CIRCULATING ANGIOPOIETIN-2 AS A PROGNOSTIC MARKER IN ACUTE MYELOID LEUKEMIA

Thesis

Submitted for Partial Fulfillment of Master Degree in **Clinical and Chemical Pathology**

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2011

الأنجيوبيوتين 2 فى الدم الطرفى كعامل منذر في سرطان الدم النقوى الحاد

رسالة

توطئه للحصول على درجة الماجستير

في الباثولوجيا الإكلينيكية والكيميائية

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First of all, I would like to express my deep gratitude to GOD *for his care and generosity throughout my life.*

I would like to express my sincere appreciation to ***Prof. Dr. Manal Fawzy Ghozlan****, Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University for her keen supervision and guidance and her overwhelming support that has been of great help throughout this work.*

I am very thankful to ***Prof. Dr. Amal Abdel Hamid Mohamed,*** *Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University for her great support & effort throughout the whole work.*

I would also like to express my great thanks to ***Dr. Deena Mohamed Mohamed Habashy,*** *Lecturer of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University for the great effort she has done in this work and for helping me through it.*

Shereen Abdel Monem

Dedication

To my Husband, *for supporting, understanding and continuous help throughout the whole work.*

To My Mother & Mother in Law, *for their continuous support, understanding and for pushing me forward.*

To The Soul of My Father, *God Bless Him*

I Love You All & Thank You

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List of Abbreviations

Abbrev.	*Full-term*
ADH	Anti diuretic hormone
AKt	Protein kinase B
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AML-NOS	Acute myeloid leukemia not otherwise specified
ANAE	Alpha naphthyl acetate esterase
Ang	Angiopoietin
ANLL	Acute non lymphoblastic leukemia
APL	Acute promyelocytic leukemia
ATRA	All trnasretinoic acid
BAALC	Brain and acute leukemia cytoplsmic gene
BCRP	Breast cancer resistance protein
bFGF	b-Fibroblast growth factor
bFGF	Basic fibroblast growth factor
BM	Bone marrow
BPDCN	Blastic plasmacytic dendritic cell neoplasm
CAE	Chloroacetate esterase
CBF β	Core binding factor β
CD	Cluster of differentiation
CEBPA	CCAAT/enhancer binding protein alpha
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
CN-AML	Cytogenetic normal acute myeloid leukemia

List of Abbreviations (Cont...)

Abbrev.	*Full-term*
CR	Complete remission
CRD 1	First complete remission
DFS	Disease free survival
DNA	Deoxy ribonucleic acid
EC	Endothelial cell
ECM	Extracellular matrix
ELISA	Enzyme linked immunosorbent assay
EM	Electron microscopy
eNOS	Endothelial nitric oxide synthase
ERG	ETS related gene
ERK	Extracellular signal regulted kinase
EV1	Ectopic viral integration
FAB	French-American British
FAK	Focal adhesion kinase
FISH	Fluorescence in situ hybridization
FLT3	Fms like tyrosine kinase 3
FReD	Fibrinogen related domain
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte monocyte colony stimulating factor
GVHD	Graft versus host disease
HCT	Hematopoietic stem cell transplantation
HIDAC	High dose cytarabine
HLA	Human leukocytic antigen

List of Abbreviations (Cont...)

Abbrev.	*Full-term*
HRP	Horse-raddish peroxidase
HSPGs	Heparan sulfate proteoglycans
ICAM	Intracellular adhesion molecule
IGF-1	Insulin like growth factor 1
IHC	Immuno-hitochemistry
IL	Interleukin
ILMA	Immuno-luminometric assay
IPT	Immunophenotyping
IRMA	Immuno-radiometric assay
ISH	In situ hybridization
ITDs	Internal tandem duplications
LDH	Lactate dehydrogenase
LM	Light microscopy
MAPK	Mitogen activated protein kinase
MDS	Myelodysplasia
MLL	Myeloid lymphoid (or) mixed lineage leukemia
MM	Multiple myeloma
MMF	Mycophenolate mofetil
MMP	Matrix metalloproteinase
MN	Meningioma
MPD	Myeloproliferative disease
MPN	Myeloproliferative neoplasms
MPO	Myeloperoxidase

List of Abbreviations (Cont...)

Abbrev.	*Full-term*
MRD	Minimal residual disease
MVD	Microvessel density
NF-κβ	Nuclear factor kappa beta
NPM	Nucleophosmin
NSE	Non specific esterase
OS	Overal survival
PAK	P21 activated kinase
PAS	Periodic acid Schiff
PBSC	Peripheral blood stem cells
PDGF	Platelet derived growth factor
PI3-K	Phosphatidyl-inositol 3V kinase
PKC	Protein kinase C
PTD	Partial tandem duplication
RA	Rheumatoid factor
RARA	Retinoic acid receptor alpha
RFS	Relapse free survival
RNA	Ribonucleic acid
RTK	Receptor tyrosine kinase
RT-PCR	Reverse transcriptase polymerase chain reaction
SBB	Sudan black B
SCT	Stem cell transplantation
SE	Specific esterase
sEng	Soluble endoglin

List of Abbreviations (Cont...)

Abbrev.	*Full-term*
SMC	Smooth muscle cell
STAT	Signal transducers and activators of transcription factor
TdT	Terminal deoxynucleotidyl transferase
Tek	Tunica endothelial kinase
Tie	Tyrosine kinase with immunoglobulin adn epidermal growth factor homology
TIMP	Tissue inhibitor of metalloproteinase
TLS	Tumor lysis syndrome
TNF	Tumor necrosis factor
TRGF	Transforming growth factor
VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
vWF	Von Willebrand factor
WPB	Weibel-Palade bodies
WT1	Wilm's tumor

INTRODUCTION

Acute myelogenous (myeloid) leukemia (AML) is a hematologic malignancy characterized by clonal proliferation of myeloblasts ***(Deschler and Lubbert, 2006).*** It accounts for 15-20% of the acute leukemias in children and 80% of the acute leukemias in adults ***(Menssen et al., 1995).***

Bone marrow (BM) neoangiogenesis plays an important role in AML, and depends on the interplay of members of the vascular endothelial growth factor (VEGF) and angiopoietin (Ang) families ***(Lee et al., 2007).*** Studies comparing the extent of BM neovascularization in normal and neoplastic BM have demonstrated significantly increased angiogenic activity in AML ***(Hussong et al., 2000).*** Angiogenesis can be subverted by tumors to allow for their continued growth and metastasis ***(Folkman, 1995).***

The angiopoietins constitute a family of angiogenic growth factors, which have been shown to be important regulators of angiogenesis and vascular stability ***(Maisonpierre et al., 1997).*** Angiopoietin-2 (Ang-2) is the naturally occurring antagonist to Angiopoietin-1 (Ang-1) and inhibits Ang1-induced activation of Tie-2 receptor ***(Teichert-Kuliszewska et al., 2001).*** Tie-2 is a receptor tyrosine kinase that is expressed on endothelial cells (ECs) and haematopoietic stem cells (HSCs) ***(Jones, 2003).*** Binding of Ang-1 to Tie-2 ensures integrity of blood vessels, while Ang-