HISTOLOGICAL STUDY ON THE EFFECT OF MOLGRAMOSTIM (LEUCOMAX) ON THE LEUCOCYTIC COUNT AND THE LIVER OF ALBINO RAT

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To my parents

To my husband

To my daughter

To my son

Table of Contents

Page

Introduction and Aim of the Work.....1

Review of Literature

Pharmacokineticsof Molgramostim (Leucomax).....4
Effect of Molgramostim (Leucomax) on the Blood.....9
Effect of Molgramostim (Leucomax) on the Liver....36
Pharmacokinetics of Methotrexate.....41
Effect of Methotrexate on the Blood.....44

Material and Methods.....48

Results

I Haematological Results.....67
II Liver Results.....136

Discussion

I Blood.....275
II Liver..... 287

Summary and Conclusion.....300

Abstract.....307

References.....309

Arabic Summary

INTRODUCTION

Introduction

In the recent years, astonishing advances have been made in the field of haematopoietic cytokines. One of these cytokines is the granulocyte-macrophage colony stimulating factor (GM-CSF) which is a multipotential haematopoietic growth factor that regulates the growth and function of granulocytes and monocytes/macrophages *(Ruef and Coleman, 1990)*.

There are minute amounts of GM-CSF produced locally in response to specific activator signals by a variety of cells in the body, thus acting as key players of the host defense system against foreign invaders *(Gasson, 1991)*. In healthy individuals, endogenous GM-CSF production suffices to maintain the homeostatic balance between myeloid cell destruction and regeneration. However, when disease, drug therapy or radiation disturb the normal myelopoiesis, exogenous GM-CSF is necessary to re-establish the equilibrium *(Monroy, Davis and McVittie, 1990)*.

These considerations lead to concerted efforts by several investigative teams to develop an exogenous source of GM-CSF

e.g. molgramostim (Leucomax) for clinical use. By means of molecular cloning and recombinant DNA technology, the human gene encoding GM-CSF has been isolated from activated T-lymphocytes and inserted into a variety of different vectors, eg. bacterial, yeast and mammalian cells, thus producing the exogenous form *(Monroy et. al., 1990).*

The ability of Leucomax to stimulate proliferation and enhance functional activity in monocytes/macrophages has resulted in practical and therapeutical advantages in clinical conditions where there is a myelopoietic dysfunction. This is applicable in cases of myelotoxicity associated with a high risk of life threatening infection which is a major obstacle to the delivery of a potentially curative chemotherapy to cancer patients. In these cases, the use of Leucomax increases the leucocytic count noticeably *(Steis, VanderMolen and Longo, 1990).*

Aside from uses in cancer chemotherapy, Leucomax is used following bone marrow transplantation in which it reduces the time to marrow recovery and the incidence of infections *(De Witte, Gratwohl, Van Der Lely, Muus, Stern, Speck, Nissen, Marmont, Bacigalupo, Gluckman, and Zwaan, 1990).* Also, it is used in myelodysplastic syndromes (defective stem cell

maturation) where it shows an increase in bone marrow cellularity and maturation of cell lineages *(Schuster, Larson and Thompson, 1990).*

Leucomax was seen to affect the liver in therapeutic doses as proved by many laboratory and clinical findings. These effects included elevated liver enzymes in general *(Groopman, Mitsuyasu, DeLeo, Oette, and Golde, 1987),* elevated transaminases *(Nimer, Champlin and Golde, 1988)* and elevated alkaline phosphatase *(Lynch, Yanes and Todd, 1988).* Also other studies showed ascites and hypoalbuminaemia as side effects *(Kaczmarski and Mufti, 1990).*

Aim of the Work

The aim of this work was to evaluate the effect of Leucomax on the leucocytic count with and without bone marrow depression induced by chemotherapy (methotrexate). Although many scientists studied the clinical effect of Leucomax on the liver, however no available references dealt with its histological effects. This study aimed to reveal the histological changes induced by Leucomax on the liver tissues.