Bruton's Tyrosine Kinase (Btk) and Nuclear Factor–Kappa B (NF-κB) Genes Expression: Prognostic Biomarkers in Pediatric B-Cell Acute Lymphoblastic Leukemia

Thesis

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Mona Ahmed

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List of Abbreviations

ABL1..... Abelson Murine Leukemia Viral Oncogene

AF4.....ALL Fusion Gene on Chromosome 4

AKT/m TOR.....Protein Kinase/Mammalian Target of Rapamycin

ALL.....Acute Lymphoblastic Leukemia

AML.....Acute Myeloid Leukemia

AML1.....Acute Myeloid Leukemia 1

AP..... Purinic/ pyrimidinic

ARNT.....Aryl Hydrocarbon Nuclear Translocator

ASCT .....Autologous Stem Cell Transplant

ATP.....Adenosine Triphosphate

BCP .....B-Cell Precursor

Bcr.....Breakpoint Cluster Region

BM.....Bone Marrow

Btk .....Bruton's Tyrosine Kinase

C.....Cytosine

CBC .....Complete Blood Count

CBF B.....Core Binding Factor B

CD .....Cluster of Differentiation

CNS .....Central Nervous System

COG.....Children's Oncology Group

CPTK.....Cytoplasmic PTK

CR .....Complete Remission

\\CRLF2 .....Cytokine Receptor Like Factor 2

CRLF2 .....cytokine Receptor-Like Factor 2

CSF.....Cerebrospinal Fluid

List of Abbreviations

CYP ..... Cytochrome P450

CYP1A1 .....Cytochrome P450 A1

DFS .....Disease Free Survival

DNA .....Deoxyribonucleic Acid

E2A, TCF3.....Early Region 2A, Transcription Factor 3

EBV .....Epstein Barr Virus

EDTA.....Ethylene Diamine Tetra-Acetic Acid

EGIL .....European Group for Immunological Classification of Leukemia

EPOR.....Erythropoietin Receptor

ETV6 .....Ets Variant 6

FAB .....French-American-British

FAD .....Flavin Adenine Dinucleotide

FISH .....Fluorescence in Situ Hybridization

FLT-3.....Fms-Like Tyrosine Kinase

G.....Guanine

GGR.....Global Genomic Repair

GST .....Glutathione S-Transferase

GSTP1 .....Glutathione S-transferase Pi Family

HIV .....Human Immunodeficiency Virus

HOX.....Homebox Gene

HTLV .....Human T. lymphotropic Virus

iAMP21.....Intrachromosomal Amplification of hromosome 21

IGH.....Immunoglobulin Heavy Chain Locus

IKAROS (IKZF) .....Ikaros Family Zinc Finger Gene

IL3.....Interlukins 3

IL7.....Interlukins 7

List of Abbreviations

ITD .....Internal Tandem Duplications

JAK2 .....Janus Kinase2

KMT2A .....Lysine Methyltransferase 2A-Protien Coding Gene

LAIPs.....Leukemia - Associated Phenotypic Markers

M-bcr.....Major Breakpoint Cluster Region

MLL .....Mixed-Lineage-Leukemia

MRD .....Minimal Residual Disease

MYC.....Myelocytomatosis Viral Oncogen

NADPH .....Nicotinamide Adenine Dinucleotide Phosphate

ND .....Newly Diagnosed

NER.....Nucleotide Excision Repair

NF-κB .....Nuclear Factor Kappa B

NGS .....New Generation Sequencing

NHEJ.....Non Homologous End Joining

NOS .....Not Otherwise Specified

OS.....Overall Survival

PAH .....Poly Aromatic Hydrocarbons

PAR1 .....Pseudoautosomal Region 1

PAS.....Periodic Acid Schiff

PAX 5 .....Paired Box 5

PBX1 .....Pre-B Cell Leukemia Transcription Factor 1

PCR .....Polymerase Chain Reaction

PDGFR.....Platelet-Derived Growth Factor Receptor

Ph.....Philadelphia

List of Abbreviations

PI3K .....Phosphoinositide 3-Kinase

POG .....Pediatric Oncology Group

pre-B-ALL .....Precursor B-Acute Lymphoblastic Leukemia

PTD .....Partial Tandem Replication

PTKs.....Protein Tyrosine Kinases

Q-RT PCR.....Quantitative Reverse Transcriptase Polymerase Chain Reaction

RAS .....Family of Retovirus-Associated DNA Sequences

Ras/Raf/MEK .....Chain of Proteins in the Cell Communicating Signals

RLT .....RPTK Receptor PTK

ROS .....Reactive Oxygen Species

RUNX1.....Runt-Related Transcription Factor 1

SJCRH.....St. Jude Children's Research Hospital

SNP.....Single Nucleotide Polymorphism

STAT .....Signal Transducer and Activator of Transcription

T.....Thymidine

T-ALL.....T-acute Lymphoblastic Leukemia

TCF3 .....Transcription Factor 3 (E2A Immunoglobulins Enhancer Binding factors)

TCR .....T Cell Receptor

TdT.....Terminal Deoxy Nucleotidyl Transferase

TEL.....Translocation-ETS-Leukemia

TKIs.....Tyrosine Kinase Inhibitors

List of Abbreviations

TLRs.....Toll Like Receptors

TLX1 .....T-cell Leukemia Homebox1

TLX3 .....T-cell Leukemia Homebox3

TP53.....Tumor Protein 53

TSLPR .....Thymic Stromal Lymphopoietin Receptor

UV.....Ultraviolet Rays

VEGFR.....Vascular Endothelial Growth Factor Receptor

WBC.....White Blood Cells

WHO .....World Health Organization

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a malignant disorder of lymphoid progenitor cells characterized by diverse cytogenetic and molecular abnormalities. It affects both children and adults, with peak prevalence in children of 2 to 5 years old and adults older than 50 years ***(Pui et al., 2008).*** Risk-adapted chemotherapy can cure more than 80% of childhood cases, but still 20% to 30% of cases relapse, with the development of serious complications including death ***(Pui, 2007).*** Moreover, the outcome of adult ALL patients are much poorer than that of children ***(Garza-Veloz et al., 2015).***

Deregulation in gene expression of several key cellular pathways has been suggested as a useful tool to define prognosis and identify novel therapeutic targets for ALL ***(Yoho et al., 2002).*** Advances in the understanding of the pathobiology of ALL proposed that drugs which specifically target the genetic defects of leukemia cells could revolutionize the management of this disease (***Pui et al., 2008).***

Bruton's tyrosine kinase (Btk), a member of the Tec family kinases, is a cytoplasmic protein expressed mainly in hematopoietic cells, except T cells ***(Smith et al., 2011).*** Btk is involved in B-cell antigen receptor (BCR) signaling ***(Tao et al., 2016)***, where gene mutation or loss of function