Expression of G Protein–Coupled Receptor 56 (GPR56) in Acute Myeloid Leukemia

Thesis

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Mai Abdel Latif Ahmed

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List of Abbreviations

Abb.	Full term
ABL	*Abelson murine leukemia viral oncogene*
ADCs	*antibody-drug conjugate*
ADGRG1	*Adhesion G-protein coupled receptor G1*
ADL	*Activities of daily living*
Ag	*Antigen*
ALC	*Absolute lymphocyte count*
ALL	*Acute Lymphoblastic Leukemia*
ALT	*Alanine aminotransferase*
AML	*Acute Myeloid Leukemia*
AP	*Alkaline phosphatase*
APL	*Acute Promyelocytic Leukemia*
AST	*Aspartate aminotransferase*
ASXL1	*Additional sex comb-like 1 mutation*
ATRA	*All-trans retinoic acid*
AYAs	*Adolescents and Young Adults*
BCL2	*B-cell lymphoma 2 gene*
BCR	*Breakpoint cluster region protein*
BFPP	*Bilateral frontoparietal polymicrogyria*
BM	*Bone Marrow*
BMT	*Bone Marrow transplantation*
BSC	*Best supportive care*
CAE	*Chloroacetate Esterase*
CBC	*Complete Blood Count*
CBF	*Core Binding Factor*
CD	*Cluster of Differentiation*
CEBPA	*CCAAT/enhancer-binding Protein Alpha*
C-KIT	*Steal factor*
CN-AML	*Cytogenically normal Acute Myeloid Leukemia*
CR	*Complete remission*

List of Abbreviations (Cont...)

Abb.	Full term
CXCR4	*Chemokine receptor type 4*
Del	*Deletion*
DFN	*Different from normal*
DIC	*Disseminated intravascular coagulopathy*
DNA	*Deoxyribonucleic acid*
ECOG	*Eastern Cooperative Oncology Group*
EDTA	*Ethylene-diamine-tetra acetic acid*
ER	*Oestrogen receptor*
ERG	*Ets related gene*
ETO	*Ethylene oxide*
EVI1	*Ecotropic viral integration site 1*
FAB	*French American British*
FCM	*Flow cytometry*
FISH	*Florescence in-situ hybridization*
FLT3	*FSM like tyrosine kinase 3*
FMS	*Fibromyalgia syndrome*
GABAB	*Gamma-aminobutyric acid B*
GAIN	*GPCR- Autoproteolysis Inducing domain*
G-CSF	*Granulocyte Colony Stimulating Factor*
GHRH	*Growth hormone-releasing hormone*
GIP	*Glucose-dependent insulinotropic polypeptide*
GLP	*Glucagon-like peptide*
GM-CSF	*Granulocyte Macrophage Colony Stimulating Factor*
GO	*Gemtuzumab Ozogamicin*
GPCR	*G-Protein Coupled Receptor*
GPR56	*G-Protein Coupled Receptor 56*
GPS	*GPCR-proteolysis site*

List of Abbreviations (Cont...)

Abb.	Full term
GRAFS	*Glutamate-Rhodopsin-Adhesion-Frizzled-Secretin*
GTPases	*Guanosine triphosphate*
Hb	*Hemoglobin*
HLA	*Human leukocytic antigen*
HLA-Dr	*Human leukocytic antigen- antigen D related*
HSCs	*Hematopoietic Stem Cells*
HSCT	*Hematopoietic stem cells transplantation*
HT	*Hypomethylating therapy*
IC	*Intensive chemotherapy*
IDH	*Isocitrate Dehydrogenase*
IL	*Interleukin*
Inv	*Inversion*
IPT	*Immunophenotyping*
IQR	*Interquartile range*
ITD	*Internal tandem duplications*
KIT ligand	*Ligand for the receptor-type protein-tyrosine kinase*
KMT2A	*Lysine (K) -specific methyl transferase 2A*
LAIP	*Leukemia associated immunophenotype*
LSCs	*Leukemic Stem Cells*
LT-LSCs	*Long term leukemic stem cells*
M0	*Minimally differentiated acute myeloblastic leukemia*
M1	*Acute myeloblastic leukemia, without maturation*
M2	*Acute myeloblastic leukemia, with granulocytic maturation*
M3	*Acute promyelocytic leukemia*

List of Abbreviations (Cont...)

Abb.	Full term

M4 eos ..... *Acute Myelomonocytic Leukemia with eosinophilia*
M4 ..... *Acute Myelomonocytic Leukemia*
M5 ..... *Acute monoblastic leukemia*
M6 ..... *Erythroblastic leukemia*
M7 ..... *Acute megakaryoblastic leukemia*
MDR ..... *Multidrug resistance*
MDS ..... *Myelodysplastic Syndrome*
MFC ..... *Multiparameter flow cytometry*
MFI ..... *Mean florescence intensity*
MLL ..... *Myeloid/lymphoid or mixed lineage leukemia*
MPAL ..... *Mixed phenotype acute leukemia*
MPD ..... *Myeloproliferative Disorders*
MPL ..... *Myeloproliferative Leukemia*
MPN ..... *Myeloproliferative neoplasm*
MPO ..... *Myeloperoxidase*
MRD ..... *Minimal / measurable residual disease*
MYH11 ..... *Myosin heavy chain 11*
NFAT ..... *Nuclear factor of activated T-cell*
NGS ..... *Next generation sequencing*
NK ..... *Natural killer*
NPM ..... *Nucleophosmin*
NPV ..... *Negative predictive value*
NSD1 ..... *Nuclear receptor binding SET domain protein 1*
NSE ..... *Non-Specific Esterase*
NUP ..... *Nuclear pore complex*
OS ..... *Overall survival*

List of Abbreviations (Cont...)

Abb.	Full term
PACAP	*Pituitary adenylate cyclase-activating polypeptide*
PAS	*Periodic Acid Schiff*
PBB	*Peripheral blood blast*
PBS	*Phosphate buffer saline*
PBSC	*Peripheral Blood Stem cells*
PCR	*Polymerase Chain Reaction*
PKC	*Protein kinase C*
PML	*Promyelocytic leukemia*
PPV	*Positive predictive value*
PRT	*Post-remission therapy*
PS	*Performance status*
PTD	*Partial tandem duplication*
Rac	*Subfamily of the Rho family of GTPases*
RAR	*Retinoic Acid Receptor*
RARA	*Retinoic Acid Receptor alpha*
RBC	*Red blood cells*
RBM15	*RNA-binding Motif protein 15*
RNA	*Ribonucleic acid*
ROC curve	*Receiver operating characteristic curve*
RUNX1	*RUNT-related transcription factor*
RUNX1T1	*RUNX1T1 gene*
SBB	*Sudan Black B*
SCT	*Stem cell transplantation*
SD	*Standard deviation*
SRF	*Serum response factor*
SSC	*Side scatter*
ST-LSC	*Short term leukemic Stem Cells*
T	*Translocation*

List of Abbreviations (Cont...)

Abb.	Full term
TdT	*Terminal deoxynucleotidyl transferase*
TLC	*Total leucocytic count*
TM	*Transmembrane*
TP53	*Tumor protein p53*
VEGF	*Vascular endothelial growth factor*
VIP	*Vasoactive intestinal peptide*
WBC	*White Blood Cells*
WHO	*World Health Organization*

Abstract

Background: Acute myeloid leukemia is a heterogeneous marrow-based clonal group of neoplasm that affects hematopoietic cells responsible for the production of myeloid lineages. Its diagnosis and sub-classification by FAB and WHO criteria require combination of morphology, cytochemistry, cytogenetics and immune-phenotyping with biological and clinical features to define specific disease entities. **Aim of the Work:** The aim of this study is to analyze GPR56 expression in de novo AML patients using flow cytometry. The results of GPR56 expression will be correlated with the clinical outcome of the patients. **Subjects and methods:** The study was carried out at Ain Shams University hospitals on a total number of 60 patients attending hematology-oncology unit during the period from November 2016 to July 2017. Patients were assessed at day 28 after induction of treatment by bone marrow examination and follow up. Informed consents were obtained from all subjects prior to enrollment in the study. **Results:** GPR56 was highly expressed above mean in 62.5% of our acute myeloid leukemia cases. **Conclusion:** Our Study revealed that high expression of GPR56 was associated with poor response to treatment where patients with high expression had incomplete remission at day 28, on the other hand it lacked prognostic significance with favorable and unfavorable patients' outcome and cytogenetic subgroups. **Recommendations:** Flow cytometry evaluation of GPR56 should be incorporated into the initial laboratory work-up for all newly diagnosed AML patients. Study of the stability of GPR56 expression during the course of the disease and its applicability as a marker for acute myeloid leukemia.

Key words: G protein-coupled receptor 56, acute myeloid leukemia

INTRODUCTION

Acute myeloid leukemia (AML) is a hematologic malignancy characterized by clonal proliferation of myeloblasts, interfering with the production of normal blood cells. AML is the most common acute leukemia affecting adults, showing an increasing incidence with age ***(Jemal et al., 2002)***. Despite high-dose chemotherapy, only 30% to 40% of AML patients survive, which is primarily due to relapse of the disease ***(Lowenberg et al., 2003)***.

Prognosis of AML is multifactorial, yet highly dependent on the presence of leukemic stem cells (LSCs). Studies have shown that LSCs are present in theCD34+ CD38- compartment ***(Dick, 2008)***. Various markers have been described to identify LSC such as anti-CD123, anti-CD44, and anti-CD33, but all have some disadvantages ***(Jin et al., 2006)***.

The surface protein G protein–coupled receptor 56 (GPR56) was introduced as a novel human LSC marker in AML patients. GPR56 is a member of the secretin family and has been linked to developmental malformations of the human brain ***(Iguchi et al., 2008)***. In cancer cells, overexpression of GPR56 is known to suppress tumor growth and metastasis in melanoma cell lines, and GPR56 functions in tumor cell adhesion in glioma cells ***(Ke et al., 2007)***.