بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

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تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

MONA MAGHRABY

PROM-1 (CD 133) overexpression in adult acute lymphoblastic leukemia Egyptian patients and relation to outcome

Thesis Submitted For Partial Fulfillment of Master Degree
In Internal Medicine

By

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

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List of abbreviations

ABC	ATP-binding cassette
ABCG2	ATP-binding cassette, sub-family G, member 2
ADAM	a disitegrin and metalloprotease
ADCs	availability of the antibody-drug conjugate
AHD	antecedent hematologic disorder
ALL	acute lymphoblastic leukemias
AML	acute myeloid leukemia
BAD	B cell leukaemia /lymphoma-associated factor 2-antagonist of cell death
B-ALL	B-cell lymphoblastic leukemia/lymphoma
Bcl-XL	B cell leukaemia associated protein 2 (Bcl-2), Bcl2-X-like
BCRP1	breast cancer resistance protein1
bHLH	basic helix–loop–helix
CALGB	Cancer and Leukemia Group B
CARs	Chimeric antigen receptors
CARTs	CAR T-cells
CEBPE	
CK1A	
CLP	common lymphoid progenitors
CMP	
CNS	central nervous system
CR	complete remission
CSCs	cancer stem cells
CSL	
DIC	Disseminated intravascular coagulation
DIFs	differentiation-inducing factors
EFS	event-free survival
FLIP	FLICE-like inhibitory protein
GLI	glioma-associated oncogene homolog
GSK-3β	glycogen-synthase kinase 3β
H3K79	histone H3 lysine-79
HES	hairy and enhancer of split
HLA	
HSC	hematopoietic stem cells
HSPCs	hematopoietic stem and progenitor cells
IAP	inhibitors of apoptosis protein
ICN	intracellular Notch
KEEs	

LEFs	lymphocyte enhance factors
LHPP	
LMPP	lymphoid-primed multipotent progenitors
MDR	multidrug resistance
MDS	myelodysplastic syndrome
MLL	Mixed Lineage Leukemia
MLL-FPs	MLL-AF4 and other MLL fusion proteins
MLLr	MLL-rearranged
MMP	
MMTV	
MPP	multipotent progenitors
MRD	
mTOR	mammalian target of rapamycin
NE	Neuroepithelial
Ngn 1	neurogenin 1
OS	overall survival
PDKs	phosphatidyl inositol-dependent kinases
PIP3	phosphatidylinositol3-phosphate
PPARγ	Peroxisome Proliferator-activated receptor γ
PROM1	
PTEN	phosphatase and tensin homolog
SEER	Surveillance, Epidemiology and End Results
SHH	Sonic HH
SNP	single-nucleotide polymorphism
STAT	signal transducer and activator of transcription
STGD	Stargardt
SUFU	suppressor of fused homolog
T-ALL	T-cell lymphoblastic leukemia/lymphoma
TCFs	T-cell factors
TRAIL	TNF-α-related apoptosis inducing ligand
VEGF-A	vascular endothelial growth factor-A
WBC	White blood cell

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ABSTRACT

Background; Cancer stem cells are the cancer cells that have abilities to self-renew, differentiate into defined progenies, and initiate and maintain tumor growth. Among the reported makers of the cancer stem cells, CD133 is the most well-known marker for isolating and studying cancer stem cells in different types of cancer. The CD133high population of cancer cells are not only capable of self-renewal, proliferation, but also highly metastatic and resistant to therapy, **Aim and objectives;** to know about PROM-1 (CD 133) overexpression in adult acute lymphoblastic leukemia Egyptian patients and relation to outcome, **Subjects and methods;** This is a Prospective study, was conducted at Ain Shams university hospitals. Internal medicine department, Clinical hematology and stem cell transplantation unit, on 47 adult patients with Acute Lymphocytic Leukemia, over aperiod of Six months, **Result;** there were 26 (81.2%) with fever, 10 (31.2%) with Bleeding tendency, 26 (81.2%) with Lymph node, 17 (53.1%) with Hepatosplenomegaly, 9 (28.1%) with Mediastinal mass and 17 (53.1%) with Bone pain, **Conclusion**; Prominin 1 positive expression is a helpful prognostic marker in patients with ALL. Prominin 1 should be routinely assessed at diagnosis in ALL patients for better prognostic assessment and should be taken in consideration in designing future therapeutic strategies based on patient specific risk factors, **Keywords; Cancer stem cells, CD133, PROM1.**

INTRODUCTION

CD133, encoded by the ***PROM1*** gene, is a pentaspan transmembrane glycoprotein of great potential value as a pan-cancer target as it is commonly associated with cancer stem cells in multiple different tumor types, including leukemia .Proof-of-principle studies have shown that targeting CD133 can be used to deliver nanoparticles to gastric stem cells ,or for chimeric antigen receptor T cell therapy in acute lymphoblastic leukemias (ALL) caused by rearrangements of the *Mixed Lineage Leukemia (MLL)* gene **(Liou GY.2019)**.

Despite vast improvements in treatment for ALL, *MLL* gene rearrangements (MLLr) still cause very poor prognosis ALLs.The most common MLL rearrangement is the t(4;11) (q21;q23) chromosome translocation that fuses MLL in frame with the AF4 gene producing MLL-AF4 and AF4-MLL fusion protein. MLL-AF4 and other MLL fusion proteins (MLL-FPs) bind to gene targets and cause inappropriate gene activation through multiple transcription elongation and epigenetic mechanisms, including recruitment of the histone H3 lysine-79 (H3K79) methyltransferase DOT1L. In addition to a role in transcription elongation, recent work has shown that H3K79me2/3 has an important role at a subset of enhancers (H3K79me2/3-marked enhancer elements (KEEs)), increasing expression of key gene targets through the maintenance of enhancer–promoter interactions **(J Clin Oncol. 2019)**.

According to Tolba et al, study which showed that CD133 expression is an independent prognostic factor in acute leukemia, especially ALL patients and its expression could characterize a group of acute leukemia patients with higher resistance to standard chemotherapy and relapse **(Tolba et al., 2013)**.

One of the most attractive features of *PROM1*/CD133 as a potential therapeutic target derives from the recognition that the gene is a direct target of MLL-AF4 regulation, suggesting that in MLLr leukemias *PROM1*/CD133 expression is tightly linked to the activity of the fusion protein itself. However, the exact details of how this locus is regulated by MLL-AF4 are unclear, and whether and how *PROM1* /CD133 contribute to MLLr leukemic growth is unknown. Understanding these mechanisms is likely to be key to the future development of *PROM1*/CD133-directed therapeutic targeting in these leukemias. **(Godfrey L.2019)**.

AIM OF THE WORK

The aim of the present study is to know about PROM-1 (CD 133) overexpression in adult acute lymphoblastic leukemia Egyptian patients and relation to outcome.