The Association between the Circulating B-cell Activating Factor Serum Level and B-cell Chronic Lymphocytic Leukemia

Thesis

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بسم الله الرحمن الرحيم

قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا

إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

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@Dalia Mohammed Ellabban

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List of Abbreviations

ABC : Avidin-Biotin-Peroxidase Complex
ALC: Absolute lymphocytic count
BAFF : B-cell activating factor
b2-MG : Beta 2 micorglobulin
bc1-xL : B-cell lymphoma-extra-large
B-CLL : B-cell chronic lymphocytic leukemia
BCMA : B-cell maturation antigen
BLyS : B-lymphocyte stimulator
CLL : Chronic lymphocytic leukemia
CRD : Cysteine-rich domain
CSR : Class switch recombination
DTH : Delayed type hypersensitivity
EBV : Epstein Barr virus
EDTA : Ethylene Diamine Tetraacetic Acid
ELISA : Enzyme-linked immunosorbent assay
FAB : French American British
FCL : Follicular cell lymphoma
FISH : Fluorescence in situ hybridization
FL : Follicular lymphoma
HCL : Hairy cell leukemia
HCV : Hepatitis C virus
IWCLL : International Workshop on Chronic Lymphocytic Leukemia
LDH : Lactate dehydrogenase
LDT : Lymphocyte doubling time
MCL : Mantle-cell lymphoma

List of Abbreviations *(Cont...)*

Mcl-1 : Myeloid leukemia cell differentiation protein
MM : Multiple myeloma
MPC : Antigen presenting cells
NHL : Non-Hodgkin's lymphoma
PBC : Primary biliary cirrhosis
PLL : Prolymphocytic leukemia
RA : Rhumatoid arthritis
SF : Synovial fluids
SG : Salivary gland
SIg : Surface immunoglobulin
SjS : Sjogren syndrom
SLE : Systemic lupus erthrematosis
SLVL : Splenic lymphoma with villous lymphocytes
s-TK : Serum thymidine kinase activity
TLR : Toll like receptor
ZAP-70 : Zeta associated protein 70

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Introduction

B-cell chronic lymphocytic leukemia (B-CLL) constitutes the most prevalentleukemia in Western countries ***(Tam and Keeting, 2010),*** and it is an incurable disease characterized by extensiveclinical heterogeneity despite a commondiagnostic immunophenotype [small mature B cells display CD19+, CD20+, CD5+, CD23 markers] ***(Wang, et al., 2011).***

A small pool of highly proliferating cells has been detected in the lymph nodes and bone marrow that feed the pool of leukemic cells in the blood, 95–98% of these cells being arrested at the G0 stage of the cell cycle ***(Zenz, 2010).*** Therefore, their accumulation mostly results from a deficient apoptosis rather than from an acute proliferation ***(Wong, 2011).***

Whether defects in the apoptotic pathway are frequently encountered in a variety of cancers, B-CLL represents a paradigm of the tumors that arise as a consequence of alterations in the processes leading to programmed cell death ***(Haiat et al., 2006).*** Indeed, B-CLL cells display multiple intrinsic defects in their apoptotic machinery and dysregulated production of survival signals from their microenvironment ***(Burger, 2011).***

B-cell activating factor(BAFF) is a molecule that identified by sequence homology with the TNF superfamily members**,** also

named BLyS (B-lymphocyte stimulator) because it induces B lymphocyte proliferation and immunoglobulin secretion**.** It is also known as THANK (TNF homologue that activates apoptosis, nuclear factor-jB and c-junN-terminal kinase) ***(Bienertova-Vasku et al., 2012).***

BAFF and its receptor play a key role in the survival and differentiation of B cells.They therefore provide not only a new insight into the development of autoreactive B cells, but also a paradigm to the interaction between survival, growth and death affecting all cells ***(Maia et al., 2011).***

Aim of the Work

The aim of this work is to investigate the association between thecirculating BAFF serum level and B-cell Chronic LymphocyticLeukemia by ELISA technique.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a neoplasm of mature-appearing monoclonal B-lymphocytes co-expressing the CD5 antigen and B-cell surface antigen CD19 and CD23 with weak expressingsurface immunoglobulin and CD79b compared with those found on normal B-cells.***(Hallek et al.,2008).***Primarily CLL involves the bone marrow, peripheral blood and may infiltrate lymphoid tissue such as lymph nodes and spleen ***(Gachard et al., 2008).***

EPIDEMIOLOGY

The B-CLL is the most common adult leukemia in western societies and it accounts for approximately one-third of all adult leukemias in the United States ***(Siegel et al., 2013).***In Egypt , CLL represents 11.9% of all leukemias ***(Egypt National Cancer Registry, 2009),*** while in Asian countries, it 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).***

Chronic lymphocytic leukemia develops mostly in the aging population, as it reported in Cancer statistics 2010, the median age of patients with CLL enrolled in most clinical trials is about 60 years***(Jemal et al.,2010),***only 10% to 15% of patients are younger than 50 years at the time of diagnosis. CLL

is a male-predominant disease (1.3–1.5:1) although the relative rate in femalesincreased with age***(Seftel et al.,2009).***

CLL is a heterogeneous disease as reflected by its highly variable natural history, ranging from indolent to aggressive clinical course***(Rai, 2008).***

ETIOLOGY

A- Environmental:

In rural areas CLL is more frequent because of the involvement of agricultural chemicals also in farming communities there is association between B-CLL and exposure to pesticides***(Nanni et al., 1996).*** Others suggest that the environmental factors do not appear to play a role in the pathogenesis of B-CLL ***(Wierda et al., 2007).***

B-Infections:

Antibodies specific for type C hepatitis virus (HCV) and/or viral RNA have been identified in some patients, suggesting a pathogenic role ***(La Civita et al., 1996).*** However other studies have failed to verify an association between the development of CLL and infection with HCV ***(McColl et al., 1997).*** Chronic lymphocytic leukemia cells are resistant to infection with Epstein Barr virus (EBV), except in unusual cases, making it unlikely that EBV plays a pathogenic role ***(Avila-Carino et al., 1997).***

C- Hereditary and Genetic Factors:

Although most cases of CLL are sporadic, a subset of B-CLL is familial ***(Summersgill, 2002).*** First degree relatives of

patients with CLL are more than three times at risk for having this disorder or other lymphoid neoplasms than the general population and often present at a younger age ***(Cuttner, 1992).***