



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

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا انك لا تعلم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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List of Contents

Title	Page No.
List of Tables	i
List of Figures	iii
List of Abbreviations	vi
Introduction	1
Aim of the Work.....	14
Review of Literature	
📖 Epidemiology of Malignant Pleural Mesothelioma	15
📖 Pathogenesis.....	22
📖 Classification	27
📖 Biomarkers	28
📖 Diagnosis	34
📖 Staging.....	46
📖 Treatment	48
Patients and Methods	57
Results	66
Discussion	89
Summary and Conclusion	95
Recommendations	97
References	98
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	Pleura Mesothelial markers	44
Table (2):	The 7th edition of the AJCC Cancer Staging of malignant pleural mesothelioma	46
Table (3):	Response criteria of Modified RECIST.....	60
Table (4):	Demographic data distribution of the study group	67
Table (5):	Past medical history distribution of the study group	67
Table (6):	Pleural effusion distribution of the study group	68
Table (7):	Side pleural and type of pathology distribution of the study group	68
Table (8):	ERCC1 expression distribution of the study group	69
Table (9):	Chemotherapy given distribution of the study group	70
Table (10):	Response to treatment of the study group.....	71
Table (11):	Surgery distribution of the study group.....	71
Table (12):	Comparison between negative ERCC1 and positive ERCC1 according to demographic data.....	72
Table (13):	Comparison between negative ERCC1 and positive ERCC1 according to associated medical comorbidities	75
Table (14):	Comparison between negative ERCC1 and positive ERCC1 according to pleural effusion and lymph nodes.....	76

List of Tables (Cont...)

Table No.	Title	Page No.
Table (15):	Comparison between negative ERCC1 and positive ERCC1 according to pleural side and type of pathology.....	77
Table (16):	Comparison between negative ERCC1 and positive ERCC1 according to response to Cisplatin based chemotherapy	78
Table (17):	Comparison between negative ERCC1 and positive ERCC1 according to response to Cisplatin based chemotherapy	78
Table (18):	Progression free survival of the study group	80
Table (19):	Progression free survival between ERCC1 expression level is shown.....	81
Table (20):	PFS between all parameters characteristics is shown.....	82
Table (21):	One year survival of the study group	83
Table (22):	1 year survival between ERCC1 expression level is shown.....	84
Table (23):	Overall survival of the study group.....	85
Table (24):	OS between ERCC1 expression level is shown.....	86
Table (25):	Overall survival between all parameters characteristics is shown	87

List of Figures

Fig. No.	Title	Page No.
Fig. (1):	Different mechanisms of asbestos-induced Mesothelioma.....	23
Fig. (2):	Asbestos-exposed mesothelial cells produce tumor necrosis factor- α (TNF- α) which binds to its receptor and activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway	23
Fig. (3):	Dysregulation of the Hippo pathway in mesothelioma leads to nuclear translocation of Yes-associated protein 1 (YAP1) and activation of TEA domain-transcription-factor (TEAD)-dependent transcription to promote cell proliferation and prevent apoptosis	26
Fig. (4):	Cisplatin reacts with N7-sites of purine bases, and a double reaction may covalently link purines.	31
Fig. (5):	NER-nucleotide excision repair begins with the formation of a DNA adduct causing a change in the DNA helix shape, damaged DNA binding factor binds to pre-incision complex which localizes the damaged area of DNA.....	32
Fig. (6):	CXR showing a right side pleural effusion	36
Fig. (7):	CXR shows circumferential right side pleural thickening, with extension along the minor fissure.....	36
Fig. (8):	Axial CT image showing right extensive nodular pleural thickening with ipsilateral volume loss	37
Fig. (9):	Axial MRI image showing right enhancing soft tissue with focal invasion of the right anterior chest wall.....	38

List of Figures (Cont...)

Fig. No.	Title	Page No.
Fig. (10):	Sagittal MRI image showing encasement of the right hemidiaphragm and invasion of the anterior liver.....	39
Fig. (11):	Axial PET/CT image showing FDG-avid nodular pleural thickening in the left hemithorax which extends along the left interlobar fissure	40
Fig. (12):	Axial PET/CT image showing FDG-avid pleural thickening in the right hemithorax and focal invasion of the posterolateral chest wall.....	41
Fig. (13):	PET/CT image showing FDG-avid pleural nodules in the anterior right hemithorax, as well as FDG-avid paracardiac (black arrow) and right hilar lymphadenopathy.....	41
Fig. (14):	Diffuse positive staining of malignant mesothelioma for ERCC1 in more than 50% of neoplastic cells.	62
Fig. (15):	Another case malignant showing positive immunostaining for ERCC1 in more than 50% of neoplastic cells.....	62
Fig. (16):	Immunostaining of ERCC1 in more than 10% of neoplastic mesothelial cells.	63
Fig. (17):	Malignant mesothelioma showing very few immunoreactivity in less than 10%.....	63
Fig. (18):	Negative immunoreactivity for ERCC1.	64
Fig. (19):	Pie chart ERCC1 expression distribution of the study group.	69
Fig. (20):	Bar chart between negative ERCC1 and positive ERCC1 according to age (years).	73

List of Figures (Cont...)

Fig. No.	Title	Page No.
Fig. (21):	Bar chart between negative ERCC1 and positive ERCC1 according to sex.	73
Fig. (22):	Bar chart between negative ERCC1 and positive ERCC1 according to residency and performance.	74
Fig. (23):	Bar chart between negative ERCC1 and positive ERCC1 according to DM and HTN.	75
Fig. (24):	Bar chart between negative ERCC1 and positive ERCC1 according to pleural effusion and lymph nodes.	76
Fig. (25):	Bar chart between negative ERCC1 and positive ERCC1 according to side pleural and type of pathology.	77
Fig. (26):	Kaplan-Meier progression free survival of the study group.	80
Fig. (27):	The progression free survival Curve According to ERCC1 Expression Level.	81
Fig. (28):	One year survival of the study group.	83
Fig. (29):	1 year survival between ERCC1 expression level is shown.	84
Fig. (30):	Kaplan-Meier overall survival of the study group.	85
Fig. (31):	OS between ERCC1 expression level is shown.	86

List of Abbreviations

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

List of Abbreviations (Cont...)

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

List of Abbreviations (Cont...)

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

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 these 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-synthesis of the excised area.