Study of CD123 (Interleukin-3 receptor alpha chain) and NF-kB (Nuclear factor kappa B) in Adult Acute Myeloid Leukemia Patients

Thesis
Submitted for partial fulfilment of the M.D degree in Clinical Haematology

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Acknowledgement

♦*I would like to express my deepest gratitude and gratefulness to* ***Prof.Dr. Inas Ahmed Asfour*** *Professor of Clinical Hematology & Internal Medicine, Faculty of Medicine,Ain Shams University, for her kind support , continuous encouragement and precious help to accomplish my research.*

♦*I am deeply indebted to* ***Prof.Dr. Soha Raouf Youssef****, Professor of Clinical Pathology,, Faculty of Medicine, Ain Shams University, for her kind work and valuable scientific advice.*

♦*My deepest gratitude and gratefulness to* ***.Dr. Maryse Soliman Ayoub*** *Assistant Professor of Clinical Hematology & Internal Medicine, Faculty of Medicine,Ain Shams University, for her kind trust ,meticulous and noble supervision, to accomplish my research.*

♦*My thanks to* ***Dr. Nevine Nabil Moustafa*** *, Assistant Professor of Clinical Hematology & Internal Medicine, Faculty of Medicine, Ain Shams University, for her kind help and care.*

♦*My thanks to* ***Dr. Dr.Ghada Metwally El-Gohary ,*** *Assistant Professor of Clinical Hematology & Internal Medicine, Faculty of Medicine, Ain Shams University, for her kind help and care.*

Genuine appreciation to my teachers, my family, colleagues& friends for their continuous support.

Dr.Hani Salman Ayyash
Cairo-2011

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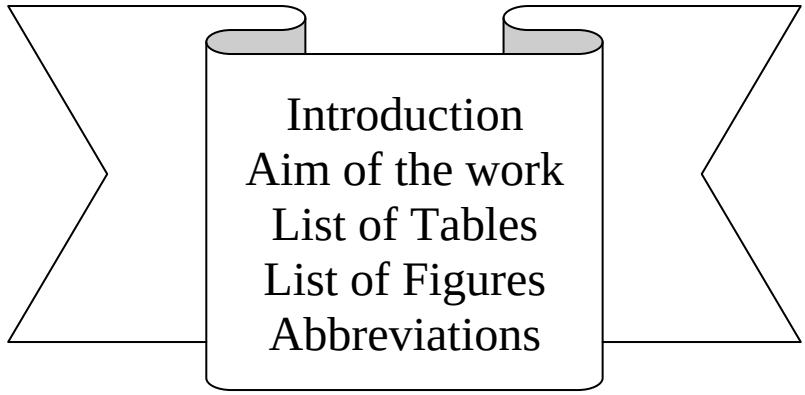
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Introduction

Acute myeloid leukemia (AML) is a genetically heterogeneous clonal disorder characterized by the accumulation of acquired somatic genetic alterations in hematopoietic progenitor cells that alter normal mechanisms of self-renewal, proliferation and differentiation. (**Dohner & Dohner ; 2008)**

The genomic alterations in AML affect the function of signaling molecules, transcription factors, and growth-factor receptors and also determine the phenotype of the leukemia and influence the response to treatment. Moreover, the multiplicity of genomic changes that frequently coexist in a single leukemic cell reflects the successive transforming events that accumulate in the leukemic clone during the development of AML.
(Löwenberg, 2008)

While a stem cell origin for myeloid leukemia has been postulated for over three decades, definitive experimental evidence for leukemia stem cells (LSC) has only been generated in recent years. These studies have demonstrated the central role of LSC in myeloid leukemia and highlighted the critical need for therapeutic strategies that directly target the LSC population.
(**Gary et al., 2004)**

In AML , LSCs are phenotypically defined as CD34+, CD38-, CD71-, CD90-, HLA-DR-, CD117-, and CD123+. Even though most of these antigenic features are shared with normal hematopoietic stem cells(HSCs) (CD34+, CD38-, CD71-, and HLA-DR-), at least three markers have been found to be unique to LSCs (CD90-, CD117-, and CD123+) .
(**Guzman & Jordan, 2004).**

Interleukin-3 receptor alpha chain (CD123) is over expressed in about 45% of acute myeloid leukemia's , this phenomenon was associated with high blast cell counts at diagnosis, high rate of cycling of leukemic blasts and with a worse prognosis**.**
(Riccocini et al., 2004)

The mechanisms underlying the elevated CD123 expression observed in AML blasts are unclear. The increased CD123 expression observed in AML could be mainly related to a transcriptional mechanism, as suggested by the observation that increased levels of CD123 mRNA are observed in most patients exhibiting high CD123 levels. (**Testa et al., 2005)**

The transcription nuclear factor kappa B (NF-kB) can intervene in oncogenesis through its capacity to regulate the expression of a large number of genes that regulate apoptosis, cell proliferation and differentiation as well as inflammation, angiogenesis and tumor migration. (**Cilloni et al., 2007)**

Constitutive or aberrant activation of NF-κB is frequently encountered in many human tumors as well as hematological malignancies including acute myeloid leukemia and is associated with a resistant phenotype and poor prognosis. In AML the mechanism of such persistent NF-κB activation is not clear but may involve defects in signaling pathways, mutations, or chromosomal rearrangements. Suppression of constitutive NF-κB activation inhibits the oncogenic potential of transformed LSC and thus makes NF-κB an interesting new therapeutic target (**Sethi et al., 2008)**

Aim of the work

-To assess the relationship between CD123 (Interleukin-3 receptor alpha) expression as a marker for acute myeloid leukemia , and Nuclear factor – kappa B(NF-κB) level, in adult patients with acute myeloid leukemia at presentation & after induction therapy.

-To find out the possible correlation of each of the two parameters to the current known diagnostic and prognostic factors in AML .

- To be translated therapeutically as a targeted therapy for AML.

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AA	aplastic anemia
AB	antibiotics
ABCB1	ATP-binding cassette sub-family b member 1
ABCG	ATP-binding cassette sub-family G member
ABL1	Abelson murine leukemia viral oncogene homolog 1
ACD	anemia of chronic disease
AHD	antecedent hematological disorder
AKT	murine thymoma viral oncogene
ALL	acute lymphoblastic leukemia
alloHSCT	allogeneic hematopoietic stem cell transplantation
ALFA	Acute Leukemia French Association
AML	acute myeloid leukemia
AMLCG	acute myeloid leukemia cooperative german group
AML-ETO	acute myeloid leukemia- eto (RUNX1) gene
ANCs	absolute neutrophil counts
APL	acute promyelocytic leukemia
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
Ara-C	cytarabine
Ara-CTP	arabinosylcytosine triphosphate
autoHSCT	autologous hematopoietic stem cell transplantation
ATRA	all-trans retinoic acid
ATG	anti-thymocyte globulin
ATO	arsenic trioxide
AV	arterio-ventricle
AUC	area under the curve
AVN	avascular necrosis
BAALC	brain and acute leukemia cytoplasmic gene
BAD	bcl-2-associated death promoter
BAFF	B cell activating factor receptor
βc	beta common chain
BCL-2	b-cell lymphoma 2
BCR-Abl	breakpoint cluster region-abselon murine leukemia viral oncogene
BCRP	b cell receptor prorien
Bcl-X_L	b-cell lymphoma-extra large
Bfla/A1	Bcl-2 related gene , anti-apoptotic
BM	bone marrow
Bmi-1	polycomb ring finger oncogene 1
BMT	bone marrow transplantation
BU	busulfan
BUN	blood urea nitrogen
c	cytoplasm
c-Able	cytoplasm of abelson murine leukemia viral oncogene
CALGB	cancer and leukemia group b
CB	cord blood
CBC	complete blood cell

CBF	core binding factor
CBFB	core-binding factor subunit beta
CBT	cord blood transplantation
CCAAT	cytidine-cytidine-adenosine-adenosine-thymidine
CD	cluster differentiation
CEBPA	CCAAT/enhancer-binding protein alpha
Chest infec.	chest infection
CIBMTR	center for international blood and marrow transplant research
CLL	chronic lymphocytic leukemia
c-KIT	cytokine kinase tyrosine receptor
CLL-1	c-type lectin-like molecule-1
CML	chronic myeloid leukemia
c-MPO	cytoplasmic myeloperoxidase
Myc	myelocytomatosis viral oncogene homolog
CML	chronic myeloid leukemia
CMV IgM/G	cytomegalovirus immunoglobulin
C/N	cytoplasmic nuclear ratio
CN-AML	cytogenetically normal acute myeloid leukemia
CNS	central nervous system
CR	complete remission
CR1	complete response to initial therapy
CRi	complete remission with incomplete recovery
CRp	complete responses with incomplete platelet recovery
Rel	proto-oncogene protein is a protein that is encoded by the *REL* gene
CSC	cancer stem cell
CSF	cerebrospinal fluid
CT	computed tomography
CXCR4	chemokine receptor
CXR	chest x-ray
DA	diagnostic accuracy
DAPT	difluorophenacetyl-l-alanyl-S-phenylglycine t-butyl ester
DEK	oncogene (DNA binding)
Del	deletion
DFS	disease free survival
DLI	donor leukocyte infusions
DIC	disseminated intravascular coagulation
DMAPT	dimethyl amino parthenolide
DNA	deoxyribonucleic acid
DNMT	DNA methyltransferase
DNR	daunorubicin
d.t	due to
DT	diphtheria toxin
DW	dextrose water
EBMT	european bone marrow transplant
EBV	Epstein–Barr virus
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
ECHO	echo-cardiography

EDTA	ethylene Diamine Tetra Acetic acid
EGFR	epidermal growth factor receptor
ELAM-1	endothelial leukocyte adhesion molecule
ELISA	enzyme-linked immunosorbent assay
EMEA	european medicine agency
EORTC	european organization for research and treatment of cancer
EPICS	experimental physics and industrial control system
ERG	v-ets avian erythroblastosis virus E26 oncogene-like
ERK	extracellular signal-regulated kinases
ESR	erythrocyte sedimentation rate
ETO	eight-twenty-one
EVI1	ecotropic viral integration site 1 gene
FAB	french-american-british
FCM	flow cytometry
FDA	food and drug administration
FDPs	fibrin degradation products
FISH	fluorescence in situ hybridization
FLAG	fludarabine + high dose ara-c + G-CSF
FLIP	FLICE inhibitory protein
FLT3	fms-like tyrosine kinase 3
FN	false negative
FP	false positive
FSH	follicle-stimulating hormone
G+ ve	gram positive
G- ve	gram negative
g/dl	gram per deciliter
g/L	gram per litter
GADD	apoptosis- and DNA damage-inducible gene.
G-CSF	granulocyte colony stimulating factor
GFR	glomerular filtration rate
GIMEMA	gruppo italiano malattie ematologiche d'adulto
GO	Gemtuzumab ozogamicin
GM–CSF	granulocyte macrophage colony stimulating factor
GM-CSFR	granulocyte macrophage colony stimulating factor receptor
GRb2	growth factor receptor-bound protein 2
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
HA	hemolytic anemia
Hb	hemoglobin
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCL	hydrogen chloride
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HDAC	Histone deacetylase
HEPA	high-efficiency particulate air
HER2	human epidermal growth factor receptor 2
HGFs	hemopoietic growth factors
HHC-8	human herpes virus