MULTI-DRUG RESISTANT PROTEIN EXPRESSION IN RETINOBLASTOMA

IN

PRIMARY ENUCLEATED EYES

VERSUS

EYES ENUCLEATED AFTER FAILURE OF CONSERVATIVE TREATMENT

THESIS

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By

Mohammed Mahmoud Abdel-Salam

M.B., B.Ch., M.S. "Ophthalmology" Ain Shams University

SUPERVISED BY

PROF. DR. ZAFER F. ISMAIL
Professor of Ophthalmology
Faculty of Medicine
Ain Shams University

PROF. DR. OTHMAN A. ZIKO
Professor of Ophthalmology
Faculty of Medicine
Ain Shams University

DR. HISHAM KHAIRY ABDEL DAYEM
Assistant Professor of Ophthalmology
Faculty of Medicine
Ain Shams University

DR. WESAM MOHAMMED OSMAN
Assistant Professor of Pathology
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
Cairo - Egypt
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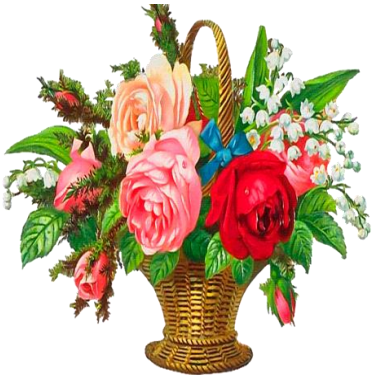

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ABC	ATP-binding cassette
ATP	Adenosine Triphosphate
CEV	Carpoblatin, Etoposide, Vincristine regimen
CFTR	Cystic fibrosis transmembrane conductance regulator
cGy	CentiGray
CNS	Central nervous system
CsA	Cyclosporin A
CT	Computed Tomography
DD	Disc Diameter
DNA	deoxyribonucleic acid
EBR	External Beam Radiation
EUA	Examination under anaesthesia
Gy	Gray
H_2O_2	Hydrogen peroxide
HDL	High density lipoprotein
IHC	Immunohistochemistry
K	Potassium
KDa	KiloDalton

MDR1	Multidrug resistant protein 1
MRI	Magnetic resonance imaging
MSD	Membrane spanning domain
NaCl	Sodium Chloride
NBD	Nucleotide binding domain
PBS	Phosphate buffer saline
P-gp	P-glycoprotein
RNA	Ribonucleic acid
SUR	Sulphonylurea receptor
TCT	Thermochemotherapy

INTRODUCTION

Retinoblastoma is the most common primary intra-ocular malignancy of childhood and accounts for about 3% of all childhood cancers. It occurs in about 1:17000 live births **(Kanski and Bowling, 2011)**. When it presents at an advanced stage, the mortality is very high up to 100% **(Shelil et al., 2003)**. It is considered one of the important conditions in pediatric ophthalmology in Egypt **(Ziko et al., 1989)**.

Histologically, retinoblastoma may be differentiated showing numerous typical rosettes, more differentiated tumor cells and very well developed inter-cellular junctions. Undifferentiated tumors show the opposite characters. Advanced retinoblastoma tumors requiring enucleation are usually of the undifferentiated type **(Ziko et al., 1989)**.

Treatment options are wide and should be tailored according to the patient condition. They include enucleation, chemotherapy, photocoagulation, thermotherapy and radiotherapy **(Shetlar et al., 2008)**.

There is an increasing trend towards conservative treatment. While chemotherapy is considered a huge leap towards such treatment, there are tumors that prove resistant to chemotherapeutic agents **(Di Nicolantonio et al., 2003)**. Enucleation is still the most commonly used treatment modality in advanced retinoblastoma **(Shelil et al., 2003)**.

The ATP-binding cassette (ABC) transporters are membrane-bound proteins that efflux xenobiotics from the liver, kidney and

gastrointestinal tract. They are thought to cause resistance to chemotherapeutic agents by their efflux from cells and are alleged to act against chemotherapy used for treatment of retinoblastoma. ABC transporters include breast cancer resistance protein (BCRP; ABCG2), multidrug-resistant protein1/P-glycoprotein (MDR1/Pgp; ABCB1), multidrug resistance-associated protein 1 (MRP1; ABCC1), MRP2 (ABCC2) and MRP4 (ABCC4) **(Wilson et al., 2006)**.

Chan et al., 1989, showed increased expression of MDR1/Pgp in retinoblastoma. Later, **Chan et al., 1996**, documented improved clinical outcomes in patients with retinoblastoma in whom chemotherapy was supplemented with cyclosporine as an inhibitor of MDR1/Pgp. In a later study, Chan et al., 1997, suggested that multidrug resistance-associated protein 1 (MRP1) conveys an alternative means of drug resistance in the presence of MDR1/Pgp inhibitors.