Expression of Vascular Endothelial Growth Factor and Its Receptors in Acute Leukemia

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BY

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بسم الله الرحمن الرحيم

قالوا سبحانك
لا علم لنا إلا ما علمتنا
إنك أنت العليم الحكيم

صدق الله العظيم

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قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم

صدق الله العظيم

سورة البقرة الآية ٣٢

Special thanks to
my parents,
all my family, friends
and all those who helped me
in fulfilling this Thesis

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Abstract

Vascular endothelial growth factor (VEGF) is one of the most potent and specific positive regulators involved in angiogenesis. The activity of VEGF is mediated by interaction with high affinity class III receptor tyrosine kinases (RTKs), expressed on most endothelial cells, which are VEGFR-1 (FLT-1), VEGFR-2 (KDR) and VEGFR-3 (FLT-4).

VEGF and its receptors may play a very important role not only in angiogenesis but also in leukemogenesis. Their expression on leukemic cells may elucidate its role as an autocrine promoter of malignant cell proliferation in acute leukemia whether myeloblastic or lymphoblastic and in other hematologic malignancies as they trigger proliferation, survival and migration of malignant hematopoietic cells. Their expression may have clinical relevance and important role as risk and prognostic factors in acute leukemia. They may be useful as predictive test for treatment outcome in acute leukemia patients.

Key Words:

VEGF, FLT-1, KDR, Acute leukemia

Master Sheet of Clinical Data of the Control Group

Case No.	Age (years)	Sex	Clinical history				Clinical examination		
			Fatigue	Bleeding tendency	Fever	Gum hypertrophy	Liver enlargement	Spleen enlargement	Lymph node enlargement
1	22	M	+	-	+	-	+	+	-
2	12	M	+	+	-	-	-	-	-
3	40	F	+	+	-	-	+	+	-
4	35	M	-	-	-	-	+	+	-
5	30	F	+	+	-	-	+	+	-
6	7	M	-	+	-	-	-	-	-
7	8	M	-	+	-	-	-	-	-
8	27	F	-	+	-	-	-	-	-
9	45	M	+	-	-	-	+	+	-
10	5	F	-	+	-	-	-	-	-

M = Male F = Female

+ = Present - = Absent

Master Sheet of Laboratory Data and Diagnosis of the Control Group

Case No.	CBC			Diagnosis
	Hb (g/dl)	TLC ($x10^3$)/cmm	Plts ($x10^3$)/cmm	
1	8.6	2.4	87	Hypersplenism
2	9.5	12.8	6	ITP
3	5.6	14.6	70	Hypersplenism
4	10.4	9	96	Hypersplenism
5	7.9	3.5	75	Hypersplenism
6	10.9	10	15	ITP
7	13.6	7.6	50	ITP
8	11.6	4.9	35	ITP
9	9.2	3.9	80	Hypersplenism
10	11.0	8.2	30	ITP

Master Sheet of VEGF, FLT-1 and KDR Expression of the Control Group

Case No.	VEGF	VEGFR-1 (FLT-1)	VEGFR-2 (KDR)	β-actin
1	Negative	Negative	Negative	Positive
2	Negative	Negative	Negative	Positive
3	Negative	Negative	Negative	Positive
4	Negative	Negative	Negative	Positive
5	Negative	Negative	Negative	Positive
6	Negative	Negative	Negative	Positive
7	Negative	Negative	Negative	Positive
8	Negative	Negative	Negative	Positive
9	Negative	Negative	Negative	Positive
10	Negative	Negative	Negative	Positive

Appendix

List of Abbreviations

Abbreviation	The Full Term
aa	Amino acid
ABL	Abelson strain of murine leukemia virus
AL	Light chain amyloid
ALL	Acute lymphoblastic leukemia
AML	Acute myeloblastic leukemia
AMM	Agnogenic myeloid metaplasia
ANLL	Acute non lymphocytic leukemia
Apaf-1	Apoptotic protease activating factor-1
APL	Acute promyelocytic leukemia
Ara-C	Cytosine arabinoside
Arg	Arginine
Asp	Aspartate
ATL	Adult T cell leukemia/ lymphoma
Bcl-2	B cell lymphoma-2
BCR	Breakpoint cluster region
bFGF	Basic fibroblast growth factor
BM	Bone marrow
BMSCs	Bone marrow stromal cells
bp	Base pair
C-ALL	Common acute lymphoblastic leukemia
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood count
CBFbeta	Core binding factor beta
CD	Cluster of differentiation
CEPs	Circulating endothelial progenitor cells
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CML-BP	Chronic myelogenous leukemia- blastic phase
c-Myc	c-Avian Myelomatosis gene
CNS	Central nervous system
Crk	Cytoplasmic regulated kinase
CSF	Cerebrospinal fluid
Cyto Ig	Cytoplasmic immunoglobulin
del	Deletion
DLB-CL	Diffuse large B cell lymphoma

Abbreviation	The Full Term
DMSO	Dimethysulfoxide
DNA	Deoxyribonucleic acid
dNTPs	Deoxynucleoside triphosphates
DTT	Dithiothreitol
DW	Distilled water (RNase-free water)
ECM	Extracellular matrix
EDTA	Ethylene diamine tetra-acetic acid
EGF	Epidermal growth factor
EGIL	European group for the immunological classification of leukemia
ERK	Extracellular signal regulated kinase
FAB	French-American-British classification
FAK	Focal adhesion kinase
FISH	Fluorescence in situ hybridization
FL	Fas ligand
FLK-1	Fetal liver kinase-1
FLT-1	Fms-like tyrosine kinase-1
G-CSF	Granulocyte colony stimulating factor
Glu	Glutamine
Grb2	Growth factor binding protein 2
GTPase	Guanine triphosphatase
GVHD	Graft-versus-host disease
Hb	Hemoglobin
HCL	Hydrochloric acid
HCPTPA	Human cytoplasmic protein tyrosine phosphatase
HGF	Hepatocyte growth factor
HIF-1	Hypoxia inducible factor-1
His	Histidine
HL	Human leucocyte
HLA	Human leucocyte antigen
HSCs	Hematopoietic stem cells
HSP 90	Heat shock protein 90
HTLV-1	Human T- cell leukemia virus-1
i.t.	Intrathecal
IGF-1	Insulin growth factor-1
IL	Interleukin
Inv	Inversion
ITP	Immune thrombocytopenic purpura
KDa	Kilodalton
KDR	Kinase domain region

Abbreviation	The Full Term
LDH	Lactic dehydrogenase
LN	Lymph node
LPA	Lysophosphatic acid
LPAAT	Lysophosphatidic acid acyltransferase
Lys	Lysine
MAPK	Mitogen activated protein kinase
M-CSF	Macrophage colony stimulating factor
MDR	Multidrug resistance
MDS	Myelodysplastic syndromes
MEK	MAP kinase / EFK Kinase
MFC	Multiparameter flowcytometry
mg	Milligram
$Mgcl_2$	Magnesium chloride
MIC	Morphologic, immunologic and cytogenetic
ml	Milliliter
MLL	Mixed lineage leukemia
MM	Multiple myeloma
mM	Millimole
MMPs	Matrix metalloproteinases
MoAb	Monoclonal antibody
MPD	Myeloproliferative diseases
MRD	Minimal residual disease
mRNA	Messenger ribonucleic acid
MTS	Multiple tumor suppressor
Mtx	Methothrexate
MVD	Microvessel density
MYH11	Smooth muscle myosin heavy chain
NCK	Nucleoplasmin cytoplasmic kinase
$NF_K\beta$	Nuclear factor kappa beta
NHL	Non-Hodgkin's lymphoma
OR	Odds ratio
P53	Protein 53 kilodalton
PB	Peripheral blood
PCR	Polymerase chain reaction
PDGF	Platelet-derived growth factor
PECAM	Platelets endothelial cells adhesion molecules
PI3K	Phosphatidyl inositol 3-kinase
PKC	Protein kinase C
PLC-γ	Phospholipase C-gamma

Abbreviation	The Full Term
PlGF	Placenta growth factor
Plts	Platelets
PML	Promyelocytic leukemia
PTEN	Penta erythritol tetranitrate
PTK	Protein tyrosine kinase
P-value	Probability value
RARalpha	Retinoic acid receptor alpha
Ras	Murine sarcoma virus
Ras GAP	Ras GTPase activating protein
RNA	Ribonucleic acid
rpm	Round per minute
RTKs	Receptor tyrosine kinases
RT-PCR	Reverse transcriptase polymerase chain reaction
SCK	Stress cytoplasmic kinase
SD	Standard deviation
SDF	Stromal cell derived factor
SHP	Src homology phosphatase
SIg	Surface immunoglobulin
STAT	Signal transducer and activator of transcription
SU	Sugen
t	Translocation
TdT	Terminal deoxynucleotidyl transferase
TGF-β	Transforming growth factor-beta
TK	Tyrosine kinase
TLC	Total leucocyte count
TNF	Tumor necrosis factor
µl	Microliter
µM	Micromole
UV-β	Ultraviolet-beta
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHL	Von Hippel-Lindau
VLA	Very late antigen
VPF	Vascular permeability factor
VRAP	VEGFR-associated protein
WBCs	White blood cells
WHO	World Health Organization

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