Prognostic Impact of 17p Deletion on Chronic Lymphocytic Leukemia Patients

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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ والْمُؤْمِنُونَ

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List of Abbreviations

BMT	: Bone marrow transplantation
CLL	: Chronic lymphocytic leukemia
Del	: Deletion
GVHD	: Graft versus host disease
HBV	: Hepatitis B virus
HCV	: Hepatitis C virus
HIV	: Human immunodeficiency virus
Hb	: Hemoglobin
IGVH	: Immunoglobulin variable heavy chain
ODN	: Oligodeoxynucleatidase
PLL	: Prolymphocytic leukemia
PRCA	: Pure red cell aplasia

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Introduction

Chronic lymphocytic leukemia, is the progressive accumulation of mature appearing, functionally incompetent, long-lived B-lymphocytes in peripheral blood, bone-marrow, lymph nodes, spleen, liver and sometimes other organs (**Cheson et al., 1996).**

CLL is a disease of adults, but in rare cases, it can occur in teenagers and occasionally in children (inherited). Most (>75%) people newly diagnosed with CLL are over the age of 50, and the majority are men **(Harris et al., 1999).**

70- 80% of patients present as asymptomatic lymphocytosis, with more advancing disease asymmetrical painless lymphadenopathy, splenomegaly, hepatomegaly and ultimately bone-marrow failure due to infiltration may occur.

The main immunophenotypic features that define B-CLL are the expression of B-cell markers CD19, CD20, and CD23 together with the expressio of CD5 antigen and the absence of other T-cell markers. The B-cell is monoclonal with regard to expression of either kappa or lambda **(Mossafa et al., 1997).** Some patients survive for many years without therapy, whereas others have a rapidly deteriorating blood counts and organomegaly denoting bad prognosis **(Eichhorst et al., 2006).**

Deletions of part of the short arm of chromosome 17 (del 17p) is found in 5-10% of patients with CLL.This genetic abnormality targets the cell cycle regulating protein (p53) involved in apoptosis, anticancer function, genomic stability and inhibition of angiogenesis.

Although the deletion of 17p is associated with poor outcome in different hematological malignancies, its impact on outcome is particularly striking in CLL **(Zens et al., 2008).**

Aim of The work

To study, the prognostic impact of 17 p deletion in CLL patients regarding the clinical and hematological response to treatment.

Chapter 1
Chronic Lymphocytic Leukemia

In 1845-1846, R. Virchow, a famous German pathologist, recognized a type of blood malignancy where cells grow out of control and accumulate in the bone marrow and blood, where they crowd out healthy blood cells, presents primarily in the lymph nodes (Harris et al., 1999) and categorized them as the two subtypes: Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma. In 1881, Einhorn named these cells lymphocytes and recognized that there were different sizes of lymphocytes, Progress improved in 1891 when Ehrlich described how to stain blood cells so that the distinct subtypes of blood cells could be reproducibly identified. In 1903, Turk further clarified the disorder and felt it was a benign condition since his patients were extremely slow in demonstrating disease progression.

During the 1950s-1970s, major new understanding of the immune system occurred. It became clear that CLL/SLL was a B-lymphocyte disorder with immunoglobulins on the cells' surface, Clinical staging systems came into use in 1970s and early 1980s **(Rai, 1975 and Binet, 1981)**. This allowed better categorization of patients, and thus better clinical research could be done.

Definition:

Chronic Lymphocytic Leukemia, is a disorder of morphologically mature but immunologically less mature lymphocytes and is manifested by progressive accumulation of these cells in the blood, bone marrow, and lymphatic tissues. The lymphocytes are not able to fight infection very well. Also, as the number of lymphocytes increases in the blood and bone marrow, there is less room for healthy white blood cells,

red blood cells, and platelets. This may cause infection, anemia and easy bleeding **(Dighiero, 2008).**

In this disorder, lymphocyte counts in the blood are usually greater than or equal to 5, 000/mm^3 with a characteristic immune-phenotype (CD5- and CD23-positive B cells). One subtype is B- Pro-lymphocytic Leukemia (B-PLL), a more aggressive subtype that expresses T-cell markers (CD4 and CD7) and has clonal rearrangements of their T-cell receptor genes. These patients have a higher frequency of skin lesions, more variable lymphocyte shape, and shorter median survival (13 months) with minimal responses to chemotherapy **(Hoyer et al., 1995).**

Predisposing factors for chronic lymphocytic leukemia:

There are very few known predisposing factors for chronic lymphocytic leukemia (CLL), does not seem to be affected by smoking, diet, exposure to radiation, or infections **(Lichtman et al., 2010).**

Certain chemical exposures:

Some studies have linked exposure to Agent Orange, a herbicide used during the Vietnam War, to an increased risk of CLL. Some other studies have suggested that farming and long-term exposure to some pesticides may be linked to an increased risk of CLL, but more research in this area is needed **(Abeloff et al., 2008).**

Family history:

First-degree relatives (parents, siblings, or children) of CLL patients have a 2- to 4-fold increased risk for this cancer **(Goldar et al., 1994).**

Gender:

CLL is slightly more common in males than females, but the reasons for this are not known **(Wierda, 1999).**

Race/ethnicity:

CLL is more common in North America and Europe than in Asia. Most experts think this is related to genetic differences rather than environmental factors because people keep the same risk even when they move from one area to another **(Shanafelt et al., 2012).**

Incidence & Mortality:

Epidemiology

CLL accounts for 7% of lymphoblastic disorders **(Turgeon et al., 2005)**, it is a disease of older adults, with a median age of 70 years at the time of diagnosis **(Shanshal et al., 2012)**. Though less common, CLL sometimes affects people between 30 and 39 years of age, CLL almost never affects children. The incidence of CLL increases very quickly with increasing age, 2/3 of patients are men and it is more common in white race than black race.

Because of the prolonged survival, which was about ten years in past decades, but nowadays extends to a normal life expectancy **(Fazi et al., 2011).** The prevalence (number of people living with the disease) is much higher than the incidence (new diagnoses).

Subclinical "disease" can be identified in 3.5% of normal adults **(Rawstron et al., 2002)**, and in up to 8% of individuals over the age of 70.

CLL is very rare in Asian countries, such as Japan and China, and may account for as few as 10 percent of all leukemia in those regions **(Shanshal et al., 2012)**.

Pathogenesis :

The molecular pathogenesis of CLL is a complex, multistep process leading to the replication of a malignant clone of B-lymphocytes. While some steps in this pathway have been elucidated, many remain unknown. It is believed that virtually all CLL cases are preceded by a premalignant B cell proliferative disorder known as monoclonal B cell lymphocytosis (MBL). MBL with a CLL-phenotype is present in 5 to 15 percent of the population above the age of 60, and progresses to CLL/SLL or a related malignancy at a rate of approximately 1 percent per year **(Rossi et al., 2009).**

The pathogenesis of CLL can be conceptualized as two sequential processes:

- Establishment of MBL, although the inciting event is unknown, MBL appears to develop as the result of cytogenetic abnormalities, many of which are thought to be the product of an abnormal response to antigenic stimulation. The result is a clone of memory B cells with a CLL phenotype.

- Progression from MBL to CLL, Further insults to the B cell clone, either through additional genetic abnormalities or changes in the bone marrow microenvironment, result in the progression of MBL to CLL **(Ghia et al., 2012)**. This progression occurs in a very minor portion of persons with MBL.

- Other factors have been involved in the pathogenesis of CLL e.g: I.G.V.H mutation, anti-apoptotic proteins (e.g: BCL-2), cytokines (e.g: T.N.F) and abnormal angiogenesis.

Clinical Manifestations:

The symptoms of CLL tend to develop over time. For many people, CLL symptoms may at first seem to be some kind of non-specific change in overall health. There may be an increased sense of fatigue or weakness. Some people may experience flu-like symptoms, like night sweats or enlarged lymph nodes. Many people are diagnosed with CLL because of a blood test for an unrelated condition. In time, the abnormal lymphocytes may fill much of the bone marrow. Because of this, it is difficult for normal cells in the bone marrow to survive and make enough normal blood cells **(Mir et al., 2012)**. Therefore, the main problems which may eventually develop include:

- Anaemia. This occurs as the number of red blood cells in the bloodstream goes down. This can cause tiredness, breathlessness and other symptoms.
- Blood clotting problems. This is due to low numbers of platelets in the bloodstream. This can cause easy bruising, bleeding from the gums and other bleeding-related problems.
- Serious infections. The abnormal lymphocytes do not protect against infection. If there are reduced numbers of normal white blood cells which usually combat infection, there is a risk of serious infections developing.

The abnormal lymphocytes may also build up in lymph glands and in the spleen. With CLL it is also common to develop swollen glands in various parts of the body, particularly in the neck and armpits, and develop an enlarged spleen. Other common symptoms include: persistent fever, night sweats and weight loss what's called B-symptoms.