Angiopoietin-2 as Marker of Angiogenesis And Its Correlation to Prognostic Factors and Treatment Outcome in Patients with Acute Myeloid Leukemia at Presentation and After Induction Chemotherapy

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا
عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ
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Contents

List of Abbreviations

ABC	:	ATP binding cassette
aFGF	:	Acidic fibroblast growth factor
Akt	:	"Ak" in Akt was a temporary classification name for a mouse strain developing spontaneous thymic lymphomas. The "t" stands for 'thymoma'.
ALK	:	Anaplastic leukemia kinase
ALL	:	Acute lymphoblastic leukemia
AlloSCT	:	Allogeneic stem cell transplantation
AML	:	Acute myeloid leukemia
AMLSG	:	German leukemia study group
Ang	:	Angiopoietin
Ang-1	:	Angiopoietin-1
Ang-2	:	Angiopoietin-2
Ang-3	:	Angiopoietin-3
Ang-4	:	Angiopoietin-4
APL	:	Acute promyelocytic leukemia
ASCO	:	American Society of Clinical Oncology
ATP	:	Adenosine triphosphate
ATRA	:	All trans retinoic acid
AutoSCT	:	Autologous stem cell transplantation
BAALC gene		: Brain, and acute leukemia, cytoplasmic gene
BAX	:	Bcl-2 associated X protein
Bcl	:	B cell leukemia/lymphoma
bFGF	:	Basic fibroblast growth factor
BM	:	Bone marrow
BMT	:	Bone marrow Transplantation
BUN	:	Blood urea nitrogen
CBF	:	Core binding factor
CCAAR	:	Cytidine-Cytidine-Adenosine-Adenosine-Thymidine enhancer binding
CCD	:	Central coiled coil domain
CD	:	Cluster designation

List of Abbreviations (Cont.)

CEC	:	Circulating endothelial cells
CGH	:	Array-comparative genomic hybridization
CI	:	Confidence interval
c-KIT	:	Steal factor
CLL	:	Chronic lymphocytic leukemia
CML	:	Chronic myeloid leukemia
CMML	:	Chronic myelomonocytic leukemia
CMV	:	Cytomegalovirus
CNS	:	Central nervous system
CR	:	Complete remission
CRp	:	Partial complete remission
CSF	:	Colony stimulating factor
CTL	:	Cytotoxic T lymphocytes
Del	:	Deletion
DFS	:	Disease free survival
DIC	:	Disseminated intravascular coagulopathy
DLBCL	:	Diffuse large B cell lymphoma
DNA	:	Deoxynucleic acid
DNMTS	:	DNA methyltransferases
E2f	:	Transcription factor
EBF	:	Enhancer binding protein
ECM	:	Extracellular matrix
ECOG	:	Eastern Cooperative Oncology Group
ECs	:	Endothelial cells
EGF	:	Epidermal growth factor
EPO	:	Erythropoietin
Erk1	:	Extracellular regulated kinases
ETO	:	Eight twenty one
EVI-1	:	Ecotropic virus integration site 1
FAB	:	French American British
FC	:	Flow cytometry
FDA	:	Food and Drug Administration
FISH	:	Fluorescence in situ hybridization

List of Abbreviations (Cont.)

FLT3	:	FMS like tyrosine kinase
FN III	:	Fibronectin type III -domains
FreD	:	Fibrinogen-related domain
FTI	:	Farnesyltransferase Inhibitors
G-CSF	:	Granulocyte colony stimulating factor
GM-CSF	:	Granulocyte macrophage colony stimulating factor
GO	:	Gemtuzumab ozogamicin
GVHD	:	Graft versus host disease
GVL	:	Graft versus leukemia
HDAC	:	High dose cytarabine
HGF	:	Hepatocyte growth factor
HGFs	:	Hematopoietic growth factors
HIF	:	Hypoxia-inducible factor
HLA	:	Human leukocyte antigen
HSC	:	Hematopoietic stem cells
HSV-1	:	Herpes simplex virus-1
HTLV-1	:	Human T-cell leukemia virus type 1
IAP	:	Inhibitors of apoptosis
IGF	:	Insulin like growth factor
IHC	:	Immunohistochemistry
Inv	:	Inversion
IRF-1	:	Interferon regulatory factor-1
ITD	:	Internal tandem duplications
IV	:	Intravenous route
kD	:	Kilodaltons
LDH	:	Lactate dehydrogenase
LLC	:	Lewis Lung carcinoma
LRP	:	Lung resistance protein
MAPK	:	Mitogen-activated protein kinase
Mdr-1	:	Multidrug resistance-1
MDS	:	Myelodysplastic syndrome
MF	:	Myelofirbrosis

List of Abbreviations (Cont.)

MLL	:	Mixed lineage leukemia
MM	:	Multiple myeloma
MMP	:	Matrix Metalloproteinase
MPN	:	Myeloproliferative neoplasms
MPO	:	Myeloperoxidase
MRD	:	Minimal residual disease
MRI	:	Magnetic resonance imaging
MTD	:	Maximum tolerated dose
mTOR	:	Mammallian target of rapamycin
MVD	:	Micro vascular density
NCI	:	National Cancer Institute
NK	:	Natural killer cells
NOS	:	Not otherwise specified
NPM-1	:	Nucleophosmin-1
NSE	:	Non specific esterase
OR	:	Overall survival
PCR	:	Polymerase chain reaction
PDEGF	:	Platelet-derived epidermal Growth Factor
PDGF	:	Platelet-derived Growth Factor
PGF	:	Placental growth factor
P-gp	:	P glycoprotein
PI3K	:	Phosphoinositide 3-kinase
PKC	:	Protein kinase C
PLCgγ	:	Phospholipase Cγ
PMA	:	Phorbol 12-myristate-13-acetate
PML	:	Promyelocytic leukemia
PT	:	Prothrombin time
PTEN gene	:	Phosphatase tension gene
PTT	:	Partial thromboplastin time
RAEB	:	Refractory anemia with excess blast
RAEB-T	:	Refractory anemia with excess blast in transformation
RARa	:	Retinoic acid receptor alpha

List of Abbreviations (Cont.)

Ras	:	Rat sarcoma
RAS	:	Retinoic acid syndrome
Rb	:	Retinoblastoma
RIC	:	Reduced intensity chemotherapy
RPTE	:	Proximal tubule epithelial cells
RQ-PCR	:	Real time polymerase chain reaction
RTKs	:	Receptor tyrosine kinases
SCD	:	Super clustering domain
SCT	:	Stem cell transplantation
SDArac	:	Standard dose cytarabine
SDF-1	:	Stromal cell derived factor-1
SEER	:	Surveillance, Epidemiology and End Results
SMCs	:	Smooth muscle cells
SNP	:	Single Nucleotide Polymorphism
STAT3	:	Signal transducer and activator of transcription 3
SWOG	:	Southwest Oncology Group
t	:	translocation
TdT	:	Terminal deoxynucleotidyl transferase
TGF- β	:	Transforming growth factor-beta
TIMPS	:	Tissue inhibitors of metalloproteinase
TKI	:	Tyrosine kinase inhibitors
TSGs	:	Tumor suppressor genes
TST	:	Time sequential therapy
UPAs	:	Urokinase plasminogen activator system
VCAM-1	:	Vascular cell adhesion molecule 1
VE	:	Vascular endothelial
VEGF	:	Vascular Endothelial Growth Factor
VHL	:	Von Hippel Lindau
WHO	:	World Health Organization
WT1	:	Wilm’s tumor-1
WTA	:	Wilm’s tumor antigen

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Introduction

Leukemia is one of the most common and worldwide malignant disease. Chemotherapy for leukemia frequently causes resistance and side effects to patients. Therefore, development of effective therapeutic treatment agents for leukemia is an important and urgent topic **(Chen et al.,2009)**

Leukemias make up to ~2% of adult cancers but comprise a heterogeneous group of diseases **(Chee, 2007).** Acute myeloid leukemia (AML) is a malignancy of the myeloid elements, the hallmark being a block in normal differentiation and/or uncontrolled growth and lack of differentiation of any one of the hematopoietic progenitors cells **Byrd et al.,(2008)**, leading to the massive accumulation of immature leukemic "blast cells" which usually results in rapid and severe disruption of normal bone marrow function **(Chee, 2007)**

Acute myeloid leukemia (AML) is the most common acute leukemia affecting adults, and its incidence increases with age. Senior patients with AML usually have poor performance status and chemotherapeutic tolerance **(Roboz, 2007).**

Acute myeloid leukemia (AML) is predominantly a disease of the elderly as more than half of the patients with this malignancy are over 60 years old. In older patients, the benefit associated with standard intensive chemotherapy remains debated because of excessive toxicity and short duration of response **(Malfuson et al., 2008)**

The most important clinical progress to date in acute myeloid leukemia (AML) has been largely focused in two major areas. One is the area of treatment modality; specifically, the more widespread use of allogeneic stem cell transplantation. The other area of progress has, occurred in the