CD86: A Novel Prognostic Marker in Acute Lymphoblastic Leukemia Patients

Thesis

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بسم الله الرحمن الرحيم
﴿ قالوا سبحانك لا علم لنا الا ما علمتنا
إنك انت العليم الحكيم ﴾
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Asmaa Mohamed Abd El Razek

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List of Abbreviations

µL	**:**	Micro liter
ALL	**:**	Acute lymphoblastic leukemia
AML	**:**	Acute myeloid leukemia
APCs	**:**	Antigen presenting cells
ARF	**:**	ADP-ribosylation factor
AUC	**:**	Area under the curve
B-ALL	**:**	B-cell Acute lymphoblastic leukemia
BCP-ALL	**:**	B-cell precursor ALL
BCR/ABL	**:**	Breakpoint cluster region/Abelson
BFM	**:**	Berlin-Frankfurt-Münster
BM	**:**	Bone marrow
CALLA	**:**	Common ALL antigen
CBC	**:**	Complete blood count
CCG	**:**	Children's Cancer Group
CD	**:**	Cluster of differentiation
CHL	**:**	Classic Hodgkin lymphoma
CLL	**:**	Chronic lymphocytic leukemia
C-Myc	**:**	Cellular myelocytoma gene
CNS	**:**	Central nervous system
CR	**:**	Complete remission
CSCs	**:**	Cancer stem cells
CSF	**:**	Cerebrospinal fluid
CTL	**:**	Cytotoxic T- lymphocytes
CTLA-4	**:**	Cytotoxic T-lymphocyte antigen 4
DCs	**:**	Dendritic cells
DNA	**:**	Deoxyribonucleic acid
EBF1	**:**	Early B cell factor 1
EDTA	**:**	Ethylene-diamine-tetra-acetic acid
EMI	**:**	Extramedullary involvement
FAB	**:**	French-american-british

FCM	**:**	Flow cytometry
FISH	**:**	Fluorescence in situ hybridization
FITC	**:**	Fluorescein isothiocyanate
FRET	**:**	Forster resonance energy transfer
GPI	**:**	Glycosyl phosphatidyl inositol
HA	**:**	Hyaluronic acid
Hb	**:**	Hemoglobin
HLA	**:**	Human leucocyte antigen
HLA-DR	**:**	Human leukocyte differentiation antigen
HS	**:**	Highly significant
HSCs	**:**	stem cells
iAMP21	**:**	Intra-chromosomal amplification of the chromosome 21
ICAM-1	**:**	Intercellular adhesion molecule-1
ICOS-L	**:**	Inducible costimulator ligand
IgC	**:**	Immunoglobulin constant
IgE	**:**	Immunoglobulin type E
IgG	**:**	Immunoglobulin type G
IGSF	**:**	Immunoglobulin superfamily
IgV	**:**	Immunoglobulin variable
IKZF1	**:**	IKAROS family zinc finger
IL	**:**	Interleukin
IPMs	**:**	Immunophenotypic markers
IPT	**:**	Immunophenotyping
IS	**:**	Immunological synapse
kDa	**:**	Kilodalton
LSCs	**:**	Leukemic stem cells
mCD86	**:**	Membranous CD86
MFI	**:**	Mean florescence intensity
MHC	**:**	Major histocompatibility complex
MLL	**:**	Myeloid–lymphoid lineage
MM	**:**	Multiple myeloma

MoAbs	**:**	Monoclonal antibodies
MPO	**:**	Myelo-peroxidase
MRD	**:**	Minimal residual disease
MS	**:**	Multiple sclerosis
NCI	**:**	National Cancer Institute
NK	**:**	Natural Killer cell
NPV	**:**	Negative predictive value
NS	**:**	Non significant
p	**:**	Short arm of chromosome
P	**:**	Probability
PAX5	**:**	Paired box 5
PB	**:**	Peripheral blood
PBS	**:**	Phosphate buffered saline
PCR	**:**	Polymerase chain reaction
PD-L1	**:**	Programmed cell death-1 ligand
PD-L2	**:**	Programmed cell death-2 ligand
PE	**:**	Phycoerythrin
PHF6	**:**	PHD finger protein 6
PLT	**:**	Platlets
PMNs	**:**	Polymorphonuclear cells
POG	**:**	Pediatric Oncology Group
PPV	**:**	Positive predictive value
q	**:**	Long arm of chromosome
RNA	**:**	Ribonucleic acid
ROC	**:**	Receiver operating characteristic
RT-PCR	**:**	Reverse transcriptase polymerase chain reaction
RUNX1	**:**	Runt related transcription factor 1
S	**:**	Significant
sCD44	**:**	Serum levels of CD44
sCD86	**:**	Serum levels of CD86
SD	**:**	Standard deviation
Sig	**:**	Significance

SLE	**:**	Systemic lupus erythematosis
t	**:**	Translocation
T-ALL	**:**	T-cell acute lymphoblastic leukemia
TCR	**:**	T-cell receptor
TCR	**:**	T cell receptor
TdT	**:**	Terminal deoxynucleotidyl transferase
Teff	**:**	Effector T cells
TEL-AML1	**:**	Tel-acute myeloid leukemia
Th1	**:**	T helper type 1
Th2	**:**	T helper type 2
TIL	**:**	Tumor infiltrating lymphocytes
TLC	**:**	Total leukocytic count
TNFR	**:**	Tumor necrosis factor receptor
TNFRSF	**:**	Tumor necrosis factor superfamily
Treg	**:**	Regulatory T cell
VISTA	**:**	V-domain immunoglobulin suppressor of T cell activation
WBC	**:**	White blood cell
WHO	**:**	World health organization
WT1	**:**	Wilms tumor 1
X^2	**:**	Chi- square test

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Introduction

Leukemia is a hematopoietic malignancy that results from the clonal proliferation of bone marrow cells with impaired differentiation, regulation, and cell death. The acute leukemias arise from neoplastic transformation of hematopoietic stem cells or progenitors with aberrant differentiation and proliferation **(Gowda and Dovat, 2013).**

Acute lymphocytic leukemia (ALL) is the most common hematological malignancy in childhood and accounts for about 20% of acute leukemia in adults **(Liew et al., 2012).**

On the basis of ontogenic classification, ALL is divided into T-lineage ALL and B-lineage ALL. B-lineage ALL is characterized by the expression of the B-cell markers CD19, CD22 and CD79a **(Pui et al., 2008)**.

T-cell acute lymphoblastic leukemia (T-ALL) is a rare, aggressive malignancy of thymocytes and corresponds to a heterogeneous group of leukemia arrested at various stages of lymphoid development. T-ALL constitutes 15% of all childhood ALL and 25% of adult ALL; approximately 30% of patients relapse within the first year of treatment and the outcome is usually death **(Pui et al., 2004-a).**

Leukemogenesis is a multistep process that requires the accumulation of alterations in a hematopoietic progenitor cell at multiple stages. The leukemic stem cell (LSC) hypothesis postulates that leukemia are hierarchically organized and leukemic stem cells have the capacity to self-renew, give rise to more differentiated progeny and maintain the leukemia long-term **(Magee et al., 2012).**

CD86 is a member of B7 family, which consists of cell-surface proteins that regulate costimulatory or coinhibitory signals by binding to their ligands **(Greaves and Gribben, 2013).**

Recognition of CD86 ligand by co-stimulatory CD28 and co-inhibitory CTLA-4 receptors plays an important role in influencing immune responses by proliferation and suppression of effector T cells respectively **(Postow et al., 2015).**

CD86 is expressed on the surface of antigen presenting cells (APCs) as monocytes and dendritic cells (DCs) **(Lim et al., 2012)**. Its expression was found to be associated with many hematological malignancies such as acute myeloid leukemia (AML) and it was reported as a marker of poor prognosis in it **(Barrett and Le Blanc,**

2010). The expression of it in ALL cells is variable but it is mostly associated with poor prognosis in those patients **(Mansour et al., 2014)**.

Some of the most recent therapeutic developments for acute leukemia depend on the involvement of costimulatory pathways and molecules including CD86 **(Couzin-Frankel, 2013).**