Correlation between ERCC1 Expression and Response to Cisplatin in Malignant Pleural Mesothelioma

Thesis

Submitted for Partial Fulfillment of MD Degree in Clinical Oncology and Nuclear Medicine

Presented by

Sara Essam Mohamed Zaki

M.B, B.Ch, M.Sc.

Faculty of Medicine, Ain Shams University

Supervised by

Prof. Dr. Tarek Hussein Kamel

Professor of Clinical Oncology

Faculty of Medicine, Ain Shams University

Prof. Dr. Khaled Elhusseiny Nasr

Professor of Clinical Oncology

Faculty of Medicine, Ain Shams University

Prof. Dr. Manal Mohamed El Mahdy

Professor of Pathology

Faculty of Medicine, Ain Shams University

Prof. Dr. Amr Lotfy Farag

Assistant Professor of Clinical Oncology

Faculty of Medicine, Ain Shams University

Dr. Mohamed Essam Saleh

Lecturer of Clinical Oncology

Faculty of Medicine, Ain shams University

Faculty of Medicine

Ain Shams University

2019

سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to ALLAH, the Most Kind and Most Merciful.

I'd like to express my respectful thanks and profound gratitude to ***Prof. Dr. Tarek Hussein Kamel,*** *Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to ***Prof. Dr. Khaled Elhusseiny Nasr,*** *Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to ***Prof. Dr. Manal Mohamed El Mahdy,*** *Professor of Pathology, Faculty of Medicine, Ain Shams University, for her great help, active participation and guidance.*

I wish to introduce my deep respect and thanks to ***Prof. Dr. Amr Lotfy Faraq,*** *Assistant Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for his kindness, supervision and cooperation in this work.*

Also, I would like to express my deep gratitude to ***Dr. Mohamed Essam Saleh,*** *Lecturer of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain shams University, for giving me the great support and encouragement throughout the whole work.*

I would like to express my hearty thanks to all ***my family*** *for their support till this work was completed.*

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Sara Essam

List of Contents

List of Tables

List of Tables (Cont...)

List of Figures

List of Figures (Cont...)

List of Figures (Cont...)

List of Abbreviations

Abb.	Full term
ALT	*Alanine Transferase*
ANC	*Absolute Neutrophilic Count*
ASS1	*ArgininoSuccinate Synthetase 1*
AST	*Aspartate Transferase*
BAP 1	*Breast cancer susceptibility Assocciated Protein gene 1*
BSC	*Best Supportive Care*
CD44	*Cell–Matrix Contact*
CDKN2A	*Cyclin-Dependent Kinase Inhibitor 2A*
CK5/6	*Cytokeratin 5/6*
CR	*Complete Response*
CRP	*C-Reactive Protein*
CT	*Chemotherapy*
CT	*Computed Tomography*
CTC	*Common Toxicity Criteria*
CTLA-4	*Cytotoxic T-Lymphocyte Associated protein*
CXR	*Chest X-Ray*
D2-40	*Podoplanin*
DMM	*Diffuse Malignant Mesothelioma*
DNA	*Deoxyribonucleic Acid*
ECOG	*Eastern Cooperative Oncology Group*
EGFR	*Epidermal Growth Factor Receptor*
EPD	*Extended Pleurectomy Decortication.*
EPP	*Extrapleural Pneumonectomy*
ERCC1	*Excision Repair Cross-Complementation Group 1*
ERM	*Ezrin, Radixin And Moesin*
FDA	*Food and Drug Administration*
FDG	*Fluoro-Deoxy-Glucose*

List of Abbreviations (Cont...)

Abb.	Full term
GM-CSF	*Granulocte Macrophage Colony Stimulating Factor*
HMGB1	*High-Mobility Group Box 1*
IARC	*International Agency for Research on Cancer*
ICI	*Immune Checkpoint inhibitors*
ICL	*Interstrand Crosslink*
IHC	*Immunohistochemistry*
IMIG	*International Mesothelioma Interest Group*
IUD	*Intrauterine Device*
LDH	*Lactate Dehydrogenase*
LMM	*Localized Malignant Mesothelioma*
LMR	*Lymphocyte-To-Monocyte Ratio*
miRNAs	*Micro Ribonucleotide Acid*
MM	*Malignant Mesothelioma*
MPM	*Malignant Pleural Mesothelioma*
MRI	*Magnetic Resonance Imaging*
mTOR	*Mammalian Target Of Rapamycin*
NCDB	*National Cancer Data Base*
NCI	*National Cancer Institute*
NER	*Nucleotide Excision Repair pathway*
NF2	*Neurofibromatosis 2*
NF-κB	*Nuclear factor kappa-light-chain-enhancer of activated B cells*
NHL	*Non Hodgkin Lymphoma*
NLR	*Neutrophil Lymphocyte Ratio*
ORR	*Overall Response rate*
OS	*Overall Survival*
PD	*Progressive Disease*
PD-L1	*Programmed Death Ligand 1*

List of Abbreviations (Cont...)

Abb.	Full term
PET-CT	*Positron Emission Tomography*
PFS	*Progression-Free Survival*
PLR	*Platelet Lymphocyte Ratio*
PR	*Partial Response*
pRb	*Retinoblastoma Protein*
PS	*Performance Status*
PSA	*Prostatic Specific Antigen*
RECIST	*Response Evaluation Criteria In Solid Tumors*
RT	*Radiotherapy*
SD	*Stable Disease*
SD	*Standard Deviation*
SE	*Standard Error*
SEER	*Surveillance, Epidemiology and End Results*
SNVs	*Single nucleotide Variants*
SUV	*Standarized Uptake Value*
SV40	*Simian-Virus 40*
TEAD	*TEA domain transcription factor*
TNF-α	*Tumor-Necrosis Factor- α*
TTF1	*Thyroid Transcription Factor 1*
ULN	*Upper Limit of Normal*
VATS	*Video Assisted Thoracoscopic Surgery*
WBC	*White Blood Cell count*
WDPMs	*Well Differentiated Papillary Mesothelioma*
WHO	*World Health Organization*
WT1	*Wilm's Tumor gene*
XPF	*Xeroderma Pigmentosum complementation Factor*
YAP-1	*Yes Assocciated Protein 1*

ABSTRACT

In case of ERCC1 deficiency, the DNA damage is not repaired, and the altered DNA is unable to replicate, or perform its function, leading to cell damage.

Expression of ERCC1 has been studied as a predictive marker for Cisplatin resistance in different tumors including MPM. Four previously published studies showed a significant correlation between Negative expression of ERCC1 and good response to Cisplatin and also with longer PFS.

Our study showed that ERCC1 was expressed in 33.9% of the patients.

ERCC1 positivity was significantly associated with poor response to treatment, shorter PFS & OS.

Keywords: Excision Repair Cross-Complementation Group 1 - Deoxyribonucleic Acid - Diffuse Malignant Mesothelioma

INTRODUCTION

Malignant pleural mesothelioma (MPM) arises from the mesothelium lining the pleural cavity. The disease is mainly linked to asbestos exposure ***(Welch, 2007)***.

Different studies have showed a relation between incidence of mesothelioma and asbestos usage in the previous decades ***(Nishikawa et al., 2008)***.

In Egypt, MPM is mostly related to environmental cause with a higher incidence in females and young adults. Epidemiological data proved that the disease incidence increased markedly, 635 cases of mesothelioma were diagnosed at the National Cancer Institute (NCI) and Abbassia Chest Hospital, Cairo between the year 2000 and 2003. This large number is four times more than the number diagnosed in the previous 11 years ***(Gaafar and Eldin, 2005).***

MPM is of poor prognosis in late stage, and only few number of patients are diagnosed at an early stage when curative treatment is possible. Inoperable patients usually receive combined platinum-based chemotherapy regimen ***(Sorensen, 2008).***

Because multimodality treatment have showed improved survival only in selected cases, most of patients with MPM are treated with systemic chemotherapy ***(Krug et al., 2009).***

First-line chemotherapy based on Platinum combined with Pemetrexed has improved average survival time up to 12 months in mesothelioma patients and is recommended as the standard treatment ***(Nowak, 2012).***

Also, combined Cisplatin and Gemcitabine therapy has showed comparable response and survival rates in various phase II trials, with response rates 12–48% and median overall survival (OS) 9.4–13 months ***(Kalmadi et al., 2008).***

Platinum compounds are used in treatment of different cancers, but their efficacy could be limited by the intrinsic or extrinsic resistance of the cancer cells toward their mechanism of action ***(Martin et al., 2008).***

Platinum cytotoxicity is based on the alteration of DNA (Deoxyribonucleic Acid) bases by formation of covalent bond with DNA leading to both inter & intra-strand cross links ***(Bhagwat et al., 2009).***

Nucleotide excision repair is an important pathway in maintaining DNA integrity by the removal of theses helix-distorting cross-links. This pathway seems to be a key element in mediating resistance toward platinum compounds.

There are three major steps in this pathway. First, the recognition of the DNA damage, its excision, and finally, the re-synthesization of the excised area.