

Expression of CD39 and CD73 by Chronic Lymphocytic Leukemia B-cells

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ
أَنْتَ الْعَلِيمُ الْحَكِيمُ

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Contents

| | |
|---|-----|
| List of Abbreviations | i |
| List of Tables | iii |
| List of Figures | iv |
| Introduction and Aim of the Work | 1 |
| Review of Literature | 4 |
| * Chronic Lymphocytic Leukemia | 4 |
| * CD73 and CD39 | 38 |
| Subjects and Methods | 48 |
| Results | 53 |
| Discussion | 84 |
| Recommendations | 94 |
| Summary | 95 |
| References | 98 |
| Arabic Summary | -- |

List of Abbreviations

| | | |
|---------------------|---|--|
| ADO | : | Adenosine |
| ADP | : | Adenosine diphosphate |
| AMP | : | Adenosine monophosphate |
| APAF-1 | : | Apoptotic protease activating factor 1 |
| ATM | : | Ataxia telangectasia mutation |
| ATP | : | Adenosine triphosphate |
| BCRs | : | B-cell receptors |
| BM | : | Bone marrow |
| CD | : | Cluster of differentiation |
| CLL | : | Chronic lymphocytic leukemia |
| CTL | : | Cytotoxic T cells |
| DDT | : | Dichlorodiphenyltrichloroethane |
| DISC | : | Death-inducing signaling complex |
| EBV | : | Epstein Barr virus |
| ELISA | : | Enzyme Linked Immunosorbent Assay |
| E-NTPDase | : | Ectonucleoside triphosphate diphosphohydrolase |
| FAB classification: | | French American British classification |
| FAS | : | FAS receptor |
| FASL | : | FAS ligand |
| FDC | : | Follicular dendritic cell |
| FITC | : | Fluorescein isothiocyanate |
| GPI | : | Glycophosphatidylinositol |
| HBV | : | Hepatitis B-virus |
| HCV | : | Hepatitis C virus |
| HIV | : | Human immunodeficiency virus |
| HMS | : | Hyperactive malarial splenomegaly |
| IL | : | Interleukin |
| INF | : | Tumor necrosis factor |
| IQR | : | Interquartile range |
| IWCLL | : | International workshop on CLL |

List of Abbreviations (Cont.)

| | | |
|---------------------|---|---|
| K ₂ EDTA | : | Di Potassium-ethylene diamine tetra acetic acid |
| LDH | : | Lactate dehydrogenase |
| LDT | : | Lymphocyte Doubling time |
| MRD | : | Minimal residual disease |
| MZ | : | Mantle zone |
| NCI.WG | : | National cancer institute working group |
| NHC | : | Non Hodgkin lymphoma |
| NPV | : | Negative predictive value |
| NT'5E | : | Ecto-5'-nucleotidase |
| PBS | : | Phosphate buffer saline |
| PBSC | : | Peripheral blood stem cell |
| PCNA | : | Proliferating cell nuclear antigen |
| PCR | : | Polymerase Chain Reaction |
| PE | : | Phycoerythrin |
| PPV | : | Positive predicate value |
| ROC | : | Receiver operator characteristic curve |
| RT-PCR | : | Real time Polymerase Chain Reaction |
| SCD23 | : | Soluble CD23 |
| SCID | : | Severe combined immunodeficiency |
| SD | : | Standard deviation |
| sICAM | : | Soluble intercellular adhesion molecule |
| SLL | : | Small lymphocytic lymphoma |
| SLVL | : | Splenic lymphoma with villous lymphocytes |
| TK | : | Thymidine kinase |
| TL | : | Tumor load |
| UA | : | Uric acid |
| VEGF | : | Vascular endothelial growth factor |
| WBC | : | White blood cells. |

List of tables

| <i>Table</i> | <i>Title</i> | <i>Page</i> |
|--------------|---|-------------|
| 1 | Similarities and differences between CD5+ B-CLL cells and normal CD5+ B cells | 7 |
| 2 | Clinical features of CLL | 12 |
| 3 | Scoring system for the diagnosis of CL | 15 |
| 4 | Incidence of common genetic aberrations in CLL | 16 |
| 5 | Criteria for the diagnosis of CLL | 21 |
| 6 | Differential Diagnosis of Chronic Lymphocytic Leukemia | 22 |
| 7 | Immune defects in CLL | 23 |
| 8 | Differences between de novo PLL and CLL/PLL | 25 |
| 9 | The Rai and Binet staging systems | 26 |
| 10 | Prognostic parameters in CLL | 27 |
| 11 | Distribution of males and females in both groups | 53 |
| 12 | Patients' clinical groups | 55 |
| 13 | Results of routine immunophenotyping with its scoring system, percentage of BM lymphocytes and β_2 microglobulin level among patients | 56 |
| 14 | Quantitative data of patients and controls | 57 |
| 15 | CD73 expression in patients and controls | 57 |
| 16 | CD39 expression in patients and controls | 58 |
| 17 | Comparison between patients and controls (intergroup analysis) as regard studied parameters | 60 |
| 18 | Comparison between patients clinical subgroups according to Binet staging | 63 |

List of tables (Cont.)

| <i>Table</i> | <i>Title</i> | <i>Page</i> |
|---------------------|--|--------------------|
| 19 | Comparison between patients' groups according to course of the disease | 65 |
| 20 | Comparison between patients' groups according to their LDT | 68 |
| 21 | Comparison between patients with low, moderate and high tumor load | 21 |
| 22 | Comparison between patients' groups according to whether in hematological remission or not at time of sampling | 74 |
| 23 | Correlation studies | 76 |
| 24 | The diagnostic performance for each of CD73, CD39, CD39/CD73 co-expression and CD39/CD73 ratio as diagnostic markers of CLL | 79 |
| 25 | The prognostic performance for each of CD73, CD39, CD39/CD73 co-expression and CD39/CD73 ratio as regards disease course | 81 |
| 26 | The prognostic performance for each of CD73, CD39, CD39/CD73 co-expression and CD39/CD73 ratio as regard hematological remission | 83 |

List of Figures

| <i>Fig.</i> | <i>Title</i> | <i>Page</i> |
|-------------|---|-------------|
| 1 | The two pathways of apoptosis: death receptor (extrinsic) and mitochondrial (intrinsic) pathways | 8 |
| 2 | Clinical photograph showing cervical lymphadenopathy and skin infiltration in CLL patients | 12 |
| 3 | May-Grumwald-Giemsa-stained PB film from a case with CLL with increased prolymphocytes (CLL/PLL) | 14 |
| 4 | Bone marrow aspirate effaced by well differentiated lymphocytes | 17 |
| 5 | Bone marrow biopsy specimen, B-cell CLL/small lymphocytic lymphoma | 17 |
| 6 | Bone marrow biopsy specimen, B-CLL /small lymphocytic lymphoma | 17 |
| 7 | Richter's transformation | 19 |
| 8 | Splenic involvement in CLL with white-pulp nodules containing proliferation centers and infiltration of the red pulp | 19 |
| 9 | Gene location of CD73 | 31 |
| 10 | Molecular structure of CD73 | 32 |
| 11 | Extracellular adenosine produced through the activity of the ecto-enzymes (CD39 and CD73) on tumor cells can sufficiently downregulate antitumor immunity | 37 |
| 12 | Gene location of CD39 | 39 |
| 13 | Molecular structure of CD39 | 40 |
| 14 | CD39 regulates vascular inflammation and thrombosis by hydrolyzing ATP and ADP | 42 |

List of Figures (Cont.)

| <i>Fig.</i> | <i>Title</i> | <i>Page</i> |
|-------------|--|-------------|
| 15 | T reg-mediated immunosuppression and tumor growth via the CD39-CD73-adenosine pathway | 44 |
| | Percent of patients and controls positive for CD73 and CD39 | 58 |
| 16 | CD 73 expression in CLL patients versus controls | 61 |
| 17 | CD39/CD73 ratio in CLL patients versus controls | 61 |
| 18 | CD39/CD73 ratio in CLL patients versus controls | 61 |
| 19 | CD39 expression among CLL patients having aggressive course versus patients with a quiescent course | 66 |
| 20 | CD39 expression among CLL patients with LDT >6months versus patients with < 6months | 69 |
| 21 | CD39 / CD73 ration among CLL patients with LDT >6months versus patients with < 6months | 69 |
| 22 | Figure showing that expression of CD39 in CLL patients varies with tumor load | 72 |
| 23 | CD39 expression in remitted CLL patients versus non remitted | 73 |
| 24 | CD39/ CD 73 ratio positively correlates with LDH level | 77 |
| 25 | CD39 expression negatively correlates with β -2 MG and CD79b | 77 |
| 26 | ROC cure shows whether CD73, CD39, their co-expression or the ratio between them are valid as diagnostic markers for B-CLL | 80 |

List of Figures (Cont.)

| <i>Fig.</i> | <i>Title</i> | <i>Page</i> |
|--------------------|---|--------------------|
| 27 | ROC curve shows whether CD73, CD39 or the ratio between them are valid as prognostic markers for B-CLL | 82 |
| 28 | ROC curve shows whether CD73, CD39, their co-expression or the ratio between them are valid as prognostic markers for B-CLL | 83 |

Introduction

Chronic lymphocytic leukemia (CLL), the most common leukemia in adults, is a lymphoproliferative disorder with a highly variable clinical course. CLL is characterized by the clonal expansion of mature antigen stimulated CD5+/CD23+ B-lymphocytes in blood, secondary lymphoid tissue and the bone marrow (*Chiorazzi et al, 2005*).

The clinical staging systems developed by Rai and Binet remain the standard methods for risk assessment in CLL, but they don't allow predictions about the risk of disease progression in early stage disease patients, which is the majority of patients. A sizable number of studies investigated prognostic markers, which can be helpful for predicting the individual risk at an early stage of the disease (*Sivina et al, 2011*).

The most accepted and widely used prognostic markers in CLL are the mutation status of immunoglobulin variable gene segments (IgVH), the expression of CD38 and ZAP-70 as well as cytogenetic risk groups (*Catovsky and Montserrat, 2011*).

Extracellular nucleotides and nucleosides such as adenosine triphosphate (ATP) and adenosine (ADO) respectively, may participate in creating favourable conditions that promote tumour growth and survival, CD39 hydrolyses ATP or ADP to adenosine monophosphate (AMP). AMP is then rapidly degraded to ADO by soluble or membrane bound CD73. ADO production is an integral component of the suppressive machinery of regulatory T-cells, blunting effector T-cell proliferation and secretion of T-helper 1-type cytokines, thus promoting tumor growth and survival (*Serra et al, 2011*).

Elevated expression and activity of CD73 have been reported in several types of solid tumors and in certain types of

leukemia, suggesting that it may be beneficial to the survival of tumour cells and could promote metastatic spread (*Stagg et al, 2010*).

On these grounds, it is justified to hypothesize that expression of CD39 and CD73 by CLL cells might have an impact on the course of the disease in CLL patients and that this warrants further studies.

Aim of the Work

In this work we aim to study the expression of CD39 and CD73 and its clinical significance among a group of Egyptian B-CLL patients.

Chronic Lymphocytic Leukemia

Introduction:

Chronic lymphocytic leukemia (CLL) is the most common adult form of leukemia (*Xu et al, 2008*). It is a monoclonal disorder characterized by a progressive accumulation of functionally incompetent lymphocytes (*Puente et al, 2013*).

CLL follows an extremely variable clinical course with overall survival times ranging from months to decades. Some patients have no or minimal signs and symptoms during their entire disease course and have a survival time similar to age-matched controls. Other patients experience rapidly deteriorating blood counts and organomegaly and suffer from symptoms at diagnosis or soon thereafter necessitating therapy (*Crowther-Swanepoet et al, 2013*).

Epidemiology:

Prevalence and Incidence:

It is the most common leukemia in the western world with an incidence of 4:100 000/year. The incidence increases to >30:100 000/year at age >80 years (*Eichhorst et al, 2010*). Generally, it creates more than 30% of all types of leukemia, with a median age at time of diagnosis of 72 years. Incidence rates increase with age and are higher among men than women (*Panovská et al, 2010*). In Asian countries, CLL represents only 5% of leukemias, with the T-cell phenotype predominating. This geographic difference in incidence is most likely the result of genetic factors (*O'Brien and Keating, 2005*).