Expression of PRAME gene in acute myeloid leukemia and correlation with clinical response

Thesis
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List of Abbreviation

ALL	Acute lymphoblastic leukemia
ABC	ATP binding cassette
AML	Acute myeloid leukemia
AML-NOS	Acute myeloid leukemia-not otherwise specified
ANA	Alpha naphthyl acetate
ANB	Alpha naphthyl butyrate
ANNL	Acute non lymphoblastic leukemia
APL	Acute promyelocytic leukemia
ATRA	All-trans retinoic acid
BCL-2	B-cell leukemia lymphoma oncogene
BM	Bone marrow
BMT	Bone marrow transplantation
CAE	Chloroacetate esterase
CALGB	Cancer and Leukemia Group B
CBF	Core Binding Factor
CD	Clusters of differentiation
CEBPA	CCAAT/enhancer binding protein
CIR	Cumulative incidence of relapse
CML	Chronic myeloid leukemia
CNS	Central nervous system
CR	Complete remission
CRD	Complete remission duration
CTA	Cancer testis antigen
DFS	Disease free survival
DIC	Disseminated intravascular coagulopathy
DNA	Deoxyribonucleic acid
DNTP	Deoxynucleotide triphosphate
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylene diamine tetra-acetic acid
EFS	Event –free survival
EGIL	European Group for the Immonological Classification of Leukemia
ERG	ERG(v-ets erythroblastosis virus E26 oncogene like (Avian)
ETO	Eight-twenty-one gene

EVI1	Ecotropic viral integration site 1
FAB	French American British Classification
FCS	Foetal calf serum
FISH	Fluorescent in situ hybridization
FLT3	FMS- like tyrosine 3
FOXO3A	The Forkhead transcription factors
FPD	Familial platelet disorder
G-CSF	Granulocyte –colony stimulating factor
GDP	Guanidine diphosphate
GTP	Guanidine triphosphate
HDAC	High dose Ara-C
HLA	Human leukocyte antigen
HOX	Homeobox genes
Hsp27	Heat shock protein 27
HTLV-I	Human T-cell leukemia virus type I
HuM195	Humanized monoclonal antibody
IARC	International Agency for Research on Cancer
IGFBP-2	Insulin growth factor binding protein-2
ITD	Internal tandem duplication
JM	Juxtamembrane
Kcl	Potassium chloride
KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene
KP1	CD68 antibody
LDH	Lactate dehydrogenase
LRP	Lung resistance protein
MDR-1	Multidrug resistance glycoprotein
MDS	Myelodysplastic syndrome
Mgcl2	Magnesium chloride
MKL1	Myocardin like protein
MLL	Myeloid /lymphoid or mixed lineage leukemia
MM	Multiple myeloma
MPN	Myeloproliferative neoplasm
MPO	Myeloperoxidase
MRC	Medical Research Council
MRD	Minimal residual disease
MRP1	Multidrug resistance-associated protein-1
NaF	Natrium fluoride

NCI	National Cancer Institute
NPM	Nucleophosmin
NSE NHL	Non specific esterases Non Hodgkin lymphoma
NUMA1	Nuclear matrix associated gene
NUP98	Nucleoporin gene
OGG1	8-oxoguanine DNA glycosylase
OS	Overall survival
P53	A Tumer Suppressor. P53=Protein 53 kilo Dalton in size
PAS	Periodic acid Schiff
PB	Peripheral blood
PBS	Phosphate buffer saline
PCR	Polymerase Chain Reaction
P-gp	p-glycoprotein
PLZF	Promyelocytic zinc finger
PMT	Promyelocytic leukemia
PMX1	Paired mesoderm homebox 1
PRAME	Preferentially Expressed Antigen of Melanoma
PTD	Partial tandem duplication
RA	Retinoic acid
RAR	Retinoic acid receptor
RARA	Retinoic acid receptor, alpha
RAS	Rat sarcoma gene
RFS	Relapse free survival
RI	Relapse incidence
RNA	Ribonucleic acid
RR	Risk of relapse
RT	Reverse transcription
RTK	Receptor tyrosine kinase
RUNX1	Runt –related transcription factor-1
SBB	Sudan black B
SbF1	SET-binding factor 1
SCT	Stem cell transplantation
SMMHC	Smooth muscle myosin heavy chain
SPOG	Spen paralog and ortholog C-terminal
SWOG	Southwestern Oncology Group
TAA	Tumor associated antigen

TdT	Terminal deoxynucleotidyl transferase
TEL	Translocation ets Leukemia
TGF	Transforming growth factor
TK	Tyrosine kinase
TLC	Total leukocytic count
TNF	Tumor necrosis factor
TPO	Thromboplastin
WBC	White blood cell
WHO	World Health Organization
WT1	Wilms tumor suppressor 1

Introduction and aim of work

INTRODUCTION

Preferentially expressed antigen of melanoma (PRAME) is a cancer-testis antigen (CTA) belongs to the group of tumor associated antigens.

It encodes an antigen recognized by autologous T cytotxic lymphocytes. The PRAME gene maps on chromosome 22 at 22q11. It was first detected in a case of malignant melanoma ***(Spanaki et al ., 2007)***.

Although the PRAME gene expression is low or absent in almost all normal adult tissues except for testis, adrenals, ovaries and endometrial tissues it was found to be expressed at high levels in a large fraction of solid tumors like non small cell lung cancer, renal cell carcinoma, head and neck tumors. Its also over expressed in hematopoietic neoplasms like acute and chronic leukemias, multiple myeloma and lymphomas ***(Tajeddine et al ., 2006)***.

In spite of the fact that the PRME antigen is recognized by autologous cytotoxic T cell-mediated immune responses, its expression is well retained. This suggest that expression of PRAME is addressed to be involved in the tumorigenic process ***(Epping et al ., 2005)***.

The mRNA level of PRAME is used as a tumor marker due to its over expression in various malignancies. The PRAME transcript was highly expressed in AML patients and was favorable marker for prognosis, so quantification of PRAME transcript can be used in monitoring disease status of AML ***(Zhu et al., 2010)***.

The expression of PRAME might play a critical role in the control of minimal residual disease (MRD) in acute myeloid leukemia (AML) where PRAME mRNA could be used to monitor MRD for AML patients with higher than normal levels and its increase over or persistently higher than normal range predict hematological relapse ***(Qin YZ et al., 2008)***.

PRAME is a good target for tumor immunotherraapy therapy and is useful marker gene for detection of MRD ***(Greiner et al ., 2006)***.

Aim of work

The aim of this work is to asses the expression of Preferentially expressed antigen of melanoma (PRAME) gene in 60 adult acute myeloid leukemia patients at diagnosis and to correlate its expression with the clinical response.

Review of literature

ACUTE MYELOID LEUKEMIA

Introduction

The term acute myeloid leukemia (AML, acute non-lymphocytic leukemia [ANLL]) refers to a group of relatively well-defined hematopoietic neoplasms involving cells committed to the myeloid line of cellular development. AML is characterized by a clonal proliferation of myeloid precursors with reduced capacity to differentiate into more mature cellular elements.

As a result, there is an accumulation of leukemic forms in the bone marrow, peripheral blood, and other tissues, with a marked reduction in red cells, platelets, and neutrophils. The increased production of malignant cells, along with reduction in these mature elements, result in a variety of systemic symptoms, anemia, bleeding, and an increased risk of infection.

Acute myeloid leukemia (AML) is a genetically heterogeneous disease with accumulation of acquired genetic alterations in hematopoietic progenitor cells that disturb normal mechanisms of cell growth, proliferation and differentiation ***(Döhner et al , 2007).***