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MOLECULAR CYTOGENETIC STUDY AND CLINICAL RELEVANCE OF CHROMOSOMAL ABNORMALITIES; t(1;19), MLL GENE REARRANGEMENT AND P53 ALTERATION IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Thesis

Submitted in Partial Fulfillment of the Requirements of the MD Degree in

" CLINICAL PATHOLOGY"

By

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بسم الله الرحمن الرحيم

*قالوا سبحانك لا علم لنا إلا ما علمتنا إنك
أنت العليم الحكيم*

صدق الله العظيم

سورة البقرة (٣٢)

TO
THE SOUL
OF MY FATHER

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To **ALLAH,** *everything in life is resumed. In this work he has helped me a lot. He offered me what I did not know and which I have to know. Hence, if only one to be thanked, God is the first and the last. Then those offered by God to advise and guide me have to be thanked.*

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CONTENTS

List of abbreviations

ALL.....Acute lymphoblastic leukemia.

BCR.....Break point cluster region.

bp.....base-pair.

CALLA.....Common acute lymphoblastic leukemia antigen.

CD..... Cluster designation.

cDNA..... Complementary deoxyribonucleic acid.

CR.....Complete remission.

CyIgM.....Cytoplasmic immunoglobulin.

der.....Derivative chromosome.

DFI.....Disease – free interval.

EFS.....Event – free survival.

FCS.....Fetal calf serum.

FISH.....Fluorescence in situ hybridization.

G_1/S.....Gap –1 phase / synthesis phase of cell cycle.

HLA-DR....Human leukocyte antigen –DR.

HLH.....Helix –Loop –Helix.

ISCN.....International system for human cytogenetic nomenclature.

kb.....Kilo base.

KD.....Kilo Dalton.

LDH.....Lactate dehydrogenase.

LSI.....Locus specific identification.

Mb.....Mega base.

M-bcr.....Major break point cluster region.

m-bcr..... Minor break point cluster region.

M-FISH....Multicolor FISH.

MIC.....Morphologic, immunophenotyping and cytogenetic.

MLL.....Myeloid lymphoid leukemia gene.

MNCs.....Mononuclear cells.

mRNA.....Messenger ribonucleic acid.

MT.....Methyl transferase.

OS.....Overall survival.

PAS.....Periodic acid schiff.

PBS.....Phosphate buffered saline.

Ph.....Philadelphia chromosome.

PHA.....Phytohemagglutinin.

PTD.....Partial tandem duplication.

Rb.....Retinoblastoma gene.

rpm.....Round per minute.

RT-PCR....Reverse transcriptase polymerase chain reaction.

sIg.....Surface immunoglobuline.

SSC.....Standard citrate saline.

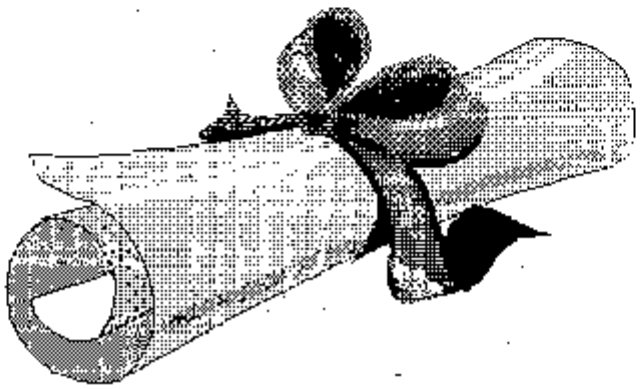
t(1;19).....Translocation between chromosomes, 1 & 19.

TCR.....T- cell receptors.

TdT.....Terminal deoxynucleotydyl transferase.

Topo-II.....Topoisomerase II inhibitors.

WCPs.....Whole chromosome paints.



INTRODUCTION AND AIM OF THE WORK

Introduction and aim of the work

Acute lymphoblastic leukemias (ALL) are characterized by clonal proliferation, accumulation and tissue infiltration of neoplastic cells. They are mainly regarded as childhood disease, where they represent about 75% of childhood leukemias *[Young et al., 1986]*.

The majority of cases of ALL demonstrate an abnormal karyotype, either in chromosome number or as structural changes such as translocations, inversions or deletions *[Faderl et al., 1998]*.

The chromosomal translocation, t(1;19)(q23;p13) was confirmed as one of the most common recurring translocations in childhood ALL, with a frequency of 5-6% *[Pui & Crist, 1992]*. A strong association exists between t(1;19) and pre-B ALL, especially in children, where this translocation is present in 25-30% of cases *[Carrol et al., 1984]*.

Abnormalities of 11q23 are among the most frequent cytogenetic abnormalities found in 60-70% of ALL in infants *[Chen et al., 1993]*. Their frequency in older children with ALL is lower "up to 10%" *[Super et al., 1993]*. The common molecular denominator is the disruption of a gene located at band q23 of chromosome 11 which was identified as "mixed lineage leukemia" or "myeloid-lymphoid leukemia gene" {MLL gene} *[Ziemin-Van der Poel et al., 1991]*.

The p53 gene is located on the short arm of chromosome 17, band p13.1, and it codes for a nuclear DNA-binding phosphoprotein *[Levine et al., 1991]*. It is one of the tumor suppressor genes whose expression can block the development of the tumorigenic phenotype *[Hollstein et al., 1993]*.

Alterations of p53 have been reported in several types of hematologic malignancies *[Felix et al., 1992]*. There is a correlation between p53 alteration and progressive or relapsing disease especially in T-cell ALL *[Hsiao et al., 1994]*.

Improvement in cytogenetic techniques have yielded significant insight as to the importance of cytogenetic abnormalities in the pathophysiology, choice of treatment and prognosis of hematologic malignancies *[Faderl et al., 1998]*.

The aims of this study are: Detection of incidence of chromosomal abnormalities; t(1;19), MLL gene rearrangement and P53 alterations in de novo, remitted and relapsed ALL patients, investigating their relations with the clinical and laboratory findings in these patients and evaluating their prognostic value.