

127, 17 27, 17 (20) 77, 17 (20









جامعة عين شمس

التوثيق الالكتروني والميكروفيلم



نقسم بللله العظيم أن المادة التي تم توثيقها وتسجيلها علي هذه الأفلام قد اعدت دون آية تغيرات



يجب أن

تحفظ هذه الأفلام بعيداً عن الغبار

في درجة حرارة من 15-20 مئوية ورطوبة نسبية من 20-40 %

To be kept away from dust in dry cool place of 15 – 25c and relative humidity 20-40 %



ثبكة المعلومات الجامعية





Information Netw. " Shams Children Sha شبكة المعلومات الجامعية @ ASUNET بالرسالة صفحات لم ترد بالأص

The Study of Cytochrome C Release in Response to Specific COX-2 Inhibitors in Patients with B-Cell Chronic Lymphocytic Leukemia. (B-CLL)

THESIS

Submitted to The Faculty of Medicine in partial fulfillment of the requirements for the Degree of Master of Hematology

By

Noha Mohamed Al-Sharkawy

 $\mathcal{M}.\mathcal{B}.\mathcal{B}.\mathcal{C}h.$

Resident in Hematology Unit
Internal Medicine Department

Faculty of Medicine Alexandria University 2005

Bonny

SUPERVISORS

Prof. Dr. Nabil Ahmed El-Halawani

Professor of Internal Medicine,
Hematology and Oncology
Faculty of Medicine,
Alexandria University

ميل لحدا للوارك

Prof. Dr. Zeinab Mourad

Professor of Clinical Pathology
Faculty of Medicine,
Alexandria University

No.

Coworker

Dr. Amany Sorour

Tecturer of Clinical Pathology,
Faculty of Medicine,
Alexandria University

الأخريس

Supervisor

Dr. Nadia El-Sayed Zaki

Assistant Professor of Internal Medicine
Hematology Unit
Faculty of Medicine,
Alexandria University

د/نوسر

ACKNOWIEDGMENT

t

First and above of all my greatest thanks to mighty Allah the most gracious for helping us all to complete this work

My sincere thanks and appreciation to Prof. Dr. Nabil Ahmed El Halawani, Professor of Internal Medicine, Hematology and Oncology, Faculty of Medicine, University of Alexandria for suggesting and planning the present study, for the valuable advice, and for the time and generous effert he devoted in closely supervising and revising the work.

My deepest thanks and gratitude to Prof. Dr. Zeinab Mourad, Professor of Clinical Pathology, Faculty of Medicine, University of Alexandria, for her kind help and support throughout the work.

I am also deeply indebted to Dr. Nadia El Sayed Zaki, Assistant Professor of Internal Medicine, Hematology Unit, Faculty of Medicine. University of Alexandria, for her meticulous guidance and for the great support and encouragement she has offered all through the work.

I would also like to express my heartful thanks to Dr. Amany Sourour. Tecturer of Clinical Pathology, Faculty of Medicine, University of Alexandria, for her kind help and sincere advice.

My deepest gratitude and appreciation to my family for their continuous support.

And last but certainly not the least my deepest thanks to my husband for his encouragement and patience.

LIST OF ABBREVIATIONS

ALC : Absolute lymphocytic count.

ALT : Alanine amino transferase.

Apaf-1 : Apoptotic protease activating factor-1

AST : Aspartate amino transferase.

ATM : Ataxia telangectasia mutated gene.

ATP : Adenosine triphosphate.

B-CLL: B-cell chronic lymphocytic leukemia.

BCR : B cell receptor.

BM : Bone marrow

BMT : Bone marrow transplantation.

β₂MG : Beta-2 microglobulin.

CARD : Caspase activation and recruitment domain.

CBC : Complete blood count.

CD : Cluster designation.

2-CDA : 2-chlorodeoxyadenosine.

Ced : Caenorhebditis elegans death gene.

CHOP : Cyclophosphamide adriamycin, vincristine, prednisolone.

CLL: Chronic lymphocytic leukemia.

COP : Cyclophosphamide, vincristine, prednisolone.

COX: Cyclooxygenase.

CR : Complete remission.

CVP : Cyclophosphamide, vincristine, prednisolone.

DD : Death domain.

DED : Death effector domain.

DNA : Deoxyribonucleic acid.

DR : Death receptor.

FADD: Fas associated death domain.

FCR : Fludarabine, cyclophosphamide, rituximab.

FGF: Fibroblast growth factor.

FISH: Fluorescence insitu hybridization.

GMCSF : Granulocyte macrophage colony stimulating factor.

Hb : Hemoglobin.

HCL: Hairy cell leukemia.

HLA: Human leucocyte antigen.

HOX: Hydroperoxidase.

IAP : Inhibitor of apoptosis proteins.

Ig : Immunoglobulin.

IgV : Immunoglobulin variable region.

IL: Interleukin.

IV : Intravenous.

KD : Kilodatlon.

L : Ligand.

LDH : Lactate dehydrogenase.

LDT : Lymphocyte doubling time.

MCL : Mantle cell lymphoma.

MRD : Minimal residual disease.

MZ : Mantle zone.

NCI : National Cancer Institute.

NF-κB : Nuclear factor kappa B.

NK: Natural killer.

PBS : Phosphate buffered saline.

PCD : Programmed cell death.

PDGF : Platelet derived growth factor.

PFS: Progression free survival.

PG: Prostaglandin.

PLL: Prolymphocytic leukemia.

PO : Per os (by mouth).

RT : Room temperature.

RT-PCR: Reverse transcriptase polymerase chain reaction.

SCT : Stem cell transplantation.

SLL : Small lymphoicytic lymph.

SMAC: Second mitochrondria derived activator of caspase.

TGF- β : Transforming growth factor-beta.

TK: Thymidine kinase.

TLC: Total leukocytic count.

TNF: Tumor necrosis factor:

TNFR: Tumor necrosis factor receptor

TRAIL: TNF-related apoptosis inducing ligand.

TRADD: TNF receptor associated death domain.

TRAF : TNFR-associated factor.

VHIg : Heavy chain genes.

WBC : White blood cells.

ZAP-70 : Zeta associated protein-70.

LIST OF TABLES

<u>Table</u>	<u>Title</u>	
I	A comparison of historical and current views of CLL	2
II	Complications and disorders associated with CLL.	12
III	Molecular, phenotypic and clinical characteristics of the IgV gene defined B-CLL subgroups.	15
IV	Differential diagnosis of CLL.	18
V	Treatment modalities in B-CLL.	21
VI	Clinical data of patients in group I.	60
VII	Clinical data of patients in group II.	61
VIII	Comparison between the two studied groups as regards age and sex.	62
IX	Comparison between the two studied groups as regards the clinical picture before treatment.	64
X	Comparison between the two studied groups as regards the Rai staging.	66
XI	Hematological data of patients in group I.	.68
XII	Hematological data of patients in group II.	-69
XIII	Comparison between the hematological parameters before and after treatment in group I.	70
XIV	Comparison between the hematological parameters before and after treatment in group II.	71
XV	Comparison between both groups as regards the hematological parameters before treatment.	72
XVI	Comparison between both groups as regards the hematological parameters after treatment.	73

XVII	Comparison between the two studied groups as regards bone marrow infiltration.	78
XVIII	LDH level in patients of both groups.	79 -
XIX	Comparison between serum LDH before and after treatment in group I.	80
XX	Comparison between serum LDH before and after treatment in group II.	82
XXI	Comparison between both groups as regards LDH before treatment.	84
XXII	Cytochrome c level in patients of both groups.	86
XXIII	Comparison between cytochrome c percentage before and after treatment in group I.	87
XXIV	Comparison between cytochrome c percentage before and after treatment in group II.	89
XXV	Comparison between both groups as regards cytochrome c percentage before treatment.	91

•

1

LIST OF FIGURES

<u>Figur</u>	<u>Title</u>	<u>Page</u>
1	A comparison of pathways of B-cell maturation according to T-cell dependency.	5
2	The promoting role of antigen stimulation and accessory signals from the microenvironment in CLL	9
3	An approach to the initial management of patients with symptomatic CLL.	25
4	The intrinsic pathway of apoptosis.	33
5	Role of mitochondria in apoptosis.	35
6	TNF receptor signaling.	39
7	Production and action of prostaglandins and thromboxane.	45
8	Comparison between the two studied groups as regards age.	63
9	Comparison between the two studied groups as regards sex.	63
10	Comparison between the two studied groups as regards the clinical picture before treatment.	65
11	Comparison between the two studied groups as regards the Rai staging.	67
	Comparison between hemoglobin concentration before and after treatment in both groups.	74

	13	Comparison between changes in TLC before and after treatment in both groups.	75
	14	Comparison between changes in ALC before and after treatment in both groups.	76
·	15	Comparison between the platelet count before and after treatment in both groups.	77
	16	Comparison between the two studied groups as regards the BM infiltration.	78
J.	17	Comparison between serum LDH before and after treatment in group I.	81
	18	Comparison between serum LDH before and after treatment in group II.	83
	19	Comparison between both groups as regards LDH before treatment.	85
	20	Comparison between cytochrome c percentage before and after treatment in group I.	88
	21	Comparison between cytochrome c percentage before and after treatment in group II.	90
	22	Comparison between both groups as regards cytochrome c percentage before treatment.	92