Prognostic Significance of Early Molecular Response in Patients Diagnosed with Chronic Myeloid Leukemia in Chronic Phase Treated with Nilotinib as a First-Line Therapy

Thesis

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By

Ahmed Youssri Elsaed

M.B.B.CH

Supervised by

Prof. Dr. Mohammed Osman Azzazi
Professor of Internal Medicine, Clinical Hematology and BMT
Faculty of Medicine, Ain Shams University

Prof. Dr. Mohamed Abdelmooti Mohamed Samra
Professor of Medical Oncology, Clinical Hematology and BMT
NCI, Cairo University

Dr. Mohammad Abdallah Shazly
Lecturer of Internal Medicine and Clinical Hematology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
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List of Abbreviations

Abbr.	Full term
ACA/Ph+	Additional chromosome abnormalities in Philadelphia-positive cells
ACAs	Additional chromosomal abnormalities
ALL	Acute lymphoblastic leukaemia
AlloSCT	Allogeneic stem cell transplantation
AML	Acute myeloid leukaemia
AP	Accelerated phase
BCR	Breakpoint cluster region
BCR-ABL	Breakpoint cluster region–Abelson
BMT	Bone marrow transplantation
BP	Blastic phase
BUS	Busulfan
CalB	Calcium binding
CCyR	Complete cytogenetic response
CE	Clonal evolution
cGVHD	chronic graft-versus-host-disease
CHR	Complete hematologic response
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CP	Chronic phase
ELN	European Leukemia Net
EMR	Early molecular response
ESMO	European Society for Medical Oncology
EUTOS	European Treatment and Outcome Study
FISH	Fluorescence in situ hybridization
GIMEMA	Gruppo Italiano Malattie Ematologiche dell'Adulto
Hb	Hemoglobin
hOCT1	Human organic cation transporter 1

HSCs	Hematopoietic stem cells
HU	Hydroxyurea
IBMTR	International Blood and Marrow Transplant Registry
IBMTR	International Blood and Marrow Transplant Registry
LPCs	Leukemia progenitor cells
MDACC	M.D. Anderson Cancer Center
MMR	Major molecular response
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
OS	Overall survival
PB	Peripheral blood
PCR	Polymerase chain reaction
PFS	Progression-free survival
Ph	Philadelphia
rIFNα	recombinant interferon-alfa
RT-PCR	Reverse transcriptase polymerase chain reaction
Scr	Serum creatinine
TKIs	Tyrosine kinase inhibitors
TLC	Total leucocytic count
UA	Uric acid
WBC	White blood cell
WHO	World Health Organization

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Abstract

Background: Chronic myeloid leukemia (CML) is a malignant hematologic disease that arises from the pluripotent hematopoietic stem cells. According to the guidelines issued by the European LeukemiaNet (ELN), BCR-ABL transcript levels on the international scale ($BCR\text{-}ABL^{IS}$) at 3 and 6 months are defined as indicators of the early efficacy of first-line TKI treatment. A $BCR\text{-}ABL^{IS} \leq 10\%$ after 3 months of TKI treatment or $BCR\text{-}ABL^{IS} < 1\%$ after 6 months of treatment indicates an optimal response to TKI therapy with no need to adjust the therapeutic strategy.

Objectives: The present study aimed to investigate the impact of early molecular response (EMR; BCR-ABL ≤ 10% on the International scale [BCR-ABLIS] at 3 or 6 months) on outcomes in patients with newly diagnosed chronic myeloid leukemia in chronic phase treated with Nilotinib.

Patients and Methods: The present study was enrolled from 2018 to 2020 at Nasser Institute for Research and Treatment and the National Cancer Institute. This is a prospective cohort study done on (94) newly diagnosed cases of CML in Chronic Phase.

Results: Results of the current study showed that (74.5%) of the studied cases were male. Baseline serum creatinine (Scr) was ≥1.4 mg/dL in (62.8%) of the studied cases. eosinophilia was present in only (12.8%). In the present study, Baseline uric acid (UA) was <6 mg/dL in (62.8%) of the studied cases. Baseline peripheral blasts were <5% in (86.2%) of the studied cases. Splenomegaly was present in only (3.2%) of the studied cases. Age at diagnosis was <55 in (87.2%) of the studied cases. The present study results showed that, in cases not achieved EMR; the majority (75%) had Scr <1.4 mg/dL, while in cases achieved EMR (64.4%) had Scr ≥1.4 mg/dL. There was none statistically significant difference between the two groups regarding baseline Scr.

Conclusion: Early molecular response (EMR) is an important prognostic significance for CML patients treated with Nilotinib. Patients who achieved EMR had significantly better outcomes. Achieving MR3.0 should be a priority in CML-CP patients who have a 3-month BCR-ABL ≤ 10% and 6-month BCR-ABL ≤ 10%.

Keywords: Early Molecular Response, Chronic Myeloid Leukemia, Chronic Phase, Nilotinib, First-Line Therapy

INTRODUCTION

Chronic Myeloid Leukaemia (CML) is the paradigm of bench-to-bedside translational research ***(Freireich et al., 2014).***

CML was between the first cancers to be clearly associated with a genetic lesion, namely the Philadelphia Chromosome, able to generate the chimeric BCR-ABL protein. A plethora of studies with cellular and murine models ***(Sontakke et al., 2016)*** converged on the assumption that one single oncogenic gene - BCR-ABL - can drive a potent leukaemogenic signal ***(Melo and Barnes, 2007).***

Since their introduction in 2001, tyrosine kinase inhibitors (TKIs) targeting BCR-ABL had become the standard therapy for CML. While allogeneic hematopoietic stem cell transplant (Allo-HSCT) is a recognized curative treatment for CML ***(Barrett and Ito, 2015)***, TKIs prevent progression to advanced phase in most patients and spectacularly improve the disease burden and the overall survival of CML patients ***(Baccarani et al., 2013; Marin, 2012).***

On TKI treatment monitoring, the BCR-ABL transcripts were recommended to be measured every three months to determine whether patients reach the molecular remission or not ***(Hochhaus et al., 2017).***

This diagnostic test was suggested to perform on the real-time quantitative polymerase chain reaction which is the current standard technique. Although the peripheral blood cells were approved recently as a sample source for BCR-ABL quantification, the diagnostic test performed on bone marrow cells still remains as the gold standard method ***(Hochhaus et al., 2017).***

Besides the BCR-ABL transcripts, the restore of hematopoiesis to normal, and some related immune cells such as neutrophils, blast cells, and basophils were used in response evaluation for CML ***(Chikkodi et al., 2015; Brück et al., 2018).***

AIM OF THE WORK

To investigate the impact of early molecular response (EMR; BCR-ABL ≤ 10% on the International scale [BCR-ABLIS] at 3 or 6 months) on outcomes in patients with newly diagnosed chronic myeloid leukemia in chronic phase treated with Nilotinib.

Review Of Literature

CHRONIC MYELOID LEUKEMIA (CML)

Leukemia:

Leukemia is the 9th most common cancer in the United States and the 6th leading cause of cancer-related death with an incidence and mortality rates of 13.8 and 6.7 persons per 100,000 respectively ***(Noone et al., 2018).***

Over the past several decades, despite advances in cancer diagnosis and treatment, leukemia incidence had continued to rise at 0.3% per year for the past decade with only an overall improvement in survival of about 1.5% annually ***(National Cancer Institute, 2018).***

There are four main subtypes: chronic myeloid leukaemia (CML), chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML), and acute lymphoblastic leukaemia (ALL). The incidence, clinical presentation, and survival all vary by subtype ***(Cancer Research UK Cancer statistics, 2014).***

Chronic Myeloid Leukemia (CML):

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm with an incidence of one to two cases per 100,000 adults ***(American Cancer Society, 2015).***

Chronic myeloid leukemia (CML) is a widely described malignant disorder of hematopoietic stem cells (HSCs) that accounts for 15%–20% of all cases of leukemia in adults ***(Soverini et al., 2016).***

The main history of CML begins in 1960 when Peter Nowel and David Hungerford discovered an abnormally small G-group chromosome – now called the Philadelphia (Ph) chromosome. This was the first proof that the disease results in some changes to DNA. In 1973, Janet Rowley recognized that the Ph chromosome was the product of a t(9;22)(q34;q11) reciprocal translocation between chromosomes, and then later in the 1980s, Nora Heisterkamp discovered that this translocation generates the *BCR–ABL* fusion oncogene ***(Goldman , 2010).***

Epidemiology

Chronic myeloid leukemia (CML) has a worldwide annual incidence rate of 0.87 people per 100,000 increasing