EXPRESSION OF ANGIOPOIETIN 1 AND 2 AND THEIR RECEPTOR TIE-2 IN DE NOVO AML PATIENTS: CLINICAL SIGNIFICANCE AND FUTURE PROSPECTS

THEISIS

Submitted for partial fulfillment of the M. D degree in clinical and chemical pathology

BY

Engy Mohammed Abd El Aziz El Khatib

M. B. B. Ch. M. Sc

Supervisors

Prof. Dr./Safaa Mostafa El Karaksy

Professor of Clinical and Chemical Pathology

Faculty of Medicine

Cairo University

Dr./Nancy Mohammed El Guindy

Assistant Professor of Clinical Pathology

Faculty of Medicine

Cairo University

Dr./Heba Mahmoud Gouda

Lecturer of Clinical Pathology

Faculty of Medicine

Cairo University

Dr./Noha Yehia Abdou Ibrahim

Lecturer of Clinical Oncology

Faculty of Medicine

Cairo University

Faculty Of Medicine

Cairo University

2009

التعبير عن انجيوبويتين ١و٢و مستقبلهما تاي ٢ في حالات سرطان الدم الميلودي الحاد حديثة التشخيص: الأهمية الاكلينيكية و التوقعات المستقبلية

رسالة مقدمة من :

الطبيبة/إنجي محمد عبد العزيز الخطيب

توطئة للحصول على درجة الدكتوراه فى الباثولوجيا الاكلينيكية و الكيميائية

تحت إشراف

أ.د/صفاء مصطفى القراقصي
أستاذ الباثولوجيا الاكلينيكية و الكيميائية
كلية الطب - جامعة القاهرة

أ.م/ نانسي محمد الجندي
أستاذ مساعد الباثولوجيا الاكلينيكية
كلية الطب - جامعة القاهرة

د/هبه محمود جوده
مدرس الباثولوجيا الاكلينيكية
كلية الطب - جامعة القاهرة

د/نهى يحيى عبده ابراهيم
مدرس علاج الأورام
كلية الطب - جامعة القاهرة

كلية الطب
جامعة القاهرة
٢٠٠٩

بسم الله الرحمن الرحيم

((و علمك ما لم تكن تعلم و كان فضل الله عليك عظيما))

صدق الله العظيم

النساء (١١٣)

To my great father

To my great mother

To my special husband

To my precious brothers and sister

To my sweet kids

Acknowledgment

First and foremost thanks to Allah the most beneficial and merciful.

I would like to express my deepest gratitude and cordial thanks to Prof. Dr./ Safaa El Karaksy, Professor of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University. I am greatly thankful for her kind guidance, continuous support, precious advice and valuable help.

My sincere appreciation and special thanks are due to Prof. Dr./Nancy El Guindy, Assistant Prof. of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, for her kind supervision, continuous encouragement and generous cooperation.

I feel greatly indebted to Dr./Heba Gouda, Dr./Mervat Khorshed, Dr./Iman Abdel Mohsen, Dr./Reham Emad , Lecturers of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University and Dr./Noha Yehia, Lecturer of Clinical Oncology, Faculty of Medicine, Cairo University, for their close supervision, indispensable direction and for the time they freely gave for guiding me.

Last but not least, I would like to express my sincere thanks to my friends and colleagues for their support and continuous encouragement during preparation of this work.

LIST OF CONTENTS

List of Abbreviations

ABL	: Abelson strain of murine leukemia virus
AKT	: Protein kinase B, a serine /therionine specific enzyme known as AKT.
ALL	: Acute lymphoblastic leukemia.
AMbL	: Acute myeloblastic leukemia
AMgL	: Acute megakaryocytic leukemia
AML	: Acute myeloid leukemia.
AMML	: Acute myelomonocytic leukemia.
AMoL	: Acute monocytic leukemia
ANAE	: Alpha naphthol acetate estrase.
Ang-1	: Angiopoietin 1.
Ang-2	: Angiopoietin 2.
Angs	: Angiopoietins.
ANLL	: Acute non-lymphoblastic leukemia.
APL	: Acute promyelocytic leukemia.
ATRA	: all-transretinoic acid.
BCR	: Break point cluster region
BM	: Bone marrow.
CBF	: Core binding factor.
CBF/A	: Core binding factor alpha subunit.
CBF/β	: Core binding factor beta subunit.
CEPBA	: CCAAT/enhancer binding protein –α.
CML	: Chronic myeloid leukemia .
CMML	: Chronic myelomonocytic leukemia.
CR	: Complete remission.
DFS	: Disease free survival
DIC	: Disseminated intravascular coagulation .
DLL4	: Delta-like ligand 4.
DNA	: Deoxyribonuclic acid.
ECM	: Extracellular matrix.
EGF	: Esinophil growth factor.
EM	: Electron microscope.
ETO	: Eight Twenty one.
FAB	: French American British classification.
FGF	: Fibroblast growth factor.
FISH	: Fluorescence in situ hybridization .

FLT3	: FMS-like tyrosine kinase-3
G-CSF	: Granulocyte colony stimulating factor.
GM-CSF	: Granulocyte-monocyte colony stimulating factor.
HGFs	: Hematopoetic growth factors.
HLA-DR	: Human leucocyte antigen DR locus.
ICAM-1	: Intracellular adhesion molecule-1.
IL	: Interleukin.
LM	: Light microscope.
M-CSF	: Monocyte colony stimulating factor.
MDS	: Myelodysplastic syndrome.
MLL	: Mixed lineage leukemia
MLLT3	: Mixed lineage leukemia translocated to,3
MMP	: Matrix metalloproteinase.
MPD	:Myeloproliferative disorder.
MPO	: Myeloperoxidase.
MRD	: Minimal residual disease.
NEC	: Non-erythroid cell.
NO	: Nitric oxide.
NOS	:Not otherwise specified
NSE	: Non-Specific esterase.
OS	: Overall survival.
PAS	: Periodic acid Schiff.
PB	: Pripheral blood.
PDGF	: Platelet derived growth factor.
PECAM-1	:Periendothelial cell adhesion molecule-1.
PKG	: cGMP-dependent protein kinase.
PML-RARA	: Promyelocytic leukemia-Retinoic acid receptor alpha.
PTD-MLL	: Partial tandem duplication-Mixed lineage leukemia.
Rb	: Retinoblastoma gene.
RT–PCR	: Reverse transcriptase polymerase chain reaction.
SBB	: Sudan black B.
SCF	: Stem cell factor.
SPECT	: Single photon emission computed tomography.
TCR	: T cell receptor.
Tdt	: Terminal deoxy nucleotydyl transferase
TLC	: Total leucocytic count.
UAL	: Undifferentiated acute leukemia.
US	: United states.
VCAM-1	: Vascular cell adhesion molecule-1.
VEGF	: Vascular endothelial growth factor.

WHO	: World Health Organization.
WT-1	: Wilm’s tumor 1 gene.

List of Figures

List of Tables

Abstract

Angiopoietins are a group of the most potent and specific positive regulators involved in angiogenesis. The activity of angiopoietins is mediated by interaction with high affinity receptor tyrosine kinase (RTKs), expressed on most endothelial cells, which is Tie-2 receptor.

Angiopoietins and their receptor may play a very important role not only in angiogenesis but also in leukemogenesis. Their expression on leukemic cells may elucidate their role as autocrine promoters of malignant cell proliferation in acute myeloblastic leukemia 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:

Angiopoietin, Tie2, Acute leukemia

Introduction

Leukemias are complex diseases with a wide range of clinical, morphologic, biologic, cytogenetic, molecular and immunophenotypic features ***(Estey, 2001)***. With this multitude of disease-assoicated variables, it is not surprising that response to treatment differs considerably among patients ***(Bennett, 2000)***.

A major component in the growth and metastasis of solid tumors is angiogenesis which is defined as the formation of new blood vessels. However, angiogenesis has been found to play a role in hematologic malignancies ***(Di Raimondo et al., 2001)***.

The process of angiogenesis is governed by a complex balance of positive and negative regulatory factors. Stimulatory molecules include VEGF, basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), tumor necrosis factor-α, tumor growth factor-β, angiogenin, epidermal growth factor and the angiopoietins ***(Folkman, 1995)***. Of the most potent positive regulatory molecules are Ang-1 and Ang-2, which may act synergistically to stimulate the formation of new blood vessels. Negative regulatory factors include platelet factor-4, thrombospondin-1, tissue inhibitors of metalloproteinases, prolactin, angiostatin, endostatin, bFGF soluble receptor, interferon-α and placental proliferin-related protein. Increased levels of positive regulatory molecules have been correlated with a poor prognosis in patients with solid tumors ***(Ugurel et al., 2001)***. Studies of human hematopoietic cell lines have demonstrated the presence of either Ang-1 mRNA or Ang-2 mRNA, or both in all cell lines examined ***(Bellamy et al., 1999)***.