Cytogenetic Analysis of Acute Myeloid Leukemia with t(8;21): Its Clinical Correlation with Loss of X Chromosome and Del (9q)

Thesis

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List of Abbreviations

Abb.	Full term
AML	*Acute myeloid leukemia*
ANC	*Absolute neutrophil count*
AT	*Adenine and thymine*
BM	*Bone marrow*
BMT	*Bone marrow transplantation*
c DNA	*Complementary DNA*
CBC	*Complete blood count*
CBF	*Core binding factor*
CBFB	*CBF subunit beta*
CDR	*Commonly deleted region*
CEBPA	*CCAAT/Enhancer-Binding Protein Alpha*
CEP	*Centromeric Enumeration Probe*
CNS	*Central nervous system*
CR	*Complete remission*
CSF2RA	*Colony-stimulating factor 2 receptor alpha*
DAPI	*4',6-diamidino-2-phenylindole*
del	*Deletion*
der	*Derivative*
DFS	*Disease free survival*
DNA	*Deoxyribonucleic acid*
DW	*Distilled water*
EDTA	*Ethylene Diamine Triacetic Acid*
ETO	*Eight twenty One*
FAB	*French American British*
FBS	*Fetal bovine serum*
FCM	*Flow cytometry*
FCS	*Fetal Calf Serum*
FISH	*Fluorescence in situ hybridization*
FITC	*Fluorescein isothiocyanate*

List of Abbreviations (Cont...)

Abb.	Full term
FLAG/ida	*Fludara, Ara C and Granulocyte/ Idrarubocin*
FLT	*FMS-like tyrosine kinase*
G banding	*Giemsa banding*
GC	*Guanosine and cytosine*
GM-CSF	*Granulocyte-macrophage colony-stimulating factor*
Gro	*Groucho*
Hb	*Hemoglobin*
HLA	*Human leucoycte antigen*
hnRNP	*Heterogeneous nuclear ribonucleoprotein*
HSCT	*Hematopoietic stem cell transplantation*
ILRA	*Interleukin receptor alpha*
inv	*Inversion*
IQR	*Interquartile range*
IR	*Incomplete remission*
KIT	*Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog*
LSI ABL	*Locus Specific Identifier Abelson*
LSI-DF	*Locus-Specific Identifier Dual fusion*
MDS	*Myelodysplastic syndrome*
MEC	*Mitoxontrone, Etoposide and Cyclophosphamide*
MoAbs	*Monoclonal antibodies*
MPO	*Myeloperoxidase*
MRD	*Minimal residual disease*
mRNA	*Messenger Ribonucleic Acid*
NGS	*Next-generation sequencing*
OS	*Overall survival*
PAR	*Pseudoautosomal region*

List of Abbreviations (Cont...)

Abb.	Full term
PB	*Peripheral blood*
PBS	*Phosphate buffered saline*
PC5	*Phycoerythrin-cyanine 5*
PE	*Phycoerythrin*
RAS	*Rat sarcoma viral oncogene homolog*
RNA	*Ribonucleic acid*
RPMI	*Roswell Park Memorial Institute (culture medium)*
RT-PCR	*Reverse transcriptase polymerase chain reaction*
RUNX	*Runt-related transcription factor*
RUNX1T1	*Runt-related transcription factor1 translocation partner 1*
SD	*Standard deviation*
SSC NP	*Saline sodium citrate Nonidet P*
t	*Translocation*
TLC	*Total leucocytic count*
TLE	*Transducin-like enhancer of split*
WBC	*White blood cell*
WHO	*World Health Organization*

INTRODUCTION

Translocation (8;21) is among the most frequent recurrent chromosome aberrations in adult de novo acute myeloid leukemia (AML) ***(Mrózek and Bloomfield, 2008).*** It involves acute myeloid gene 1 (AML1) of chromosome 21 and eight twenty one (ETO) gene of chromosome 8 and it gives rise to AML1–ETO positive AML ***(Fu et al., 2013).***

The majority of patients with t(8;21)(q22;q22) seem to have additional cytogenetic or molecular genetic abnormalities ***(Klug, 2012)***. These aberrations act synergetically with AML1-ETO in leukomogenesis ***(Lin et al., 2008).*** The two most common recurrent cytogenetic abnormalities associated with t(8;21) are loss of a sex chromosome and deletion (9q) ***(Klug, 2012).*** However, their impact on survival is controversial ***(Lin et al., 2008).*** Other abnormalities include trisomy 4 and 8, tetraploid or near-tetraploid clones ***(Reikvam et al., 2011).***

The deletion of the long arm of chromosome 9 (del (9q)) is usually associated with loss of tumor suppressor genes belonging to Groucho (Gro)/ Transducin-like enhancer of split (TLE) family. Gro/TLEs have tumor suppressor-type activities in regulating cell death, apoptosis and cellular proliferation in the context of myeloid cells expressing AML1-ETO ***(Dayyani et al., 2008).***

Therefore, the loss of TLE-1 and TLE-4 results in increased cell division ***(Paschka and Döhner, 2013)*** and significant decrease in apoptosis**.** Whereas, gro3 loss appears to cooperate with AML1-ETO expression to arrest myeloid differentiation and prevent migration into the bloodstream ***(Dayyani et al., 2008).***

X and Y chromosomes are highly divergent in structure, except for short segments of homology called pseudoautosomal regions (PARs) that contain certain genes that may inhibit leukomogenesis by AML1-ETO ***(Matsuura et al., 2012).*** One gene of interest in the PARs is colony-stimulating factor 2 receptor alpha (CSF2RA), which encodes the alpha subunit of the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor ***(Weng et al., 2013)*.**

GM-CSF reduces the self-renewal potential of AML1-ETO expressing cells and promotes myeloid differentiation ***(Weng et al., 2013).*** Thus, the deficiency of GM-CSF signaling may be a contributing factor to t(8;21) induced leukemia ***(Matsuura et al., 2012)*** by blocking of the normal differentiation and creating an enlarged pool of progenitors that are prone to malignant transformation ***(Sharabi et al., 2008)***.

AIM OF THE WORK

This work aims to:

Investigate the effect of additional aberrations (loss of X chromosome and del (9q)) on the clinicopathological and prognostic behavior of t(8;21) de novo AML patients.

Chapter 1
TRANSLOCATION (8;21) ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia is an aggressive clonal neoplasm with maturation arrest in granulopoiesis resulting in accumulation of immature myeloblasts in the bone marrow. Genetically, it is associated with acquired genetic changes in hematopoietic progenitor cells that lead to alteration of the normal mechanisms of proliferation and differentiation ***(Sultan et al., 2016).***

Studies of chromosomal abnormalities by cytogenetics followed by molecular genetics have played a prominent role in decoding the heterogeneity of AML as well as providing a profound insight into the biology of leukemia. Moreover, recurrent chromosomal and molecular abnormalities that are detected at diagnosis have provided valuable prognostic information such as response to induction chemotherapy, relapse risk and overall survival (OS) ***(Ilyas et al., 2015).***

Conventional karyotyping is the cornerstone of risk stratification in AML, classifying AML into favorable, unfavorable and intermediate-risk prognostic groups. The cytogenetic favorable group includes patients with t(15;17)(q22;q12) and the core binding factor AML ***(He et al., 2015).***