Study of Interleukin 6 (IL-6) in Chronic Lymphocytic Leukemia

Thesis

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List of Abbreviations

Abb.	Full term
2CDA	2-chlorodeoxyadenosine
AIHA	Autoimmune haemolytic anemia
AML	Acute myeloid leukemia
ATM	Ataxia telangiectasia mutated
BCR	B-cell antigen receptor
B-PLL	B-cell prolymphocytic leukaemia
BR	Bendamustine with rituximab
CARs	Chimeric antigen receptors
CBC	Complete blood count
CFAR	Alemtuzumab with FCR
CIRS	Cumulative Index Rating Scale
CLL	Chronic lymphocytic leukaemia
CMV	Cytomegalovirus
CNTF	Ciliary neurotropic factor
CR	Complete response
CRi	Complete response incomplete
CT-1	Cardiotropin-1
DAT	Direct antiglobulin test
DIC	Disseminated intravascular coagulation
DLBCL	Diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
ELISA	Enzyme-linked immunosorbent assay
ERIC	European Research Initiative on CLL
FC	Fludarabine plus cyclophosphamide
FCR	Fludarabine, cyclophosphamide, rituximab
FISH	Fluorescent in situ hybridization
FR	Fludarabine and rituximab
GVHD	Graft-versus-host disease
GVL	Graft-versus-leukemia

List of Abbreviations Cont...

Abb.	Full term
Hb	Hemoglobin
HCL	Hairy cell leukaemia
HHV- 8	Human herpes virus 8
HiB	*Haemophilus influenza* B
IgD	Immunoglobulin D
IGHV	Immunoglobulin variable region heavy chain
IgM	Immunoglobulin M
IGVH	Immunoglobulin variable heavy chain
IL	Interleukin
ITP	Immune thrombocytopenia
LDT	Lymphocyte doubling time
LIF	Leukemia inhibitory factor
LO	Lenalidomide + ofatumumab
LR	Lenalidomide + rituximab
MAbs	Monoclonal antibodies
MBL	Monoclonal B-cell lymphocytosis
MCL	Mantle cell lymphoma
MDD	Minimum detectable dose
MDR	Minimally deleted region
MDS	Myelodysplasia
MIRs	microRNAs
MRD	Minimal residual disease
NHL	Non-Hodgkin lymphomas
NPN	Neuropoietin
O.D.	Optical density
ORR	Overall response rates
OS	Overall survival
OSM	Oncostatin M
PAR	Pentostatin and rituximab

List of Abbreviations Cont...

Abb.	Full term
PCO	Pentostatin, cyclophosphamide, and ofatumumab
PCR	Pentostatin + cyclophosphamide + rituximab
PD	Progressive disease
PFS	Progression-free survival
PL	Prolymphocytoid leukaemia
PML	Progressive multifocal leucoencephalopathy
PR	Partial response
PRCA	Pure red cell aplasia
PRL	Partial response with lymphocytosis
PRn	Nodular partial response
RANKL	RANK ligand
RBC	Red blood cell
RS	Richter's syndrome
SCT	Stem cell transplantation
SD	Stable disease
SLL	Small lymphocytic lymphoma
SLVL	Splenic lymphoma with circulating villous lymphocytes
SMZL	Splenic marginal zone lymphoma
SOCS	Suppressor of cytokine signals
SST	Serum separator tube
STAT	Signal transducer and activator of transcription
sTK	Serum thymidine kinase
TNF	Tumor Necrosis Factor
TRM	Transplant-related mortality
TTF	Time to failure
VEGF	Vascular endothelial growth factor
VGEF	Vasculargrowth endothelial factor
WBC	White blood cell

ABSTRACT

Background Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults. These malignant B-CLL cells represent over 99% of peripheral blood mononuclear cells (PBMCs) in CLL patients. In case of an aggressive form, the cell number may quickly double and, as a result, the disease may be fatal within a relatively short period of time .Currently several biomarkers are being used as CLL prognosticators, including: elevated protein levels (e.g. TCL-1, ZAP-70, CD38), elevated RNA levels (e.g. CLLU1, LPL, miRNAs), gene mutations (e.g.TP53, SF3B1, BIRC3, NOTCH1) and epigenetic changes. Early reports implicated IL-6 as pro-tumorigenic factor in various human tumors. IL-6 levels increased significantly in serum of CLL patients and correlated with adverse clinical features and short survival.

Aim of the work: **Is** to evaluate IL 6 level in patients with CLL at time of presentation and 6 months after chemotherapy and to study its relevance to disease prognosis**.**

Patients and Methods: This Study is a cross sectional study that was conducted on 55 patients newly diagnosed with chronic lymphocytic leukemia (CLL) in Clinical Hematology Unit in Ain-Shams University Hospitals in Cairo, Egypt. **Result:** The initial serum IL 6 level in the patient group (pre-treatment) ranged from 36-91pg/mL (median 57), and in the control group it ranged from 1-2 pg/mL (median 1).The initial serum IL 6 level in patient group (pre-treatment) range from 36-91 pg/mL (median 57), and in patient group (post treatment) range from 1-32 pg/mL (median 2).There are positive correlations between IL6 level and with WBC, B2 microglobulin, LDH, ESR, B symptoms, Uric Acid, BM Aspirate (% of lymphocytes)and Binet and Rai staging system.

Conclusion: Serum IL 6 is a useful poor prognostic marker in newly diagnosed CLL patients, its prognostic value goes with the other known prognostic markers as the lymphocytic count, ESR and LDH.

Key words: CLL; IL 6; Prognostic markers; cytogenetics

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults, accounting for approximately 30 % of all leukemia cases in European and North American countries with an incidence of 3–5 cases per 100,000 ***(Talab et al., 2013).***

CLL is rare under 45 years of age, and its prevalence increases with age. The median age of patients at diagnosis is 70 years and only 10–15% of the patients are diagnosed under 50 years of age. It is characterized by accumulation of non-functional B-cells with a high expression of CD5, CD19, CD20 and CD23 and a low expression of surface immunoglobulins IgM, IgD and CD79a compared to normal B-cells ***(Herman et al., 2010).***

These malignant B-CLL cells represent over 99% of peripheral blood mononuclear cells (PBMCs) in CLL patients. Approximately 2–5% of CLL patients show a T-cell phenotype, and these patients have a less favorable prognosis than patients with a B-CLL phenotype ***(Shackelford et al., 2006).***

CLL develops through increased proliferation of immature lymphocytes in lymphoid organs, which results from an increased expression of antiapoptotic BCL-2 family proteins ***(Willimott et al., 2013).***

As a result, CLL cells can survive for months (unlike normal cells, which only survive for a few days), thereby

decreasing the number of normal lymphocytes and inducing immunodeficiency ***(Chen et al., 2008).***

In case of an indolent form, the disease does usually not progress to a severe form, and the patient may survive for years without treatment. In case of an aggressive form, the cell number may quickly double and, as a result, the disease may be fatal within a relatively short period of time ***(Chiorazzi et al., 2005; Palomba et al., 2014).***

Currently several biomarkers are being used as CLL prognosticators, including elevated protein levels (e.g. TCL-1, ZAP-70, CD38), elevated RNA levels (e.g. CLLU1, LPL, miRNAs), gene mutations (e.g.TP53, SF3B1, BIRC3, NOTCH1) and epigenetic changes ***(Chen et al., 2008).***

Prognostic serum markers that can be used to predict the survival and response to treatment include increased lactate dehydrogenase (LDH) levels, which are associated with a poor prognosis and a likelihood of progressing to Richter's syndrome, increased thymidine kinase (TK) levels, which are associated with aggressive disease, and unmutated immunoglobulin heavy chain variable region (IGHV) genes, which are associated with a high risk for genomic aberrations ***(San Jose et al., 2013).***

Evaluation of the IGHV mutation status and FISH are among the most reliable molecular tools used in routine diagnostics