

Assessment of CD⁴⁵ Expression as a Prognostic Factor in Chronic Lymphocytic Leukemia

Thesis

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List of Abbreviations

ALC	Absolute lymphocyte count
alloHSCT	Allogeneic hematopoietic stem cell transplantation
APC	Antigen presenting cell
AT	Ataxia telangectasia
ATM	Ataxia telangectasia mutation gene
BM	Bone marrow
CBC	Complete blood count
C.CD⁴³	Cytoplasmic CD ⁴³
CLL	Chronic lymphocytic leukemia
CRM¹	Chromosome region maintenance ¹
CTL	Cytotoxic T-cells
DCs	Dendritic cells
DNA	Deoxyribonucleic acid
EAE	Experimental autoimmune encephalomyelitis
EBV	Ebstein Barr virus
ELISA	Enzyme Linked Immunosorbent Assay
FAB	French American British

FCM	Flow Cytometry
FISH	Fluorescence in situ hybridization
FITC	Fluorescein isothiocyanate
GM-CSF	Granulocyte monocyte-colony stimulating factor
HCL	Hairy cell leukemia
HCMV	Human Cytomegalovirus
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HSV-1	Herpes simplex virus type 1
IAP	Inhibitors of apoptosis protein
ICC	Invasive cervical cancer
iDCs	Immature dendritic cells
Ig	Immunoglobulin
Ig VH	Immunoglobulin heavy-chain variable region
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgHV	Immunoglobulin variable region
IgM	Immunoglobulin M

IL-11	Interleukin-11
iwCLL	International workshop on CLL
LDH	Lactate Dehydrogenase
LDT	Lymphocyte doubling time
LPS	Lipopolysaccharide
MBL	Monoclonal B-cell lymphocytosis
mCD43	Membrane-bound CD43 form
MCL	Mantle cell lymphoma
mDCs	Mature dendritic cells
MHC	Major histocompatibility complex
MLR	Mixed leukocyte reaction
MLRs	Mixed leukocyte reactions
MoDCs	Monocyte-derived dendritic cells
MRD	Minimal residual disease
mRNA	Messenger Ribonucleic acid
MZ	Mantle zone
NCIWG	National Cancer Institute Working Group
NHL	Non Hodgkin's lymphomas
PB	Peripheral blood

PCNA	Proliferating cell nuclear antigen
PCR	Polymerase Chain Reaction
PLL	Prolymphocytic leukemia
S.CD⁴⁵	Surface CD ⁴⁵
sCD⁴⁵	Soluble CD ⁴⁵ form
SIg	Surface immunoglobulin
SLVL	Splenic lymphoma with circulating villous lymphocytes
s-TK	Serum thymidine kinase
TAP	Transporter associated with antigen processing
TEC	Thymic epithelial cells
TK	Thymidine kinase
VEGF	Vascular endothelial growth factor
WBC	White blood cell
ZAP-γ	Zeta chain associated protein γ

Introduction

Chronic lymphocytic leukemia (CLL) is a hematopoietic neoplasm of lymphocytes found in the peripheral blood, bone marrow, and /or lymph nodes. The morphology reveals a monomorphic small round cell population of lymphocytes. It is the most common adult leukemia, with a variable clinical course. Some experience an aggressive disease course that lead to premature death while others live for decades and never require therapy (*Glassman and Hayes, 2005 and Shanafelt et al., 2008*).

Although the pathogenesis of CLL depends primarily on intrinsic defects within the leukemic cells, interaction with the microenvironment of bone marrow, lymph node and spleen as well as other components of the immune system are likely to affect the clinical course of the disease (*Ghia et al., 2003*).

The glycoprotein CD $\alpha\beta$, which is expressed by activated lymphocytes, dendritic cells (DC) and neutrophils, plays a central role in immunoregulation and is the focus of considerable interest as a therapeutic target (*Prazma and Tedder, 2008*). It is clear however that CD $\alpha\beta$ plays a critical role in thymic CD ξ + T cell development and the involvement of CD $\alpha\beta$ in increasing not only DC function but also lymphocyte survival, differentiation and immunosuppressive activity has been reported (*Prechtel and Steinkasserer, 2007 and*

Kretschmer et al., 2007).

More than 90% of acute myeloid leukemia (AML) and multiple myeloma (MM) patients have normal or only weakly increase in CD43 expression, while 20% of chronic lymphocytic leukemia (CLL) patients and 0% of mantle cell lymphoma (MCL) patients have significantly increased expression of CD43 (*Hock et al., 2009*).

The report of significantly elevated expression of CD43 in patients with CLL together with the immunosuppressive activity of CD43 raises the possibility that CD43 may play a role in enabling CLL cells to escape Immunosurveillance (*Hock et al., 2009*).