Study of PTCH1 Gene as a Prognostic Marker to Predict Imatinib Response on Egyptian CML Patients in Chronic Phase

Thesis

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List of Abbreviations

Abb.	Full term
ABMT	*Autologous bone marrow transplantation*
ACAs	*Additional chromosomal abnormalities*
ALL	*Acute lymphoblastic leukemia*
alloSCT	*Allogeneic stem cell transplantation*
AML	*Acute myeloid leukemia*
AP	*Accelerated phase*
BCC	*Basal cell carcinoma*
BP	*Blast phase*
BUS	*Busulfan*
CCyR	*Complete cytogenetic response*
CHR	*Complete hematologic response*
CIBMTR	*Center for international blood and marrow transplant research*
CML	*Chronic myeloid leukemia*
CNL	*Chronic Neutrophilic Leukemia*
CP	*Chronic phase*
CTL	*Cytotoxic T lymphocytes*
DLI	*Donor lymphocyte infusion*
EBMT	*European Society for Blood and Marrow Transplantation*
ELN	*European leukemia.Net*
ET	*Essential thrombocytosis*
FISH	*Fluerescence in situ hybridization*
GVHD	*Graft versus host disease*
GVL	*Graft versus leukemia*
Hh pathway	*Hedgehog signaling pathway*
HU	*Hydroxyurea*
MMR	*Major molecular response*

List of Abbreviations cont...

Abb.	Full term
NCCN	*National comperhensive cancer network*
OS	*Overall survival*
PAH	*Pulmonary arterial hypertension*
PCR	*Polymerase chain reaction*
Ph	*Philidelphia chromosome*
TFR	*Treatment-free remission*
TKI	*Tyrosine kinase inhibitors*
TRM	*Transplantation-related mortality*
TSG	*Tumor suppressor gene*
WHO	*World health organization*

INTRODUCTION

Chronic myelogenous leukemia (CML), also known as chronic myeloid leukemia, is a myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate. It accounts for 20% of all leukemia's affecting adults ***(Radich, 2018).***

The clinical manifestations of CML are insidious, changing somewhat as the disease progresses through its 3 phases (chronic, accelerated, and blast). Signs and symptoms in the chronic phase are Fatigue, weight loss, Low-grade fever and splenomegaly on routine assessment***(Radich, 2018).***

Chronic myeloid leukemia (CML) was the first human malignancy to be associated with a specific genetic lesion, the Philadelphia chromosome, harboring the BCR-ABL oncogene. Since then, it has become a paradigm for the discovery of molecular mechanisms and targeted therapeutic approaches in the field of hematologic neoplasias ***(Sawyers, 1999).***

The median age of onset of CML is 50 years; the peak incidence occurs between ages 50 and 60. There is no sex preference. The first phase of the disease, the chronic phase, terminates in a second, more acute or abrupt course, called the blast phase. Sometimes there is an intervening short-lived phase between the chronic and blast phases called the

accelerated phase, characterized by a more gradual increase in blast cells in the peripheral blood, progressive anemia, thrombocytopenia, and increasing splenomegaly. The median survival approximates 3 to 5 years ***(Sawyers, 1999).***

CML is often suspected on the basis of a complete blood count, which shows increased granulocytes of all types, typically including mature myeloid cells. Basophils and eosinophils are almost universally increased; this feature may help differentiate CML from a leukemoid reaction ***(Tefferi, 2006).***

CML is characterized by a balanced genetic translocation, t (9;22)(q34;q11.2), involving a fusion of the Abelson gene (ABL1) from chromosome 9q34 with the breakpoint cluster region (BCR) gene on chromosome 22q11.2. This rearrangement is known as the Philadelphia chromosome (ph) ***(Jabbour and Kantarjian, 2018).***

The BCR-ABL1 fusion gene results in the formation of a unique gene product, the BCR-ABL1 fusion protein.This protein product includes an enzymatic domain from the normal ABL1 with tyrosine kinase catalytic activity, It is this deregulated tyrosine kinase that is implicated in the pathogenesis of CML ***(Druker, 2001).***

The medications used for patients with CML aim at delaying the onset of the accelerated or blastic phase. This has

traditionally included a myelosuppressive agent to achieve hematologic remission, but more effective drugs—successively, interferon alfa then and targeted therapy with tyrosine kinase inhibitors such as imatinib mesylate, have gained greater importance. Chemotherapy may be used, particularly in preparation for bone marrow or hematopoietic stem cell transplantation. Cytogenetic monitoring was required at 3, 6, 12, and 18 months. Molecular monitoring was required every 3 months. On the basis of the degree and the timing of hematologic, cytogenetic, and molecular results, the response to first-line imatinib was defined as optimal, suboptimal, or failure ***(Baccarani, 2009).***

The PTCH1 gene provides instructions for producing the patched-1 protein, which functions as a receptor. Receptor proteins have specific sites into which certain other proteins, called ligands, fit like keys into locks. A protein called Sonic Hedgehog is the ligand for the patched-1 receptor. Together, ligands and their receptors trigger signals that affect cell development and function. PTCH1 is called a tumor suppressor gene. It's Cytogenetic Location: 9q22.32, which is the long (q) arm of chromosome 9 at position 22.32 ***(Adolphe, 2006).***

PTCH1 expression at diagnosis should be considered a promising molecular marker for predicting the probability of imatinib response in patients with CP-CML. These findings may facilitate clinicians' ability to tailor a first-line TKI treatment to the individual patient. PTCH1 expression does not