

استخدام تحليل التهجين الموضعي بالوميض  
الفلوري لاكتشاف الانحرافات في الذراع الطويل  
للكروموسوم السادس و الكروموسوم الثامن في  
مرضى سرطان الدم الليمفاوى المزمن: و علاقتها  
بعوامل التنبؤ بمآل المرض

### رسالة

توطئة للحصول على درجة الماجستير  
فى الباثولوجيا الاكلينيكية و الكيميائية

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INTERPHASE FLUORESCENCE IN SITU HYBRIDIZATION  
ANALYSIS OF 6Q21 AND 8Q24 ABERRATIONS IN CLL  
PATIENTS: RELATION TO PROGNOSTIC MARKERS

Thesis

Submitted For the Partial Fulfillment of Master  
Degree

In Clinical and Chemical Pathology

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2011

## **SUMMARY AND CONCLUSION**

The B-cell chronic lymphocytic leukemia (CLL) is a disease with a very low proliferative activity. It is characterized by the accumulation of clonal B-lymphocytes that seem to be arrested in early G0/G1 phase of the cell-cycle. Although the pathogenesis of B-CLL remains largely unknown, several investigators have focused on the role of cytogenetic aberrations that may contribute to defective apoptosis, deregulation of cell-cycle regulatory genes and expansion of the malignant clone.

Despite its homogeneity at cellular level, B-CLL is clinically heterogeneous. Some patients survive for a long-time without therapy, while others progress towards more advanced stages and die despite aggressive treatment. Reliable prognostic markers capable of predicting the progression and outcome of the disease include chromosomal analysis by conventional cytogenetics and interphase FISH, CD38 expression, ZAP-70 and examination of bone marrow infiltration pattern.

Clonal chromosomal aberrations are detected in about 40-50% of B-CLL patients. Recently, higher percentages were documented when using molecular techniques such as fluorescence in-situ hybridization (FISH). Therefore, this study aimed to evaluate patients with a clinical diagnosis of CLL by FISH technique for the following chromosomal abnormalities: 6q21 deletion and c-Myc amplification in addition to the common aberrations (trisomy 12, 13q14 del, 11q23 del and p53

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَقُلْ رَبِّ  
زِدْنِي عِلْمًا

سورة طه  
الاية (١١٤)

صَدَقَ اللَّهُ الْعَظِيمُ



*First thanks to **ALLAH** to whom I relate any success in achieving any work in my life.*

*I wish to express my deepest thanks, gratitude and appreciation to **Hoda Mohamed El-Gendi**, Professor of Clinical and Chemical Pathology for her meticulous supervision, kind guidance, valuable instructions and generous help.*

*Special thanks are due to **Prof. Dina Adel Fouad Mohamed**, Professor of Clinical and Chemical Pathology for her sincere efforts, fruitful encouragement.*

*I am deeply thankful to **Dr Doaa Ahmed Gamal Eissa**, Lecturer of Clinical and Chemical Pathology for her great help, outstanding support, active participation and guidance.*

*Last but not least, I would like to express my gratitude to **my parents & my husband** for their continuous efforts through the whole work.*

**Nada Sheta**

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## List of Abbreviations

|                      |                                         |
|----------------------|-----------------------------------------|
| <b>β2M</b> .....     | Beta 2 microglobulin                    |
| <b>+12</b> .....     | Trisomy 12                              |
| <b>aCLL</b> .....    | Atypical Chronic Lymphocytic Leukemia   |
| <b>ADAM29</b> .....  | A Disintegrin and Metalloproteinase 29  |
| <b>AIHA</b> .....    | Autoimmune hemolytic anemia             |
| <b>ALC</b> .....     | Absolute lymphocyte count               |
| <b>ALK</b> .....     | Anaplastic lymphoma kinase              |
| <b>Ampl</b> .....    | amplification                           |
| <b>Apaf1</b> .....   | Apoptotic peptidase activating factor 1 |
| <b>ATM</b> .....     | Ataxia-telangiectasia mutated           |
| <b>Bad</b> .....     | Bcl-2 associated death promoter         |
| <b>Bag-1</b> .....   | Bcl-2-associated Athanogene 1           |
| <b>Bak</b> .....     | Bcl-2 homologous antagonist/killer      |
| <b>Bax</b> .....     | The Bcl-2–associated X protein          |
| <b>Bcl 1,2,3</b> ... | B-cell CLL/lymphoma1,2,3                |
| <b>B-CLL</b> .....   | B cell chronic lymphocytic leukemia     |
| <b>BCR</b> .....     | B-cell receptor                         |
| <b>Bid</b> .....     | BH3-interacting death domain protein    |
| <b>Bik</b> .....     | Bcl-2 interacting killer                |
| <b>BML</b> .....     | Bone Marrow lymphocytes                 |

**CCA**.....Conventional cytogenetic analysis  
**CD** .....Cluster of differentiation  
**cDNA**.....Complementary deoxyribonucleic acid  
**CEP**.....chromosome enumeration probes  
**CGH**.....Comparative genomic hybridization  
**CHK2**.....Check point kinase 2  
**cm**.....centimeter  
**CR**.....Complete remission  
**CT**... ..... Computed tomography  
**D segment** ..Diversity segment  
**DAPI**.....4'-6-diamidino-2-phenylindole  
**DAT** .....Direct antiglobulin test  
**dATP/ATP** . deoxyadenosine triphosphate/ adenosine triphosphate  
**del**.....Deletion  
**dL**.....decilitre  
**DFS** .....Disease free survival  
**DLBCL** .....Diffuse large B-cell lymphoma  
**DNA**.....Deoxyribonucleic acid  
**DR** .....Death receptor  
**DW**.....Distilled water  
**EBV** .....Epstein-Barr virus

**EDTA**.....Ethylene diamine tetraacetic acid  
**ERIC**.....European Research Initiative on CLL  
**FAB** .....French American British  
**FCM**.....Flow cytometry  
**FCS**.....Fetal calf serum  
**FISH**.....Fluorescence in-situ hybridization  
**FITC** .....Fluorescein isothiocyanate  
**FMC7**.....Mouse anti-human B-cells  
**G 0, 1, 2** .....Gap 0, 1, 2  
**G-banding** ..Giemsa banding  
**GC**.....Germinal Centre  
**GCLLSG**....German CLL Study Group  
**H**.....Heavy chain  
**HDACi** ..... Histone deacetylase inhibitor  
**HLA**.....Histocompatibility antigen  
**Hrk**.....Harakini, Bcl-2 interacting protein  
**hTERT** ..... human telomerase reverse transcriptase  
**Ig**..... Immunoglobulin  
**IgV<sub>H</sub>** ..... Immunoglobulin heavy chain variable  
region  
**IHC**.....Immunohistochemistry  
**IL**.....Interleukin

**IP** .....Immunophenotyping  
**iso3q** ..... .. Isochromosome 3q  
**ITP**.....Immune mediated thrombocytopenia  
**IU**..... International Unit  
**IVIg** .....Intravenous immunoglobulin  
**IWCLL**.....International Workshop on CLL  
**J segment** ..Joining segment  
**Kb** .....Kilobase  
**KD** .....Kilodalton  
**LDH**.....Lactate dehydrogenase  
**LDT** .....Lymphocyte doubling time  
**LPD** .....Lymphoproliferative disorder  
**LPL**.....Lipoprotein lipase  
**LSI probe**....Locus specific identifier probe  
**M**.....Molar  
**McAbs**.....Monoclonal antibodies  
**Mcl-1**.....Myeloid cell leukemia sequence 1  
**MdM2** .....Murine double minute 2  
**MDS** .....Myelodysplastic syndrome  
**MHC** .....Major histocompatibility complex  
**miRNA**.....micro RNA  
**MRD** .....Minimal residual disease

**mRNA**.....Messenger RNA  
**NaCl**.....Sodium chloride  
**NCI-WG** ....National Cancer Institute Working Group  
**NCSS**.....Number Cruncher Statistical System  
**ng**.....nanogram  
**NHL**.....Non-Hodgkin lymphoma  
**NK**.....Natural killer  
**Noxa**.....PMAIP1(phorbol-12-myristate-13-acetate-  
induced protein 1)  
**NS**.....non significant  
**NP-40** .....Tergitol-type NP-40  
**ORR**.....Overall response rate  
**OS**.....Overall survival  
**p**.....Short arm of the chromosome  
**PBL**.....Peripheral blood lymphocytes  
**PBS**.....Phosphate buffer saline  
**PBSC** .....Peripheral blood stem cell  
**PCR** .....Polymerase chain reaction  
**PD**.....Progressive disease  
**PE**.....Phycoerythrin  
**PFS**.....Progression free survival  
**PH**.....Pleckstrin homology

**PLL**.....Prolymphocytic leukemia  
**PR**.....Partial remission  
  
**PRCA**.....Pure red cell aplasia  
**PTK** .....Protein tyrosine kinase  
**q** .....Long arm of the chromosome  
**Rb** .....Retinoblastoma  
**RNA**.....Ribonucleic acid  
**rpm** .....Revolution per minute  
**RPMI** .....Roswell Park Memorial Institute  
**RQ** .....Research question  
**RQ-PCR**.....Real-time quantitative PCR  
**RT-PCR** .....Reverse transcriptase PCR  
**sCD**.....soluble CD  
**SD**.....Stable disease  
**SD**.....standard deviation  
**sIg**.....Surface immunoglobulin  
**SLL**.....Small lymphocytic lymphoma  
**Smac**..... second mitochondria-derived activator of  
caspases  
**SPSS**.....Statistical package for Social Science  
**SSC**.....Standard saline citrate  
**SyK**.....spleen tyrosine kinase

**t** .....Translocation  
**TCR**..... T-cell receptor  
**TK**.....Thymidine kinase  
**TLC**.....Total leucocytic count  
**TNF- $\alpha$** .....Tumor necrosis factor-alpha  
**TRM**.....Treatment related mortality  
**VEGF**.....Vascular endothelial growth factor  
**V segment** ..Variable segment  
**WHO**.....World Health Organization  
**ZAP70**.....Zeta- associated protein 70

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