Assessment of Serum Vimentin Level in Adult Egyptian Acute Lymphoblastic Leukemia (ALL) Patients and Evaluation of its Prognostic Value

Thesis

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Contents

List of Abbreviations

Abb.	Full term
6MP	6-mercaptopurine
ABL 1	Abelson kinase gene
ALL	Acute lymphoblastic leukemia
AlloHCT	Allogeneic hematopoietic cell transplantation
AML	Acute myeloid leukemia
ANOVA	Analysis of variance
AYA	Adolescents and young adults
BCP-ALL	B-cell precursor acute lymphoblastic leukemia
BCR	Breakpoint cluster region
BFGF	Basic fibroblast growth factor
CAR	Chimeric antigen receptor
CBC	Complete blood picture
CLL	Chronic lymphocytic leukemia
CN-AML	Cytogenetically normal AML
CNS	Central nervous system
CR	Complete remission
CTC	Circulating tumor cells
DFS	Disease free survival
DLBCL	Diffuse large B cell lymphoma
DLI	Donor lymphocyte infusion
ECM	Extracellular matrix
EFS	Event free survival
ELISA	Enzyme-linked immune sorbent assay
EMT	Epithelial-mesenchymal transition
ETP-ALL	Early T-cell precursor ALL
FISH	Fluorescence In Situ Hybridization
GVHD	Graft-*versus*-host disease
HCV	Hepatits C virus
HO-1	Heme oxygenase-1
HR	High risk
HSM	Hepatosplenomegaly
iAMP21	Intrachromosomal amplification of chromosome 21
IF	Intermediate filament

Abb.	Full term
IL7Ra	Interleukin-7 receptor a chain
IT	Intrathecal chemotherapy
JALSP	Japan Adult Leukemia Study Group
LALA	Leucémie Aiguës Lymphoblastique de l'Adulte
MFC	Multi-channel flow cytometry
molCR	Molecular complete remission
MRD	Minimal residual disease
MT1-MMP	Membrane type-1 matrix metalloproteinases
MTX	Methotrexate
MUD	Matched unrelated donor
Non-APL	Non-acute promyelocytic leukemia
OS	Overall survival
P1f	Plectin isoform 1f
PCR	Polymerase chain reaction
Ph	Philadelphia
PTM	Posttranslational modifications
R/R	Relapsed/refractory
RS	Reed-Sternberg
S1P	Sphingosine-1-phosphate
Scvf	Single-chain variant fragment
SD	Standard deviation
SR	Standard risk
TBI	Total body irradiation
TKIs	Tyrosine kinase inhibitors
TLS	Tumor lysis syndrome
TRM	Transplant-related mortality
TSLPR	Thymic stromal-derived lymphopoietin receptor
TTT	Time from diagnosis to initial treatment
ULF	Unit-length filament
VEGF	Vascular endothelial growth factor
VIM	Vimentin
VM	Viral markers
WBC	White blood cell
WHO	World health organization
WSS	Wall shear stress

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INTRODUCTION

Vimentin (VIM), a major component of type III intermediate filament (IF) protein, is encoded by the VIM gene and is expressed in endothelial and other mesenchymal cells ***(Ivaska et al., 2007)***. VIM is instrumental in vital physiological and pathological processes, such as adhesion, migration, cell signaling, inflammation, neurite extension, and vascularization ***(Kidd et al., 2014).***

Though VIM is a cytoskeletal protein, it has been shown to be involved in apoptotic progression. During apoptosis, VIM is cleaved by caspase-3, -7 and -6 resulting in cytoskeletal collapse and is thought to be the basis of the morphological changes that occur in a cell undergoing apoptosis***. (Zhang et al., 2006)***

Increased VIM expression has been found in various epithelial tumors including lung cancer, hepatocellular carcinoma, breast cancer, gastrointestinal tumors, central nervous system tumors, malignant melanoma, and hematopoietic malignances, which may be concerned with tumor growth and invasion resulting into poor prognosis ***(Satelli and Li, 2011).***

In solid cancers, VIM has been shown to promote metastatic progression by participating in the cytoskeletal reorganization that occurs during epithelial mesenchymal

transition (EMT) as well as regulate pro-EMT signaling pathways. VIM has also been used as a marker for pre-metastatic cells undergoing EMT and therefore, high VIM expression is associated with worse outcomes in patients with solid cancers. The role of VIM in haematological malignancies is not clear, particularly acute lymphoblastic leukemia (ALL), its role wasn't assessed before**. *(Wu et al., 2018)***

ALL is a hematologic malignancy propagated by impaired differentiation, proliferation, and accumulation of lymphoid progenitor cells in the bone marrow and/or extramedullary sites. Although ALL occurs predominantly in children, it is adult ALL that is more challenging to treat. Despite high rates of complete remission (CR) (80%- 90%) in adult ALL, the cure rates are only 40% to 50% because of relapses**. *(Paul et al., 2016)*** With such high mortality rates, a better understanding of the cellular and molecular mechanisms regulating leukemia cells are required**.**

Aim of the work

This study aimed at measurement of serum vimentin level in the peripheral blood of Egyptian patients with acute lymphoblastic leukemia and correlating it with clinical outcome and prognosis of the disease.

ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy driven by the proliferation and accumulation of lymphoid progenitor cells in the bone marrow and other tissues. While 80% of ALL occurs in children, it represents a devastating disease when it occurs in adults. It occurs in a bimodal distribution with an overall age-adjusted incidence of 1. 7 per 100,000 persons; it affects 4 to 5 children per 100,000 and half that number around the fifth decade of life. Roughly, 60% of cases are diagnosed in patients younger than 20 years. While dose-intensification strategies have led to a significant improvement in outcomes for pediatric patients, the prognosis for the elderly remains very poor. Despite a high rate of response to induction chemotherapy, only 30–40% of adult patients with ALL will achieve long-term remission. ***(Jabbour et al., 2015)***

Etiology

The etiology of ALL is largely unknown. Less than 5% of cases can be attributed to genetic syndromes such as Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, ataxia-telangiectasia, and Nijmegen breakdown syndrome. Other risk factors include increasing age (>70 years) and radiation exposure. There has also been an association between Epstein-Barr virus in mature B-cell ALL, human T-lymphotropic virus type 1 in adult T-cell leukemia/lymphoma, and human immunodeficiency virus in lymphoproliferative disorders. ***(Paul et al., 2016)***

Clinical presentation

Most of the clinical manifestations of ALL reflect the accumulation of malignant, poorly differentiated lymphoid cells within the bone marrow, peripheral blood, and, extramedullary sites. The presentation can be nonspecific, with a combination of constitutional symptoms and signs of bone marrow failure (anemia, thrombocytopenia, and leukopenia). Common symptoms include B symptoms (fever, weight loss, night sweats), easy bleeding or bruising, fatigue, dyspnea, and infection. Involvement of extramedullary sites commonly occurs and can cause lymphadenopathy, splenomegaly, or hepatomegaly in 20% of patients. Central nervous system (CNS) involvement at the time of diagnosis occurs in 5–8% of patients and presents most commonly as cranial nerve deficits or meningism. T-cell ALL also may present with a mediastinal mass. ***(Terwilliger and Abdul-Hay, 2017).***

Diagnosis

Diagnosis is established by the presence of 20% or more lymphoblasts in the bone marrow or peripheral blood. Evaluation for morphology, flow cytometry, Immunophenotyping, and cytogenetic testing is valuable both for confirming the diagnosis and risk stratification. Lumbar puncture with CSF analysis is standard of care at the time of diagnosis to evaluate for CNS involvement. If the CNS is involved, a brain MRI should be performed.