Serum Leptin Level in Children with Acute Lymphoblastic Leukemia

Thesis

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List of Abbreviations

Abb.	Meaning

1.25 (OH)2 → 1.25 dihydroxy chonecalicferi
ACC..... Acetyl COA carboxylase
AID enzymes..... Activation –induced cytidine deaminase
ALL ..... Cute lymphoblastic leukemia
AML ..... Acute myeloid leukemia
AMPK..... 5' adenosine monophosphate-activated protein kinase
APL..... Acute promyelocytic leukemia
ASBMT..... American Society for Blood and Marrow Transplantation
BCP-ALL ..... B-cell precursor ALL
b-FGF ..... Basic fibroblast growth factor
BMI..... Body mass index
CAMP..... Cyclic AMP
CAMP..... Cyclic AMP
CAP/ASH ..... College of American Pathologists & American Society of Hematology
CCK..... Cholecystokinin
CHR..... Cytoicine Binding homology region
CLL..... Chronic lymphocytic leukemia
CML ..... Chronic myelogenous leukemia
CNTF..... Ciliary neurotrophic factor
COL IV ..... Collagen type IV
COX-2 ..... Cyclo-oxygenase-2
CPCS ..... Chondrogenic progenitor cells
CRLF2 ..... Cytokine receptor–like factor 2
CRP..... C-reactive protein
CRT ..... Cranial radiotherapy
CY..... Cytoplasmic

List of Abbreviations

Abb.	Meaning
DIC	Disseminated intravascular coagulation
DLBCL	Diffuse large B cell lymphoma
ELSA	Enzyme linked immuno sorbent opany
EPOR	Erythropioetin receptor
ESMO	Guidelines
ESR	Erythorcyte sedimentation rate
ETP	Early T-precursor
FA	Fanconi Anemia
FFPE	Formalin fixed paraffin-embedded
FGF23	Fibroblost growth factor 23
FISH	Flouresence in situ hybridization
FLI	Free leptin index
FN3	Fibronectin type 3 domain
G-CSF	Granulocyte colony stimulating factor
GH	Growth hormone
GLP1	Glucagon-like peptide 1
GM-CSF	Gronulocyte – monocyte colony stimulating factor
GnRH	Gonadotrophin-releasing hormone
HCG	Human chonanic gonadotropin
HT	Hanhimoto thyroiditus
IGH	Ig heavy chain
IGK	Ig kappa chain
IGL	Ig labda chain
IPSS	International Prognostic Scoring System
IRS	Insulin receptor substrate
JAK2	Janus kinase 2
JIA	Juvenile Idiopathic Arthritis
LH	Latinizing hormone

List of Abbreviations

Abb.	Meaning
LOP-R	Leptin receptor
MAb	Monoclonal antibody
MAPK	Mitogen-activated protein kinase
MM	Multiple myeloma
MMP	Matrix metalloproteinase
MN	Modal number
MO	Monthes
MPO	Myeloperoxide
MRD	Multiagent therapy
MS	Multiple sclecnosis
NASH	Non-alcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NO	Nitnic oxide
NOS2	Type 2 nitric oxide syntheses
NPY	Neuropertide gamma
NSE	Non specific esterase
NSI	National cancer unistitute
NTS	Nucteus of solitary tract
OA	Osteo arthritis
PAS	
PB	Peripheral blood
PI3K	Phosphoinositide 3-kinase
PI3K	Phospnatidylionstiol 3-kinone
PTH	Parathyroid hormone
PTP1B	Posphotyrosine ohosphatase 1B
RA	Rheumatoid arthritis

List of Abbreviations

Abb.	Meaning
RAG enzymes	Recombination Activation Gene
Ras	
RLH	Reactive lymphoid hyperplasia
SCT	Stem cell transpiontation
SHP2	SH2-containing protein tyrosine phosphatase 2
SICAM1	Soluble intercellular adhesion molecule 1
SLDH	Serum lactate dehydrogenase
SLE	Systemic lupus enthnomatosis
SOB-R	Soluable leptin receptor
SOCS-3	Supprensor of cytolcine signaling
STAT	Signal transuducer and activator of transcription
SVCAM1	Soluble intercellular adhesion protein 1
T.reg	T- regulatory
T2DM	Type 2 diabetes milletus
TdT	Terminal deoxymcleotidyl transferase
TGF-B	Transforming growth factor B
TKI	Tyrosine kinase inhibitor
TRH	Thyrotropin-releasing hormone
TSH	Thyroid stimulating hormone
Tyr	Tyrosine
V SMCS	Vascular smooth munde cells
VCAM	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor Receptor-2
WCC	White cell wont
Ys	Years

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a disease of monoclonal proliferation of hematopoietic precursor cells of the lymphoid series within the bone marrow ***(Zhu et al., 2016).***

ALL is the most common pediatric cancer ***(Inaba, 2018)*** representing more than a quarter of all pediatric malignancies, An estimated 6000 new cases (3400 male and 2600 female) of ALL are diagnosed annually in the US. Patients are predominantly children; approximately 60% of cases occur at age <20 years (***Inaba et al., 2013)*.**

Improvements in ALL therapy might readily be achieved by developing additional biomarkers that can predict and refine prognosis in patients with ALL ***(de Lourdes Perim et al., 2015).***

Leptin is a16-kD peptide hormone composed of 146 aminoacids and it is a protein product of (ob) gene. Leptin is predominantly produced by white adipose tissue, and many other sites including placenta, fetal tissue, gastric mucosa and hepatic stellate cells ***(Yilmaz et al., 2008)*** moreover marrow adipocytes are a significant source of leptin in the bone marrow ***(Yue et al., 2016)***.

The main function of leptin in the human body is the regulation of energy expenditure and control of appetite. Serum level of leptin reflects the amount of energy stored in the adipose tissue and is in proportion to body fat mass **(*Tsai 2017)***. It also has a role in homeostasis, angiogenesis, inflammation, immunity, hematopoiesis, and cell cycle *(**Shahramian et al., 2016**).*

Leptin is supposed to be involved in the pathogenesis of hematological malignancy through its proliferative, anti-apoptotic, and differentiating effects on hematopoietic neoplastic cells ***(Han et al., 2015)***. Leptin plays a role in growth and differentiation of leukemic cells. Leptin receptor (ob-R) is expressed by B-cells, T-cells and CD34+ stem cells.

In acute leukemia, an angiogenic role for leptin has been reported through leptin's synergestic effect on vascular endothelial growth factor (VGEF). Moreover, mutations occurring in ALL were mentioned to predispose to leptin receptor gene polymorphism resulting in increase in leptin level (***Shahramian et al., 2016)*.**

AIM OF THE WORK

The primary outcome

To evaluate serum leptin level in children with acute lymphoblastic leukemia at diagnosis and at day 28 post induction chemotherapy

Secondary outcome

- To test the association between serum leptin levels and anthropometric measures of ALL patients.
- To examine the association between serum leptin levels and prognostic markers of ALL as age, Gender, Initial WBCS count, extramedullary infiltration to organs and CSF, cytogenetics, response to treatment.

Chapter I
ACUTE LYMPHOBLASTIC LEUKEMIA

A. Definition:

Acute lymphoblastic leukemia (ALL) is a malignant (clonal) disease of the bone marrow ,in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow ***(Terwilliger et al., 2017)*.**

It is the most common cancer among children, and the most frequent cause of death before age of 20 ***(Smith et al., 2010)*.**

B. Epidemiology:

ALL is the most common type of cancer and leukemia in children in the United States, it accounts for 75% of pediatric leukemia cases, in adults, this disease is less common than acute myeloid leukemia (AML). It is estimated that there will be 5960 cases of ALL (adult and pediatric) in the United States in 2018, resulting in 1470 deaths ***(Siegel et al., 2017)***.

Worldwide, the highest incidence of ALL occurs in Italy, the United States, Switzerland, and Costa Rica .In Europe overall B-cell precursor ALL has been increasing by around 1% each year ***(Arber et al., 2017)*.**

The incidence is higher in Hispanic Americans (4.1 per 100, 000/year), and is lower in African American children (2.1 per 100, 000/year) ***(Linabery et al., 2008)*.**

In general, low-income countries have lower incidences of ALL than high-income countries, however these differences may be the result of incomplete registration ***(Schmiegelow et al., 2008)*.**

B-lineage ALL accounts for 80% of pediatric ALL cases, while T-lineage ALL accounts for 10-15% of ALL cases ***(Jain et al., 2016)*.**

The incidence of B-ALL shows a bimodal distribution, with the first peak occurring in childhood peak between 2 and 5 years, and a second peak occurring around the age of 50 years ***(Hjalgrim et al., 2003)*.**

T-lineage ALL is characterized by an older age of onset, with peak around (4-9) years, male sex preponderance, and inferior outcome in comparison with B-ALL ***(Szczepanski et al., 2010)***.

Age-related ALL risk differs substantially by cytogenetic subtype, ALL in infants (<1 year) is characterized by MLL gene rearrangements in most cases which are rare in older children, while between 2 and 5-years old ,ALL is dominated by high-hyperdiploid (chromosome number >50) and t(12;21)[ETV6-RUNX1] karyotypes, ***(Szczepanski et al., 2010)*.**