Significance of cyclin D١ overexpression in patients with Non-Hodgkin's lymphoma.

Thesis

Submitted for partial fulfillment of Masters Degree in Internal Medicine

Presented by

Sameh Refat Gaballa

M.B.B.CH

Supervised by

Professor Doctor Mohamed Osman Azzazi

Professor of Internal Medicine
Faculty of Medicine- Ain Shams University

Professor Doctor Maha El-Zimaity

Professor of Internal Medicine
Faculty of Medicine- Ain Shams University

Doctor Mohammed Mahmoud Moussa

Lecturer of internal medicine
Faculty of Medicine- Ain Shams University

Faculty of Medicine
Ain Shams University
٢٠٠٦

بسم الله الرحمن الرحيم

﴿ قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ ﴾

صدق الله العظيم

سورة البقرة / الآية {٣٢}

I dedicate this Thesis to my loving and supportive family to them I owe everything

List of Abbreviations:

ATM: Ataxia telengectasia mutated gene

AR: androgen receptor

AL: light chain amyloidosis

BL: Burkitt's lymphoma

CKIs: Cyclin kinase inhibitors

CDKs: Cyclin dependent kinases

CAK: CDK-activating kinase

C/EBP: CCAAT/enhancer binding protein

CT: computerized tomography

CLL: chronic lymphocytic leukemia

CD: cluster of differentiation.

CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)

DLBCL: Diffuse large B cell lymphoma

ECM: Extracellular matrix

ER: estrogen receptor

FL: Follicular lymphoma

HL: Hodgkin's lymphoma

HRS: Hodgkin/ReedSternberg cell

HCL: Hairy cell leukemia

HCV: Hepatitis C virus

IPI: International prognostic index

ICAM: Intercellular adhesion molecule

IL-٦: Interleukin-٦

INK٤A: Inhibitor of cyclin-dependent kinase ٤

IGF: insulin like growth factor

JAK: Janus Associated Kinase

JH: Immunoglobulin heavy chain joining region

LPL: Lymphoplasmacytic Lymphoma

MALT: Mucosa associated lymphoid tissue

MCL: Mantle Cell Lymphoma

MM: Multiple Myeloma

MGUS: monoclonal gammopathy of undetermined significance

NHL: Non Hodgkin’s lymphoma.

PCNA: proliferating cell nuclear antigen

P/CAF: p٣٠٠/CBP-associated factor

PPAR: peroxisome proliferator-activated receptor

pRB: RB protein

PLL: Prolymphocytic leukemia

RT-PCR: reverse transcriptase–polymerase chain reaction

REAL classification: Revised European-American Lymphoid classification

S L L : S mall l y m p h o c y t i c l y m p h o m a

SLL: small lymphocytic lymphoma

SMZL: Splenic marginal zone lymphoma

STAT: Signal transducer and activator of transcription

TdT: terminal deoxynucleotidyl transferase.

TNF-alpha: Tumor necrosis factor-alpha.

TNF: tumor necrosis factor

VEGF: Vascular endothelial growth factor

TSGs: tumor suppressor genes

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Acknowledgment

Thanks first and last to God as we owe him for His great care, support and guidance in every step in our life.

I would like to express my thanks and gratitude **to Professor Doctor Mohamed Osman Azzazi**, *Professor of Internal Medicine, Clinical Hematology Oncology unit, Faculty of Medicine, Ain Shams University*, for his kind supervision and continuous guidance and indispensable advice all through my work.

I am deeply grateful to the **Professor Doctor Maha El-Zimaity**, *Professor of Internal Medicine, Clinical Hematology Oncology Unit, Faculty of Medicine, Ain Shams University* for her extreme interest that made this work possible. Her effort is forever appreciated.

I want to express my great thanks to **Doctor Mohammed Mahmoud Moussa,** *Lecturer of Internal Medicine, Clinical Hematology Oncology Unit, Faculty of Medicine, Ain Shams University*, for his meticulous revision and constructive guidance and sharing the vision of this work that helped formulating it in its final form.

I would like to express my deep thanks and gratitude to the **Professor Doctor Bassima El Essawi** and **Professor Doctor Mohamed Refat Gaballa**, *Professors of Clinical Pathology, Faculty of Medicine, Ain Shams University* for their priceless help they offered in the practical work and for their continuous guidance.

Introduction:

Cyclins are very important components of the cell cycle machinery because their levels regulate cell proliferation. Cyclin Dl is one of the G١ cyclins that control cell cycle progression by allowing G١ to S transition. Overexpression of cyclin Dl has been postulated to play an important role in the development of human cancers. Cyclin D١ is a proto-oncogene that is overexpressed in mantle cell lymphomas and several other hematolymphoid malignancies **(Zukerberg et al., ١٩٩٥).**

Cyclin Dl also plays a key role in cell cycle regulation by cooperating with cyclin-dependent kinases (CDKs). It can function as an oncogene, the overexpression of which may lead to growth advantage for tumor cells by way of cell cycle progression. They have also been found to be prognostic factors in various cancers **(Jaroslav et al., ٢٠٠٥)**. Among hematolymphoid

malignancies, cyclin D١ overexpression has been recognized in mantle cell lymphoma, subset of B-chronic lymphocytic leukemia (B-CLL), multiple myeloma, splenic marginal zone lymphoma, and hairy cell leukemia **(Yatabe et al., ٢٠٠٠).**

Cyclin D١ expression appears to be a useful diagnostic adjunct to discriminate mantle cell lymphoma from other non-Hodgkin's lymphomas. Mantle-cell lymphomas (MCL) are associated with a characteristic chromosomal translocation, t(١١;١٤)(q١٣;q٣٢). This translocation involves rearrangement of the bcl-١ proto-oncogene from chromosome ١١ to the immunoglobulin heavy chain gene on chromosome ١٤, resulting in an overexpression of cyclin D١ mRNA. Clinically, mantle-cell lymphoma is more aggressive than many other so-called small B-cell lymphomas. Because cyclin D١ expression is not seen in normal hematopoietic cells, the demonstrated expression of cyclin D١ in lymphomas other than MCL