Bcr – Abl Mutations in Chronic Myeloid Leukemia

M.Sc. Thesis

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`The longer you can look back - the further you can look forward'

Winston Churchill
Addressing the Royal College of Physicians,
London 1944.

At the time that Churchill was speaking in 1944, leukemia was a fatal disease that had been identified 100 years before. The disease was described as the dreaded leukemias, sinister and poorly understood.

بسم الله الرحمن الرحيم

قَالَ رَبِّ اشْرَحْ لِي صَدْرِي # وَيَسِّرْ لِي أَمْرِي

وَاحْلُلْ عُقْدَةً مِّن لِّسَانِي # يَفْقَهُوا قَوْلِي

صدق الله العظيم

سورة طه (٢٥ : ٢٨)

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To all of them, I am greatly indebted …

Amr

This Work is dedicated

To…

My Parents …

My Brothers …

And to everyone who helped me accomplish this work …

Abstract

Chronic myeloid leukemia is one of the myeloproliferative disorders characterized by t(9;22)(q34;q11) known as Philadelphia chromosome. This leads to the formation of a fusion gene Bcr-Abl tyrosine kinase having properties necessary for malignant transformation. Imatinib is a leading tyrosine kinase inhibitor that showed marked cytogenetic responses, but sometimes out casted by presence of resistance. Resistance has been traced mainly to occurrence of mutations within Bcr-Abl domain making it insensitive to Imatinib. Our aim is to determine the presence of Bcr-Abl kinase domain mutations among chronic myeloid leukemia patients before and during therapy with Imatinib. 24 patients at different phases of the disease were recruited and mutation analysis was done using ASO-PCR for 3 mutations: T315I, M351T, and E255K. One patient with accelerated phase CML demonstrated presence of M351T mutation and switched to second generation tyrosine kinase inhibitor Nilotinib. Further large scale studies are recommended to detect presence of Bcr-Abl mutations and assess their frequency among Egyptian chronic myeloid leukemia.

Key words:

- Bcr-Abl.
- Mutations.
- Imatinib.
- CML.

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aCML	Atypical chronic myeloid leukemia
ALL	Acute lymphoblastic leukemia
Allo-SCT	Allogeneic stem cell transplantation
A-loop	Activation loop
AML	Acute myeloid leukemia
A-MuLV	Abelson murine leukemia virus
AP	Accelerated phase
ATP	Adenosine triphosphate
ATR	Ataxia telangiectasia related protein
BCR	Breakpoint cluster region
BCR-ABL	Break point cluster region - Abelson murine leukemia
BM	Bone marrow
BMT	Bone marrow transplant
BP	Blastic phase
CBL	Casitas B-lineage lymphoma
CCR	Complete cytogenetic response
CCyR	Complete cytogenetic response
CEL	Chronic eosinophilic leukemia
CG	Cytogenetic
CgR	Cytogenetic Response
CHR	Complete hematologic response
CML	Chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia

CMPD	Chronic myeloproliferative disorders
C-myc	Cellular myelocytomatosis viral oncogene
CNL	Chronic neutrophilic leukemia
CR	Cytogenetic response
CP	Chronic phase
CYP 450	Cytochrome P450
DLI	Donor lymphocyte infusion
DNA	Deoxyribonucleic acid
ET	Essential thrombocythemia
FAK	Focal adhesion kinase
FDA	Food and Drug Administration
FISH	Fluorescent in-situ hybridization
FTI	Farnesyl transferase inhibitors
GIT	Gastro intestinal tract
GIST	Gastrointestinal stromal tumor
GM-CSF	Granulocyte Macrophage - Colony Stimulating Factor
GST	Glutathione S -Transferase
GTP	Guanosine triphosphate
GvHD	Graft versus host disease
GVL	Graft versus leukemia
HES	Hypereosinophilic syndrome
HHT	Homoharringtonine
HLA	Human leukocyte antigen
HOXA9	Homeobox gene A9