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**SERUM INTERLEUKIN-6 LEVEL AND
ITS CORRELATION WITH OTHER
PARAMETERS OF DISEASE ACTIVITY
IN MULTIPLE MYELOMA**



Thesis

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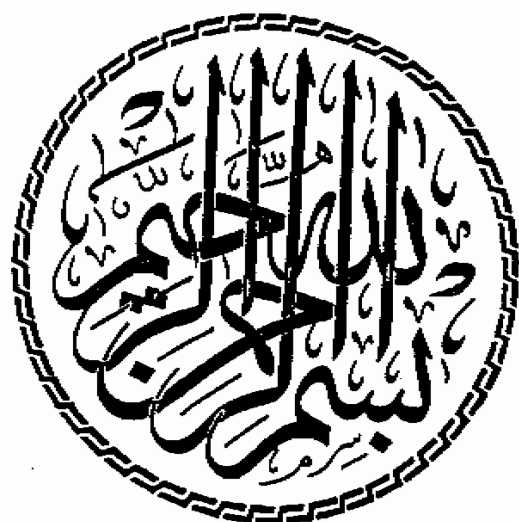
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ABSTRACT

Multiple myeloma is a clonal disorder where terminally differentiated B-cells and plasma cells infiltrate the bone marrow, produce large amounts of monoclonal Igs, and secrete osteoclast-activating factor leading to bone lesions.

The present study was conducted to confirm the elevation of serum level of IL-6 in MM patients and to correlate this elevation with the levels of other parameters of disease activity such as bone marrow plasmacytosis, β 2-microglobulin, CRP, LDH, Alkaline-phosphatase. Furthermore to study the effect of this elevation of IL-6 on programmed cell death (apoptosis) in myeloma cell lines and myeloma cells using a very sensitive method to detect apoptosis by flow cytometry.

We have shown that the level of IL-6 was highly elevated in all newly diagnosed patients (16 cases) using a sensitive ELISA technique. The level of this cytokine was not elevated, neither in the normal control group (10 cases) nor in the follow up patients group (8 cases).

The present study has also revealed that IL-6 has inhibited apoptosis induced by serum starvation in myeloma cell lines and myeloma cells.

The results shown in the present ^{study} are suggestive of a major role for IL-6 in MM. This role is not only as a growth factor for myeloma cells but also as a critical factor in inhibiting programmed cell death.

LIST OF ABBREVIATIONS

BM	= Bone marrow
CD	= Cluster of differentiation
CNTF	= Ciliary neurotrophic factor
CR	= Complete remission
CRP	= C-reactive protein
EFS	= Event-free survival
FISH	= Fluorescence in situ hybridization
G-CSF	= Granulocyte colony-stimulating factor
GVM	= Graft-versus-myeloma
HLA	= Human leukocytic antigen
IFN	= Interferon
Ig	= Immunoglobulin
IL	= Interleukin
kD	= Kilo Dalton
LDH	= Lactate dehydrogenase
LIF	= Leukemia inhibitory factor
LN	= Lymph nodes
MAP	= Mitogen activated protein
MDR	= Multi drug resistance gene
MGUS	= Monoclonal gammopathy of unknown significance
MM	= Multiple myeloma
MoAbs	= Monoclonal antibodies
MP	= Melphalan and prednisone
MRI	= Magnetic resonance imaging
NF	= Nuclear factor
OAF	= Osteoclast activating factor
OS	= Overall survival
OSM	= Oncostatin M
PCD	= Programmed cell death
PCL	= Plasma cell leukemia

PCLI	= Plasma cell labeling index
PEP	= Protein electrophoresis
PLT	= Platelets
RIA	= Radioimmunoassay
rIL	= Recombinant interleukin
RP	= Retinoblastoma gene
sIL-6	= Soluble IL-6
sIL-6R	= Soluble IL-6 receptor
t	= Translocations
TCL	= Total leukocytic count
TGF β	= Transforming growth factor Beta
TNF	= Tumor necrosis factor
TP	= Total proteins
β 2m	= Beta-2-microglobulin

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INTRODUCTION

INTRODUCTION

During the past few years many insights have been gained into the immunobiology of multiple myeloma. Of great importance to our understanding of the regulation of the immunobiology of multiple myeloma has been the appreciation of the roles of various biological response modifying cytokines, produced by lymphocytes. The importance of understanding how these cytokines or interleukins control the tumor growth can improve our understanding of the biology of multiple myeloma and provide insights which will facilitate the development of biologically specific therapeutic control regimens for this disease (Barlogie et al., 1989).

Interleukin-6, a pleotropic cytokine with the capacity to induce proliferation in human B cells, is a potent growth factor for murine plasmacytomas and B cell hybridomas (Van Damme et al., 1987). IL-6 also is a strong in vitro growth factor for human myeloma cells (Kawano et al., 1989).

The in vitro responsiveness of myeloma cells to IL-6 was shown to be directly and positively correlated to the proliferative capability of these cells in vivo (Zhang et al., 1989). IL-6 was shown to be over produced in bone marrow of patients with multiple myeloma (Klein et al., 1989). Consistent with this observation, serum levels of IL-6, determined in a bioassay (Bataille et al., 1989) and Radioimmunoassay (RIA) (Solary et al., 1992) were shown to be good reflectors of disease severity in plasma cell dyscrasias.