بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / هناء محمد علي

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: ....

The relation between serum SETD2 And response to treatment in CML Patients on TKI

Thesis

Submitted in Partial Fulfillment of the Requirement of the Master Degree in Internal Medicine

By

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2021-2022

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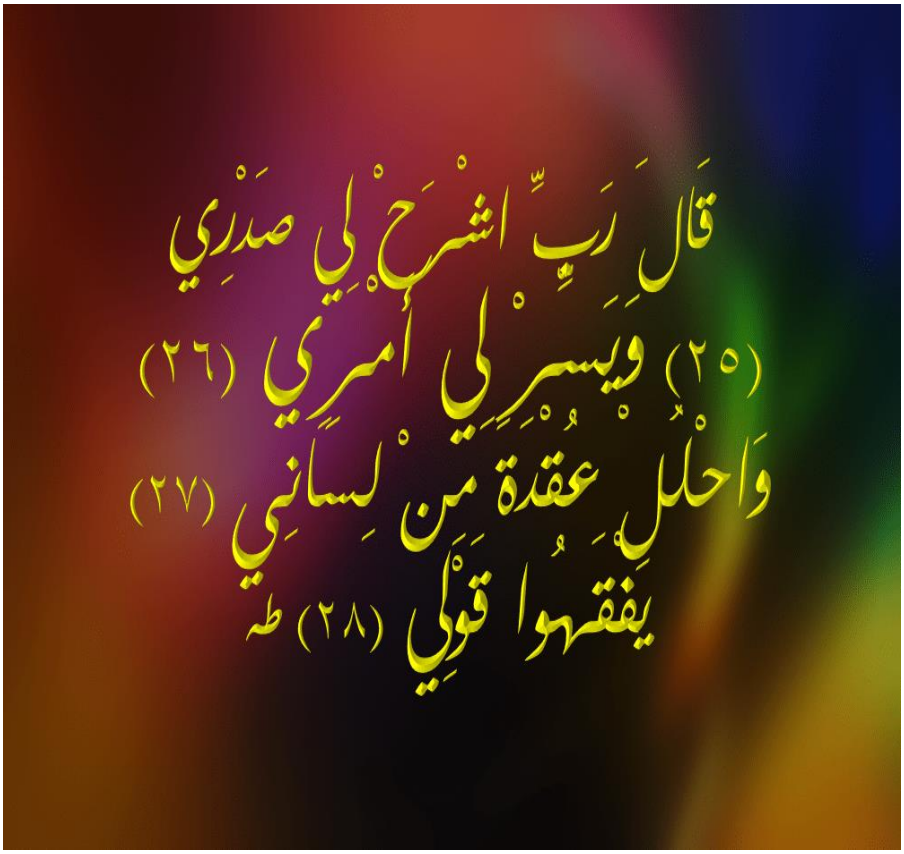

صدق الله العظيم
سورة طه

Acknowledgments

First and foremost, my deep gratefulness and indebtedness is to Allah, "The Most Gracious and The Most Merciful".

I would like to express my sincere gratitude to **Prof. Dr Mohamed Ossman Azzazi el Messeri, Professor of Internal Medicine and Clinical Hematology Faculty of Medicine, Ain Shams University** who offered me advice during the present work. I will appreciate his continuous guidance, valuable directions, extensive revision, objective criticism, and he was helping me to overcome many difficulties during the study.

In addition, my deep appreciation and sincere thanks to **Prof. Dr Nermeen Adel Nabih, professor of Internal Medicine and Clinical Hematology, Faculty of Medicine, Ain Shams University** for his valuable and expert supervision. She offered me advice during the present work. Her kind insight and encouragement helped me to bring out the best work.

Furthermore, I would like to express my sincere gratitude to **Dr Rania Abd Elmeneam Radwan, Assistant professor of Internal Medicine and Clinical Hematology Faculty of Medicine, Ain Shams University**, for his continuous guidance, sincere help during the stages of this work, and for her continuous advice and encouragement during the preparation of the thesis.

Furthermore, I would like to express my sincere gratitude to **Gehad Hamda Fekry, Lecturer of Internal Medicine and Clinical Hematology Faculty of Medicine, Ain Shams University**, for his continuous guidance, sincere help during the stages of this work, and for her continuous advice and encouragement during the preparation of the thesis.

At last but not least all thankfulness, deep respects to Internal Medicine and Clinical Hematology department, Faculty of Medicine, **Ain Shams** University, where this study was done.

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2022

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Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disease marked by chromosome translocation t(9;22) (q22;q11) that leads to the BCR-ABL1 fusion Gene. The resulting BCR-ABL1 fusion protein (p210), is a constitutively activated tyrosine kinase that drives the leukemic transformation of hematopoietic stem cells, and induces the progression of the disease from the early chronic phase (CP) to the blastic phase (BP) which fatally close the course of the disease (2–3)

TKIs in the 2000s radically changed the fate of CML, since Imatinib (IM), before, Nilotinib (NIL), Dasatinib (DAS) or bosutinib (BOS), after, showed to be able to prevent the disease and Blastic transformation and significantly prolong the survival (4).

CML is often divided into three phases based on clinical characteristics and laboratory findings. In the absence of intervention, CML typically begins in the chronic phase, and over the course of several years progresses to an accelerated phase and ultimately to a blast crisis. Blast crisis is the terminal phase of CML and clinically behaves like an acute leukemia. Drug treatment will usually stop this progression if started early. Some patients may already be in the accelerated phase or blast

crisis by the time they are diagnosed.(5)

SET domain containing 2 is an enzyme that in humans is encoded by the SETD2 gene. The SETD2 gene is located on the short arm of chromosome 3 and has been shown to play a tumor suppressor role in human. SET domain-containing 2 (SETD2) is the major mammalian methyltransferase responsible for catalyzing the trimethylation of Histone 3 on lysine 3 (H3K36me3). Mutations of SETD2 have been found in various types of tumors, such as clear cell renal cell carcinoma,(6) breast cancer,(7) glioma,

Acute leukemia and chronic lymphocytic leukemia.(8). mutation of the histone methyl transferase SEDT2 affects alternative splicing fates of several key regulatory genes, including those involved in Wnt signaling. As a consequence, loss of SEDT2 in the intestine aggravated Wnt/β-catenin signaling effects, thereby leading to colorectal cancer.(9)

Down regulation of SETD2 facilitates imatinib resistance in CML cells, with LSC marker upregula-tion, which could be successfully rescued by SETD2 overexpression. Additionally, by restoring the H3K36me3 level through treatment with JIB-04 (a small-molecule inhibitor of H3K36me3 demethy-lase, the sensitivity of

CML cells towards imatinib was effectively increased, providing a potential therapeutic strategy to overcome Imatinib-resistant CM L (10).

Aim of the work

Our aim is to measure serum SETD2 in CML patient and to correlate serum SETD2 and outcomes and other prognostic factors.

CHAPTER (1): CML

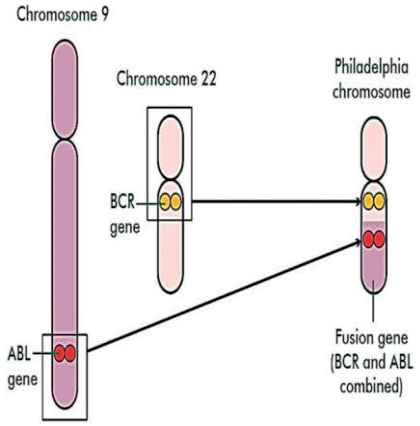
Overview, incidence, and prevalence

Chronic myeloid leukemia (CML) is a pluripotent hematopoietic stem cell neoplasm characterized by the *BCR- ABL* fusion gene, which is usually derived from a balanced translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11), resulting in a derivative chromosome known as the Philadelphia (Ph) chromosome. CML accounts for 15% to 20% of adult leukemia cases. The worldwide annual incidence of CML is one to two cases per 100,000 persons, with a slight male predominance (male- to- female ratio, 1.3:1) **(1).**

Because successful targeted therapy has returned life expectancy to that of the unaffected general population in many, the prevalence of CML continues to increase and is projected to reach 150,000 cases in the United States by 2040. In Eu rope, the median age of diagnosis ranges between 60 and 65 years, and in the United States, CML is most frequently diagnosed in individuals between the ages of 65 and 74. However, in countries where life span is shorter, the median age of diagnosis is substantially lower.

CML in children and young adults is rare, constituting only 2% of all leukemias in children <15 years of age and 9% of all leukemias in adolescents 15 to 19 years of age.

Radiation exposure has been implicated as a risk factor; however, unlike other myeloid leukemias, there has been no evidence for a causal association between CML and exposure to organic solvents, industrial chemicals, or alkylating agents. **(2).**



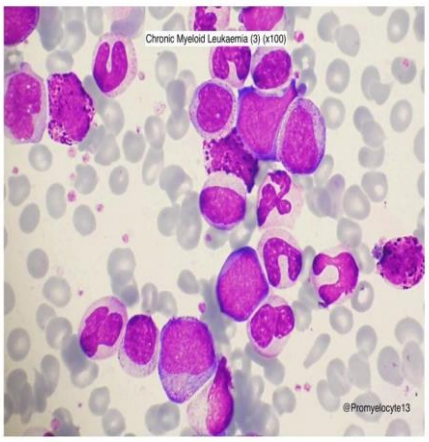


Figure (1) Molecular pathogenesis of t(9;22)(q34;q11) in CML **(3).**

The main teaching of the countless clinical and biological studies conducted over all these years is that the cure of CML can only pass through the abrogation of the

Ph+ clone, which can be detected and monitored by cytogenetics (chromosome banding analysis (CBA), or fluorescent in-situ hybridization (FISH)) or by real time quantitative reverse transcription polymerase chain reaction (RT-qPCR) **(4).**

Sign and symptoms

The way CML presents depends on the stage of the disease at diagnosis as it has been known to skip stages in some cases **(4).**

Most patients (~90%) are diagnosed during the chronic stage which is most often asymptomatic. In these cases, it may be diagnosed incidentally with an elevated white blood cell count on a routine laboratory test **(5).** It can also present with symptoms indicative of hepatosplenomegaly and the resulting left upper quadrant pain this causes. The enlarged spleen may put pressure on the stomach causing a loss of appetite and resulting weight loss. It may also present with mild fever and night sweats due to an elevated basal level of metabolism **(6).**

Some (<10%) are diagnosed during the accelerated stage which most often presents bleeding, petechiae and ecchymosis.In these patients fevers are most commonly the result of opportunistic infections.Some patients are initially diagnosed in the blast phase in which the symptoms are

most likely fever, bone pain **(7).**

Symptom	Blood and bone marrow findings (WHO classification)
Chronic phase	
Fatigue	Neutrophilic leukocytosis with immaturity
Weight loss	Peripheral blasts <10%
Nocturnal sweats	Thrombocytosis
Left upper-quadrant abdominal pain	Basophilia and/or eosinophilia
Early satiety	Normocytic anemia
Palpitations and/or dyspnea	*BCR-ABL1* rearrangement (usually p210 BCR-ABL1, may be e13a2 or e14a2 variants or both)
Bleeding/bruising	High lactate dehydrogenase
Priapism	Hyperuricemia
	Marrow myeloid and megakaryocytic hyperplasia, mild/moderate fibrosis, <10% blasts, minimal dysplasia,
	t(9;22) ± other abnormalities
Accelerated phase (several definitions exist)	
Unexplained fever or bone pain, progressive weight loss, and sweats	Increasing WBC count unresponsive to therapy
Increasing spleen size (can also result in splenic infarction)	Peripheral blood basophils ≥20%
	Persistent thrombocytopenia ($<100\times10^9$/L) unrelated to therapy, or persistent thrombocytosis ($>1{,}000\times10^9$/L) unresponsive to therapy
	Blasts 10% to 19% of WBCs in peripheral blood and/or nucleated bone marrow cells
	Cytogenetic evidence of clonal evolution
Blast phase	
Bleeding, bruising, bone pain	Blasts ≥20% of peripheral blood white cells or of nucleated bone marrow cells
Infections	Extramedullary blast proliferation
Prominent constitutional symptoms	Large foci or clusters of blasts in the bone marrow biopsy
Massive splenomegaly	
Tissue manifestations of extramedullary disease	

Table (1) Clinic pathological features of chronic-, accelerated-,and blast-phase **in** CML **(8)**

Pathophysiology

CML was the first cancer to be linked to a clear genetic abnormality, the chromosomal translocation known as the Philadelphia chromosome. This chromosomal abnormality is so named because it was first discovered and described in 1960 by two scientists from Philadelphia, Pennsylvania, USA: Peter Nowell of the University of Pennsylvania and David Hungerford of Fox Chase Cancer Center **(9).**