STUDY OF IMMUNOGLOBULIN LIKE TRANSCRIPT 3 (ILT3) EXPRESSION IN ACUTE MYELOID LEUKEMIA

Thesis

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List of Abbreviations

AML	Acute myeloid leukemia
APCs	Non-professional antigen presenting cells
APL	Acute promyelocytic leukemia
ATRA	All-trans retinoic acid
B19V	Parvovirus B19
BM	Bone marrow
CBC	Complete blood count
CBF	Core binding factor
CR	Complete remission
CTL	Cytotoxic T-lymphocyte
DCs	Dendritic cells
DIC	Disseminated intravascular coagulopathy
FAB	French-American-British
FCM	Flow cytometry
FcyRIII	Fc portion of IgG
FITC	Fluorescein isothiocyanate
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte-macrophage colony stimulating factor
GVL	Graft-versus leukemia
HLA	Human leukocytic antigen
HSC	Hematopoietic stem cells
IFN-γ	Interferon-γ
IHC	Immunohistochemistry
ILT3	Immunoglobulin Like Transcript 3

List of Abbreviations (Cont...)

ILTs	Immunoglobulin-like transcripts
ITAM	Immunoreceptor tyrosine-based activation motif
ITIM	Immunoreceptor tyrosine-based inhibitory motifs
K	Kappa index
MDCs	Monocytoid dendritic cells
MDS	Myelodysplastic syndrome
MIC	Morphologic-Immunologic Cytogenetic
MoAbs	Monoclonal antibodies
MPO	Myeloperoxidase
MRD	Minimal Residual Disease
NSE	Non-specific esterase
PAS	PeriodicAcidSchiff
PNH	paroxysmal nocturnal hemoglobinuria
r	Pearson's correlation coefficient
RAR	Retinoic acid receptor
RBC	Red blood cells
ROC	Receiver operator characteristics
rs	Spearman's rank correlation coefficient
RT-PCR	Reverse transcriptase-polymerase chain reaction
SBB	Sudan Black B
SPSS	Statistical Program for Social Science
t-AML	AML transformation
TdT)	Terminal deoxynucleotidyltransferase
TLC	The total leucocytic count

List of Abbreviations (Cont...)

TNFs ..... Tumor necrosis factors

WBCs ..... White blood cells

WHO ..... World Health Organization

x^2 ..... Chi-square

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INTRODUCTION

Acute myeloid leukemia (AML) is one of the most common types of leukemias in adults ***(Arber et al., 2008; Foran, 2010).*** Despite major advances in our understanding of the biology of AML, the five- year survival of AML patients is only 20-40%. It has been proposed that AML originates from self renewing hematopoietic stem cells (HSC)/progenitors that have acquired multiple genetic and/or epigenetic changes ***(Becher, 2011).***The heterogeneity of AML is evident from the wide variety of clinical manifestations, phenotypic features and response to therapy ***(Estey and Dohner, 2006; Schlenk et al., 2008; Marcucci et al., 2011).***

In clinical practice, the accurate diagnosis of AML subtypes is essential for risk stratification and treatment planning. The World Health Organization (WHO) and the French-American-British (FAB) classification systems are most commonly used to subtype AML ***(Arber et al., 2008).***

AML with monocytic differentiation includes FAB M4, M5a and M5b subtypes and shows distinct clinical features ***(Tallman, 2004; Dohner et al., 2008).*** Although the expression of some markers by leukemic cells is helpful for lineage assignment. The diagnosis of AML with monocytic differentiation remains challenging ***(Klco et al., 2011).***

Flow cytometry (FCM), is a powerful tool for the investigation of normal and neoplastic cells, and their classification at every level. Therefore, it has great prognostic and therapeutic implications. Its ability to measure multiple parameters (chemical or physical characteristics) on individual cells, in a suspension at high speed, is ideal for the study of leukemic cells. It identifies cell markers by applying monoclonal antibodies against them ***(Pervez et al., 2005).***

The inhibitory receptor Immunoglobulin Like Transcript 3 (ILT3) is a member of immunoglobulin –like transcript (ILT, LIR, or LILR) family and is expressed by dendritic cells, monocytes, endothelial cells and osteoclasts, but not by lymphocytes***(Cella et al., 1997; Kim et al., 2006).*** Dendritic cells expressing high levels of inhibitory receptors ILT3 and ILT4 were shown to induce anergy of CD4+ T helper cells and differentiation of CD8+ T suppressor cells. ***(Anderson and Allen, 2009; Chang et al., 2009).***

Recently ILT3 expression was reported to be a reliable marker that could distinguish AML with monocytic differentiation from other types of AML ***(Dobrowolska et al., 2013).***

AIM OF THE WORK

This study aims to study the pattern of ILT3 expression by leukemic myeloid precursors in AML cases with respect to its different subtypes & clinical relevance.

Chapter 1

ACUTE MYELOID LEUKEMIA

Definition

AML is a malignancy originating from a multipotential hematopoeitic cell characterized by clonal proliferation of abnormal blast cells in the marrow and impaired production of normal blood cells resulting in aneamia, thrombocytopenia and low, normal, or high white cell counts depending on the number of leukemic cells in the blood. It occurs in nine morphologic variants, each with characteristic cytologic, genetic, and sometimes clinical features ***(Lichtman et al., 2011).***

Epidemiology

AMLs are infrequent, yet highly malignant neoplasms responsible for a large number of cancer-related deaths ***(Deschler and Lübbert, 2006)***.

1. Incidence

It accounts for about 80% of all leukemias in adults and 15%-20% in children ***(Lichtman et al., 2011).***

2. Age

Acute myeloid leukemia is generally a disease of older people and is uncommon before the age of 45. The average