Cytochrome P_{450} 3A4 gene Polymorphism among Egyptian Children with Acute lymphoblastic Leukemia

Thesis

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بسم الله الرحمن الرحيم
وأنزل الله عليك
الكتاب والحكمة
وعَلَّمَكَ مَا لَمْ تَكُنْ
تَعْلَمُ وكَانَ فَضْلُ اللهِ
عَلَيْكَ عَظِيماً
صدق الله العظيم
سورة النساء الآية
(113)

*Thanks to **ALLAH** who helped me to accomplish this work*

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List of Abbreviations

ALL	: Acute lymphoblastic leukaemia
AML	: Acute myolegenous leukemia
AML	: Myeloid leukemia
BFM	: Berlin-Frankfurt-Muenster
CCG	: Children's Cancer Group
CNS	: Central nervous system
CNS	: Central Nervous System
COG	: Children's Oncology Group
CR	: Complete remission
CSF	: Cerebrospinal fluid
CYP3A4	: Cytochrome P450, family 3, subfamily A, polypeptide 4
DFCI	: Dana-Farber Cancer Institute
DFS	: Disease-free survival
EBV	: Epstein-Barr virus
EFS	: Event-free survival
FAB	: French-American-British
FCM	: Flow cytometry
FISH	: Fluorescence in situ hybridization
GST	: Glutathione S-transferase
HIV	: Human immunodeficiency virus
HTLVI & II	: Human lymphotropic viruses I and II
IM	: Intramuscular
M : E	: Myeloid to erythroid ratio
MILL	: Mixed lineage leukemia
MRC	: Medical Research Council
MRD	: Minimal residual disease
NG2	: Neural-glial antigen 2
PCR	: Polymerase chain reaction
POG	: Pediatric Oncology Group
RB	: Retinoblastoma protein
SJCRH	: St. Jude Children's Research Hospital
SNPs	: Simple nucleotide polymorphisms
WBC	: White blood cell count

List of Tables

List of Tables *(Cont.)*

List of Tables *(Cont.)*

List of Tables *(Cont.)*

List of Figures

List of Figures

Figure No.	Title	Page No.

List of Contents

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common paediatric cancer with a cure rate of approximately 80%. Relapse occurs despite treatment stratification based on clinical criteria ***(Aplenc et al., 2003).***

Several biological risk factors for relapse, such as age, sex, initial white blood cell count and translocation (9;22) modify relapse risk ***(Pui & Evans, 1998).*** Other factors, such as ethnicity, have a controversial impact on relapse risk ***(Pui et al., 1995), (Bhatia et al., 2002).***

Relapse risk in ALL may be also related to simple nucleotide polymorphisms (SNPs) of enzymes that metabolize chemotherapeutic agents ***(Aplenc et al., 2003).*** Simple nucleotide polymorphisms (SNPs) in drug metabolizing enzymes may alter the metabolism of chemotherapy agents and modify the risks of relapse and toxicity ***(Relling & Dervieux, 2001).***

Cytochrome P450, family 3, subfamily A, polypeptide 4 (CYP3A4), a member of the cytochrome P_{450} mixed-function oxidase system, is the most abundant hepatic and intestinal P450 enzyme and is involved in the metabolism of more than 50% of all drugs used in humans including glucocorticoids such as dexamethasone, phenobarbital, and anticancer drugs such as ifosfamide, etoposide, doxorubicin and taxol ***(Li et al., 1995).***

Recently CYP3A4 has also been identified in the brain, however its role in the central nervous system is still unknown ***(Robertson et al., 2003).***

CYP3A4 protein is encoded by the CYP3A4 gene ***(Hashimoto et al., 1993).*** This gene is part of a cluster of cytochrome P_{450} genes on chromosome 7q21.1 ***(Inoue et al., 1992).*** Most drugs undergo deactivation by CYP3A4, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYP3A4 to form their active compounds, and many protoxins being toxicated into their toxic forms.

While over 28 single nucleotide polymorphisms (SNPs) have been identified in the CYP3A4 gene, it has been found that this does not translate into significant inter individual variability *in vivo*. It can be supposed that this may be due to the induction of CYP3A4 on exposure to substrates.

Most frequent CYP3A4 polymorphism is a -392A>G substitution (CYP3A4*1B) in a 5regulatory element that exhibits frequencies ranging from 0.0% among Chinese-Americans to 54.6% among black Americans ***(Lamba et al., 2002), (Rebbeck et al., 1998), (Kuehl et al., 2001), (Paris et al., 1999).***

Studies of the relationship of this polymorphism to gene expression and substrate metabolism have been inconclusive ***(Lamba et al., 2002).*** However, CYP3A41B has been associated with a higher clinical stage and grade of prostate cancer ***(Plummer et al., 2003),*** the presence of distant metastatic disease in osteosarcoma ***(Dhaini et al., 2003),*** increased risk of small cell lung cancer ***(Dally et al., 2003)*** and indeed the occurrence of treatment related leukemia ***(Felix et al., 1998).***

Aim of the Study

The aim of this study is:

1- To clarifythe prevalence of CYP3A4 genotype among Egyptian children with acute lymphoblastic leukemia in comparison to healthy control.

2- To explore whetherthe polymorphism of CYP3A4 is related to the response to chemotherapy and risks of relapse.

Acute Lymphoblastic Leukemia

Definition:

Acute lymphoblastic leukemia (ALL) is a malignant proliferation of lymphoid cells blocked at an early stage of differentiation. ALL is a biologically heterogeneous disorder, so that morphologic, immunologic, cytogenetic, biochemical, and molecular genetic characterizations of leukemia lymphoblasts are needed to establish the diagnosis or to exclude other possible causes of bone marrow failure and, finally, to classify ALL subtypes. This heterogeneity reflects the fact that leukemia may develop at any point during the multiple stages of normal lymphoid differentiation ***(Conter et al., 2004).***

Epidemiology:

Acute leukemia, the most common form of cancer in children, comprises approximately 30 percent of all childhood malignancies, with acute lymphoblastic leukemia (ALL) being five times more common than acute myeloid leukemia (AML). Each year in the United States approximately 2500 to 3500 new cases of ALL are diagnosed in children. Survival rates for leukemia have improved dramatically since the 1980s, with a current five-year survival rate of approximately 78 percent. This improvement is in large part because of treatment of large numbers of children with sequential standardized research protocols. Approximately 75 to 80 percent of children with newly diagnosed ALL participate in clinical research trials, the