THE VALUE OF IMMUNE INHIBITORY RECEPTOR IMMUNOGLOBULIN-LIKE TRANSCRIPT 3 EXPRESSION IN THE DIAGNOSIS OF ACUTE MYELOID LEUKEMIA WITH MONOCYTIC DIFFERENTIATION

Akram Abdel Moneim Deghady, Abeer Shawky Mohamed El Hadidi, Omar Mohamed Ghallab*, Asmaa Elsayed Abd Elaziz Mohamed

Department of Clinical and Chemical Pathology, Department of Hematology*, Faculty of Medicine, University of Alexandria

INTRODUCTION

Acute myeloid leukemia (AML) represents a heterogeneous disease characterized by clonal proliferation of abnormal blast cells in the bone marrow interfering with the production of normal hematopoietic cells. The 2017 World Health Organization (WHO) classification includes four major entities: AML with recurrent genetic abnormalities, AML with myelodysplasia related changes, therapy-related myeloid neoplasms, and AML-not otherwise specified (NOS). A subset of AML-NOS is AML with monocytic differentiation has a high risk of extra medullary infiltration, high leukocytic count and specific cytogenetic abnormalities. Flowcytometric (FC) immunophenotyping is suited for identification of monocytes by available antibodies such as CD11b, CD13, CD4, CD14, CD15, CD34, CD36, CD64, CD11c and CD117. However, neoplastic monocytes variably express these markers. The ILT3 molecule is a transmembrane protein immune inhibitory receptor expressed by APCs as monocytes and DCs. Therefore, the current study was designed to investigate the usefulness of ILT3 expression to distinguish AML with monocytic differentiation from other types of AML.

AIM OF THE WORK

The aim of this work was to study the expression of ILT3 in monocytic lineage AML and the possibility of its use as a specific monocytic marker in the routine diagnostic workup.

PATIENTS AND METHODS

PATIENTS: The current study was conducted on110 patients:

Group I: Fifty-five adult patients diagnosed with AML with monocytic differentiation were randomly recruited from the hematology unit of Alexandria main university hospital and Medical Research Institute.

Group II: Thirty-five adult patients diagnosed with other types of AML without monocytic differentiation.

Group III: Fifteen adult patients of matching age and sex admitted for bone marrow aspiration for other benign conditions such as hypersplenism and ITP as a control group.

METHODS: All patients included in the study were subjected to the following:

I. Full history taking including age, gender and presenting symptoms.

II. Complete clinical examination including the presence of fever, fatigue, weight loss, signs of bone marrow failure including pallor, purpura, ecchymosis, lymphadenopathy, hepatosplenomegaly.

III. Laboratory investigations including CBC, bone marrow aspiration for morphological examination, flowcytometry and cytogenetic analysis.ILT3 was evaluated by standard eight-colour flowcytometry using Becton Dickinson FACS Canto II flow cytometer in all AML patient samples and the control group samples. Immunophenotypic studies included the combination of CD85K-PE/CD33-FITC/CD45-v500.

RESULTS

ILT3 or CD85K was positively expressed in 52 out of 55 cases of AML cases with monocytic differentiation (94.5%) with a mean of expression equal to 47± 26.19% of cells from the gated blast population, while AML cases without monocytic differentiation were all negative for ILT3 expression with a mean of 5.03 ± 2.98% of cells from the gated blast population. Also, all the control cases showed negative expression for ILT3 with a mean equal to 4± 2.45% of the gated blast population. The cut off for ILT3 positivity was >10% of cells of the gated blast population expressing the marker.

Table 1: Comparison between the three studied groups according to ILT3 (CD85K) expression on the gated blast population

ILT3 expression	Group I (n = 55)		Group II (n = 35)		Group III (n = 15)		Test of Sig.	p
	No.	%	No.	%	No.	%		
Negative	3	5.5	35	100.0	15	100.0	χ^2= 93.654*	<0.001*
Positive	52	94.5	0	0.0	0	0.0		
Sig. bet. grps.	p_1<0.001*, FE p_2<0.001*, p_3–							
% of cells expressing ILT3 (CD85K) from the gated population								
Min. – Max.	3.0 – 96.0		0.0 – 10.0		0.0 – 8.0		H= 68.597*	<0.001*
Mean ± SD.	47.25 ± 26.19		5.03 ± 2.98		4.0 ± 2.45			
Median (IQR)	43.0 (29.0 – 72.0)		5.0 (2.70 – 8.0)		4.0 (2.50 – 6.0)			

Among all other monocytic markers such as CD4, CD14, CD64, CD11c and CD11b, ILT3 had a 100% specificity equal to CD14, and it was the most accurate in differentiating AML with monocytic differentiation from other AML types. ILT3 also had a very high sensitivity second to CD64. Although CD14 had a 100% specificity, it had the lowest sensitivity (27.27%). (See *table 2*)

Table 2: Sensitivity, Specificity, PPV, NPV and Accuracy of the expression of ILT3 and other monocytic markers in the two studied AML groups (n = 55 vs. 35)

	Sensitivity	Specificity	PPV	NPV	Accuracy
ILT3	94.55	100.00	100.00	92.11	96.67
CD4	85.45	94.29	95.92	80.49	88.89
CD14	27.27	100.00	100.00	46.67	55.56
CD64	100.00	88.57	93.22	100.00	95.56
CD11c	81.82	85.71	90.0	75.0	83.33
CD11b	78.18	94.29	95.56	73.33	84.44

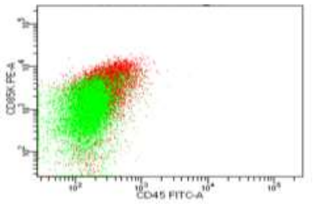

Figure 1: A case of AML (FAB-M5b) showing positive expression of ILT3 (CD85K) on about 86% of the 45-dim gated blast population with MFI=930.

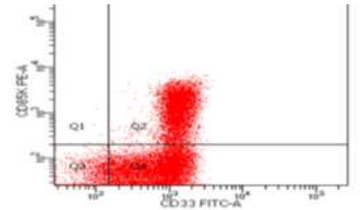

Figure 2: A case of AML (FAB-M4) showing positive expression of ILT3 (CD85K) on about 26% of the abnormal population representing the monocytic element with a moderate MFI=1303.

CONCLUSION

ILT3 is a highly specific and sensitive biomarker that is used as a diagnostic tool to distinguish AML with monocytic differentiation from other types of AML. This is the basis for new methods for the diagnosis, the monitoring, and the treatment of AML expressing ILT3.