accordingly, the balance between CD155/CD226 and CD155/TIGIT or CD155/CD96 maintains normal NK and T cell function. However, this balance may be disrupted in the tumor microenvironment. On one hand, tumor cells usually overexpress CD155; on the other hand, tumor-infiltrating immune cells may express decreased CD226 and increased TIGIT. Therefore, CD155/TIGIT or CD155/CD96-mediated inhibitory signaling may be dominant in the tumor microenvironment [28].

The expression of CD112 and CD155 (DNAM-1 ligands) on leukemic blasts induces a decreased expression of the activating receptor DNAM-1 on natural killer (NK) cells from acute myeloid leukemia (AML) patients. The patients with AML have depressed NK cell function and NK cell activity has been positively correlated with relapse-free survival [29].

Immunotherapy is emerging as an alternative to standard anticancer therapies, with the successful treatment of a proportion of various advanced cancer patients with anti-programmed death 1 (anti-PD-1), anti-programmed death ligand 1 (anti-PD-L1), [30] [31] [32] and/or anti-CTLA4 [33] [34] by CD112R as novel checkpoint for human T. cells. However, many patients still do not benefit from these immunotherapies. CD155 expressed by tumors and activated myeloid cells has the potential to subvert immune responses through interaction with the immune checkpoint receptors CD96 and TIGIT, PVR receptors could be therapeutic potential [35] [36] [37].

5. Conclusion

Our study revealed variability in expression of CD155 in AML patients due to dual costimulatory and inhibitory function, high expression associated with tumor bulk and progression, short OS, increased relapse rate. Cox regression analysis shows its independent risk factor. It could be implemented in routine laboratory for risk stratification into low, high risk that needs more therapeutic modalities with new immunotherapy. In future could be targeted therapy such as PDL, CTLA-4 and open more therapeutic hope for those patients.

Conflicts of Interest

The authors have no conflicts of interest.

Participants Included in the Study

Informed consent was obtained from all patients

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