THE PROGNOSTIC SIGNIFICANCE OF BCL2 ONCOGENE EXPRESSION IN MALIGNANT OVARIAN TUMORS

THESIS

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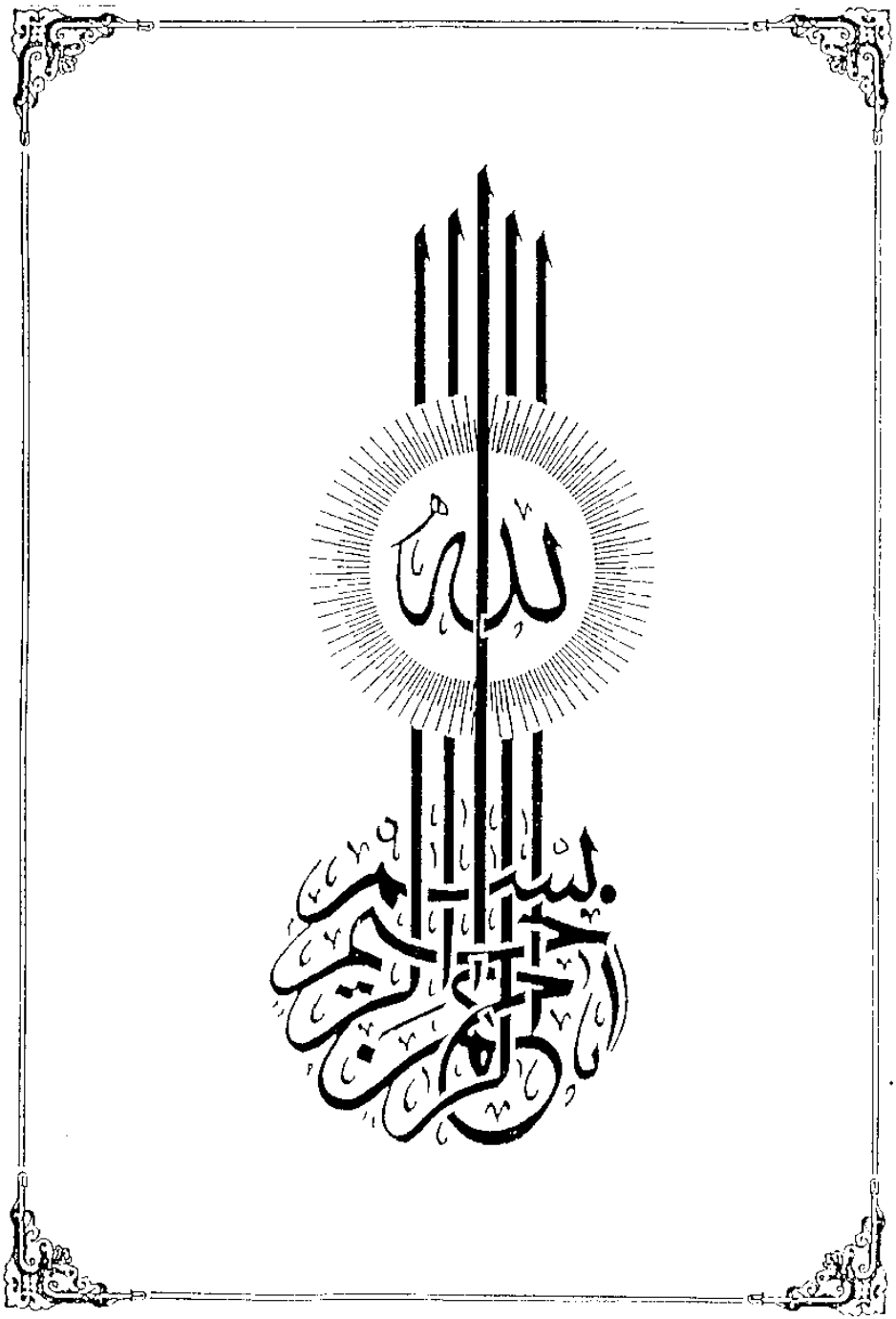

Dedication

To My

Family

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Introduction

Ovarian malignancy accounts for almost 25% of gynaecological cancer, making it the fifth common malignancy in females. The disease has a very high mortality rate and account for 50% of all deaths from cancer of female genital tract. No satisfactory investigations for screening, early diagnosis has yet been established and the disease has often spread widely when first found. Ovarian cancer, without doubt, presents the greatest challenge to the gynaecological oncologist **(K.R. Peel, 1995)**.

Treatment of ovarian cancer is aggressive primary debulking surgery followed by chemotherapy in most cases especially advanced disease. Although different clinical trials have been carried out, only a marginal increase in survival has been obtained. Our lack of basic knowledge of the tumour biology underlying this disease presents a major obstacle to improve treatment, as well as to establish treatment modalities based on aetiological and pathogenetic evidence **(Henriksen et al., 1993)**.

Development as well as maintenance of many adult tissues is achieved by several dynamically regulated processes that include cell proliferation, differentiation, and programmed cell death (apoptosis).

Although a great deal has been learned in recent years about the regulation of cell proliferation, relatively little is known about the regulation of cell death **(Ellis et al., 1991; Raff, 1992)**. Recnetly attention has begun to focus on the mechanisms that regulate programed cell death (apoptosis) **(Williams, 1991)**. Apoptosis is an active process by which many cells die during their development and self-maintenance in complex eukaryocytes **(Kerr et al., 1972)**. Cell death by apoptosis occurs when a cell activates an internally encoded suicide program as a result of either extrinsic or interinsic signals.

Apoptotic cell death is characterized by plasma membrane blebbing, cell volume loss, nuclear condensation, and endonucleolytic degradation of DNA at nucleosomal intervals **(Wyllie et al., 1980)**.

Although apoptosis plays an important role in normal physiological situations, where it help to ensure the rate of new cell production in proliferative tissues is offest by commensurate (متعادل مع) rate of cell death, it is also important clinically because many chemotherapeutic drugs appear to ultimately kill cancer cells by activating undefiend biochemical pathways leading to programmed cell death.

Some of genes involved in the regulation of the physiological cell death have been identified, among these bcl-2 gene has emerged as a key regulator of the cell death process. Bcl-2 appears to control a down-stream event in a final

common pathway leading to apoptotic cell death, and can protect cells from death induced by myriad of insults including radiation, chemotherapeutic drugs, cytotoxic lymphokines, some viruses, excitatoxic neutrotransmitters and growth factor depreviation. In vivo, Bcl-2 expressed in a variety of cell types particularly long lived cells such as memory lymphocytes and some types of neurons, as well as regenerating stem cells that line the basement membrane and prostate.

The Bcl-2 (B-cell lymphoma/leukaemia 2) gene was first discovered because of its involvement in the t(14,18) chromosomal translocations found in the majority of non-Hodgkin's lymphomas. As consequence of this translocation, Bcl-2 gene from 18q21 moves into juxtaposition with powerful enhancer elements located within immunoglobulin heavy chain locus at 14Q32, thus deregulating the expression of Bcl-2 gene in these tumors of B-lympocyte origin. The end result is the continous production at high level of the normal Mw 26,000 of Bcl-2 protein which is the principle product of Bcl-2 gene **(John C. Reed et al., 1991)**.

The human Bcl-2 protein is an intracellular integral membrane protein. The topic of intracellular membranes in which Bcl-2 residues. However is controversial, Recently **Jacobson et al. (1993)** obtained evidence from 2-color immunofocal microscopy suggesting that Bcl-2 can enter membranes of endoplasmic reticulum, nuclear envelop and mitochondria. Where

overexpressed in fibroblast like cells. In separate study involving primarily immunoelectromicroscopic methods, **Monghan et al.,** Reported that Bcl-2 residues in nuclear envelop and outer mitochondrial membranes.

PROGNOSTIC FACTORS IN OVARIAN CARCINOMA

Histopathological type as serous tumours are said to be more aggressive than endometroid and mucinous type, tumor grade, tumor stage presence of ascites, residual tumor after surgery, new prognostic markers include DNA ploidy, S-phase Fraction, Estrogen and Progesterone receptor status, cerb B2 oncogen expression, Epidermal growth factor receptor expression and Bcl-2 oncogen expression appear to be an important prognostic factor in ovarian carcinoma.

AIM OF THE WORK

1. To study Bcl-2 expression in:
   a) Normal ovarian tissues.
   b) Benign ovarian neoplasms.
   c) Malignant ovarian neoplasms.
2. Evaluate the Correlation between Bcl-2 expression in ovarian tumors and survival.