

RECENT PROGNOSTIC PARAMETERS IN ACUTE MYELOID LEUKEMIA AND THEIR RELATION TO CLINICAL OUTCOME

Essay

*Submitted for partial fulfillment of M.Sc. Degree
In **Clinical and Chemical Pathology***

Presented by

Botheina Ahmed Thabet Farweez

M.B., B. Ch., Ain Shams University

Supervised by

Prof. Dr. Salwa Mohamed Abu-El-Hana
Professor of Clinical and Chemical Pathology
Faculty of Medicine – Ain Shams University

Dr. Iman Mohamed Amin Omar
Assistant Professor of Clinical and Chemical Pathology
Faculty of Medicine – Ain Shams University

Dr. Manal A. Shams El-Din Eltelbany
Assistant Professor of Clinical and Chemical Pathology
Faculty of Medicine – Ain Shams University

**Faculty of Medicine
Ain Shams University
2005**

RECENT PROGNOSTIC PARAMETERS IN ACUTE MYELOID LEUKEMIA AND THEIR RELATION TO CLINICAL OUTCOME

Essay

*Submitted for partial fulfillment of M.Sc. Degree
In Clinical and Chemical Pathology*

Presented by

Botheina Ahmed Thabet Farweez

M.B., B. Ch., Ain Shams University

Supervised by

Professor Doctor/ Salwa Mohamed Abu-El-Hana
Professor of Clinical and Chemical Pathology
Faculty of Medicine – Ain Shams University

Professor Doctor/ Iman Mohamed Amin Omar
Professor of Clinical and Chemical Pathology
Faculty of Medicine – Ain Shams University

Doctor / Manal A. Shams El-Din Eltelbany
Assistant Professor of Clinical and Chemical Pathology
Faculty of Medicine – Ain Shams University

**Faculty of Medicine
Ain Shams University
2005**

Acknowledgment

*First of all, thanks to **Allah** the most merciful for guiding me through and giving me the strength to complete this work the way it is.*

*It is a pleasure to express my deepest thanks and profound respect to my honored professor, **Professor Doctor/ Salwa Mohamed Abu-El-Hana**, Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University, for her continuous encouragement and valuable supervision and guidance throughout this work. It has been an honour and a privilege to work under her generous supervision.*

*Also, I wish to express my deep gratitude to **Professor Doctor/ Iman Mohamed Amin Omar**, Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University, for her kind support, help and careful supervision.*

*I am also deeply grateful and would like to express my sincere thanks and gratitude to **Doctor/ Manal A. Shams El-Din Eltelbany**, Assistant Professor of Clinical and Chemical Pathology, Faculty of medicine, Ain Shams University, for her great help and support and her continuous guidance, correction and explanation. I wish to be able one day to return to her a part of what she had offered to me.*

*I also wish to extend my thanks to **Professor Doctor/ Ahmed Bastway**, Professor of Pharmacology, Faculty of Medicine, Ain Shams University, for his help in the presentation and support throughout this work.*

No words could adequately express my deep appreciation to my family, especially my father for his continuous support and guidance. I shall remain indebted to them all my life.

Botheina Ahmed Thabet Farweez

CONTENTS

Page

List of Abbreviations	
List of Tables	
List of Figures	
Introduction and Aim of the Study	1
Acute myeloid leukemia	3
* Aetiology	4
* Leukemogenesis	5
* Classification of AML	9
* Diagnosis	22
* Classic prognostic criteria in AML	34
* Therapy	41
* Minimal residual disease	48
Cytogenetics and molecular genetics in AML	51
* Cytogenetics	51
* Molecular genetics	58
* Molecular and cytogenetic approach to AML	59
* Chromosomal abnormalities restricted to AML	64
* Chromosomal abnormalities characteristic of AML but seen in other myeloid disorders	73
* Techniques for diagnosis of cytogenetic and molecular abnormalities in AML	77
Recent prognostic criteria in AML	79
* Cell cycle	79
* Apoptosis	90
* Cytokines and cytokine receptors	102
* Adhesion molecules	109
* Signal transduction and transcription factors	111
* Angiogenesis	116

CONTENTS (Cont.)

	<i>Page</i>
* Marrow matrix metalloproteinase	119
* Drug resistance	121
* Other prognostic factors	125
- Wilm's tumor gene	125
- Neurofibromatosis 1 protein	126
- Telomerase	127
- Proliferative abilities in vitro	128
- Serum nm 23 H1 protein	129
- Deleted colorectal carcinoma gene	130
- Percentage of myeloperoxidase positive blasts	130
- Complete remission duration	130
Summary and Conclusion	131
References	133
Arabic Summary	--

Special Dedication To :

My Mum

My Father

My Lovely Sister Yousra

My Brother Mohammed

My Be loving Husband Mostafa

List of Abbreviations

-5	: Monosomy 5
-7	: Monosomy 7
AIDS	: Acquired immune deficiency syndrome
AKT	: Protein kinase B, a serine / threonine specific enzyme known as AKT
AL	: Acute leukemia
ALL	: Acute lymphoblastic leukemia
AML	: Acute myeloid leukemia
Ang	: Angiopoietin
ANLL	: Acute non-lymphoblastic leukemia
AP	: Acid phosphatase
Apaf-1	: Apoptotic protease activating factor
APL	: Acute promyelocytic leukemia
ARF	: Alternate reading frame
As ₂ O ₃	: Arsenic trioxide
ATP	: Adenosine tri-phosphate
ATRA	: All trans retinoic acid
BAALC	: Brain and acute leukemia cytoplasmic gene
BAX	: Bcl-2 associated protein
Bcl-2	: B-cell lymphoma/leukemia-2 oncogene
BCR	: Break point cluster region
b-FGF	: basic fibroblast growth factor
BMMC's	: Bone marrow mononuclear cells
BMT	: Bone marrow transplantation
BRCP	: Breast cancer resistance protein
CAE	: Chloroacetate esterase
CAK	: CDK-activating kinase complex
CBC	: Complete blood count
CBF	: Core binding factor
CBF α	: Core binding factor alpha subunit
CBF β	: Core binding factor beta subunit
CBP	: Core binding protein
CD	: Cluster of differentiation

List of Abbreviations (Cont.)

CDK	: Cyclin dependent kinase
CDKI	: Cyclin dependent kinase inhibitor
cDNAs	: Complementary DNAs
CEBP α	: CAAT enhancer binding protein alpha
CGH	: Comparative genomic hybridization
CML	: Chronic myeloid leukemia
C-myc	: Cellular myelocytoma
CNS	: Central nervous system
CR	: Complete remission
CRD	: Complete remission duration
CREB	: C-AMP response element binding protein CBP
CRR	: Complete remission rate
CSF	: Colony stimulating factor
CSFs	: Colony stimulating factors
CXCR-4	: Chemokine receptor-4
DCC	: Deleted colorectal carcinoma gene
del	: deletion
DFS	: Disease free survival
der	: derivative
DIC	: Disseminated intravascular coagulopathy
DNA	: Deoxyribonucleic acid
Dup	: Duplication
EFS	: Event free survival
EGF	: Epidermal growth factor
EM	: Electron microscope
EMD	: Erythroblastic and/or megakaryocytic dysplasia
ETO	: Eight twenty one
EVI1	: Ectropic virus integration I gene
FA	: Fanconi anemia
FAB	: French-American British
FADD	: Fas-associated death domain
FAK	: Focal adhesion kinase

List of Abbreviations (Cont.)

Fas L	: Fas-ligand
FISH	: Fluorescence in-situ hybridization
FLT ₃	: Fms-like tyrosine kinase 3 receptor
FLT ₃ -L	: Fms-like tyrosine kinase 3 ligand
FS	: Free survival
G0	: Gap phase zero
G1	: Gap phase one
G2	: Gap phase two
G-CSF	: Granulocyte-monocyte colony stimulating factor
GIT	: Gastrointestinal tract
GST	: Glutathione-S-transferase
GSTM	: Glutathione-S-transferase of mu class
GSTT	: Glutathione-S-transferase of theta class
Hb	: Hemoglobin
HDM-2	: Human homologue of the mouse MDM-2 protein
HIDAC	: High dose Ara-c
HLA	: Human leucocyte antigen
HSVtK	: Herpes simplex virus thymidine kinase gene
IAPs	: Inhibitors of apoptosis proteins
IL1 β	: Interleukin 1 beta
IL-3	: Interleukin-3
IL6	: Interleukin-6
ILS	: Interleukins
INK4	: Inhibitors of cyclin dependent kinase 4
INF	: Interferon
Inv	: Inversion
ITD	: Internal tandem duplication
JM	: Juxtamembrane
kDa	: Kilodalton
LDH	: Lactate dehydrogenase
LM	: Light microscope
LN	: Lymph node

List of Abbreviations (Cont.)

LRP	: Lung resistance protein
M-CSF	: Macrophage-colony stimulating factor
MDR	: Multi drug resistance
MDR-1 gene	: Multi drug resistant gene
MDS	: Myelodysplastic syndrome
M-FISH	: Multi-colour FISH
MIC	: Morphologic-immunologic-cytogenetic
MLL	: Mixed lineage leukemia gene
MMPS	: Marrow matrix metalloproteinases
MoAb's	: Monoclonal antibodies
MPD	: Myeloproliferative disorder
MPF	: M-phase promoting factor
M-phase	: Mitotic phase
MPO	: Myeloperoxidase
MRD	: Minimal residual disease
m-RNA	: Messenger RNA
MRP	: Multiple drug resistance related protein
MVP	: Major vault protein
MYHII	: Smooth muscle myosin heavy chain
NFI	: Neurofibromatosis I
NK	: Natural killer cell
NSE	: Non specific esterase
OS	: Overall survival
P	: Short arm of the chromosome
p21	: Protein 21 kDa
p53	: Protein 53 kDa
PAS	: Periodic acid schiff
PBSC	: Peripheral blood stem cell
PCR	: Polymerase chain reaction
PDGF	: Platelet derived growth factor
P-gp	: P-glycoprotein
PLC γ	: Phospholipase C γ

List of Abbreviations (Cont.)

PLZF	: Promyelocytic leukemia zinc finger
PML	: Promyelocytic leukemia
PRb	: Phosphorylated retinoblastoma
PRINS	: Primed in-situ hybridization
PTD	: Partial tandem duplication
q	: Long arm of the chromosome
RARA	: Retinoic acid receptor alpha
RAS-GAP	: RAS GTPase-activating protein
Rb	: Retinoblastoma
RIA	: Radioimmunoassay
RNA	: Ribonucleic acid
RQ-PCR	: Real time PCR
RTKs	: Receptor tyrosine kinases
RT-PCR	: Reverse transcriptase-polymerase chain reaction
S-phase	: Synthetic phase
SBB	: Sudan black-B
SCF	: Stem cell factor
sE	: Soluble E-selectin
SHGF	: Soluble hepatocyte growth factor
SKY	: Spectral karyotyping
sL	: Soluble L-selectin
sNRP1	: Soluble neuropilin 1
SOCS	: Suppressors of cytokines signaling
SOS	: Son of sevenless guanine nucleotide exchange factor
STAT	: Signal transducer and activator of transcription proteins
t	: Translocation
TA	: Telomerase activity
TdT	: Terminal deoxynucleotide transferase
TGF- β	: Transforming growth factor-beta
TIMPS	: Tissue inhibitors of metalloproteinases

List of Abbreviations (Cont.)

TLC	: Total leucocytic count
TNF	: Tumor necrosis factor
TSG	: Tumor suppressor gene
VEGF	: Vascular endothelial growth factor
VEGFR	: Vascular endothelial growth factor receptors
WAF	: Wild type p53 activated fragment 1
WBC's	: White blood cells
WHO	: World Health Organization
Wt-1	: Wilim's tumor 1 gene

List of Figures

<i>Figure</i>	<i>Subject</i>	<i>Page</i>
(1)	Branching network of genes involved in chromosome translocations.	6
(2)	Flow chart showing how individual patients are categorized in the WHO classification.	15
(3)	Phases of therapy.	42
(4)	Standard regimen for treatment of newly diagnosed AML.	43
(5)	Deletion of the chromosome may be interstitial or terminal.	56
(6)	Inversion of the chromosome may be paracentric or pericentric.	57
(7)	A diagrammatic representation of t(8;21) (q21;q22) abnormality.	65
(8)	A diagrammatic representation of the t(15;17) (q22;q21) abnormality.	67
(9)	A diagrammatic representation of inv(16) (p13q22).	69
(10)	A diagrammatic representation of t(8;16) (p11;p13).	72
(11)	A diagrammatic representation of t(6,9) (q23;q34).	75
(12)	Life cycle of a somatic cell.	80
(13)	Phases of mitosis.	81
(14)	Cell cycle control systems.	82
(15)	The interactions between the cyclins, CDKs and CDKIs during the cell cycle.	83
(16)	Specific cyclins are synthesized and degraded at specific stages of the cell cycle.	85
(17)	CDKI proteins.	87
(18)	The INK4A/ARF locus.	89
(19)	Pathways of apoptosis.	91

List of Figures (Cont.)

<i>Figure</i>	<i>Subject</i>	<i>Page</i>
(20)	Induction of p53-dependent cell cycle arrest and apoptosis following DNA damage.	95
(21)	Activation of multiple signal transduction pathways consequent to tyrosine phosphorylation of growth factor receptors.	112
(22)	Activation of the p21 ^{RAS} initiated signaling cascade following tyrosine phosphorylation of growth factor receptors.	113
(23)	Model of regulation of specific gene expression by a transcription factor.	115

List of Tables

<i>Table</i>	<i>Subject</i>	<i>Page</i>
(1)	Conditions predisposing to the development of acute myelogenous leukemia.	4
(2)	Most common frequent genetic abnormalities in AML and related oncogenes.	7
(3)	Morphologic (FAB) classification of AML.	11
(4)	MIC classification of AML.	12
(5)	The WHO classification of AML.	13
(6)	The WHO classification–AML not otherwise categorized.	14
(7)	Characteristics of AML associated with rearrangement of the RARA gene.	17
(8)	Translocations and deletions involving 11q23	18
(9)	Score for biphenotypic acute leukemia.	21
(10)	Signs and symptoms at presentation in AML.	23
(11)	Cytochemical stains used for diagnosis of AML.	27
(12)	Panel of monoclonal antibodies identifying antigens expressed mainly in myeloid cells.	28
(13)	Pattern of reactivity with monoclonal or polyclonal antibodies commonly observed in FAB categories of AML.	30
(14)	Associations between specific chromosome aberrations and FAB subtypes of AML.	32
(15)	Prognostic factors in acute myeloid leukemia.	35
(16)	Methods for the detection of MRD in AML.	50
(17)	Numerical abnormalities in AML.	54
(18)	Structural chromosomal abnormalities in AML.	55
(19)	Molecular markers additional to cytogenetics with independent prognostic significance for remission duration or survival in AML.	59