Value of Soluble Mesothelin Related Protein (Mesomark) and Osteopontin as Markers for Malignant Pleural Mesothelioma

Thesis

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By

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Ehab Thabet Aziz

☙ Dedication ❧

TO .....

MY

FAMILY

☙ List Of Abbreviations ❧

5 fu	: 5 Fluro uracil
ADA	: Adenosine deaminase
AUC	: Area Under the Curve
BCG	: Bacillus Calmette-Guerin Vaccine
BMI	: Body Mass Index
BRD	: Benign Respiratory Diseases
C	: Cisplatinum
CALGB	: Cancer and leukaemia group B
CBC	: Complete Blood Count (Picture)
CEA	: Carcinogenic Embryonic Antigen
CGy	: Centi Grey
CI	: Confidence Interval
COPD	: Chronic Obstructive Pulmonary Diseases
CT	: Computed Tomography
CXR	: Chest X Ray
dl	: deci-litre
DMP1	: Dentin Matrix Protein 1
DNA	: Deoxyribonucleic acid
EGFR	: Epidermal Growth Factor Receptor
ELISA	: Enzyme Linked Immuno Sorbent Assay
EM	: Electron Microscope
ENAM	: Enamelin
EPP	: Extra-Pleural Pneumonectomy
Eta-1	: Early T lymphocyte activation 1
EWG	: Environmental Working Group
FDG	: 2-Floro 2-deoxy-D glucose
FEV1	: Forced Expiratory Volume in the first second
FOB	: Fiber Optic Bronchoscope
GCV	: Ganciclovir
gm	: Gram
Gy	: Grey
H&E	: Haematoxyline and Eosin
HBME-1	: Anti mesothelial antibody
Hsvtk	: Herpes Simplex Virus Thymidine Kinase
I 125	: Iodine 125
ICM	: Ischemic Cardio-Myopathy
IG	: Immunoglobulin
IL	: Interleukins
INF	: Interferon
Ir 192	: Iridium 192
KD	: Kilo-Dalton
LC	: Lung Cancer
LDH	: Lactate Dehydrogenase
LDR	: Length / Diameter Ratio

☙ List Of Abbreviations (Cont.) ❧

L-NDDP	: Liposomal- Cisplatin analogue (Liposome-entrapped Cisplatin)
LSD	: Least Significant Difference
M	: Mitomycin
mAb	: Monoclonal Antibody
MEPE or MEP	: Matrix Extra-cellular Phophoglycoprotien
ml	: Millilitre
µm	: Micro meter
MM	: Malignant Mesothelioma
mm	: Millimeter
MPF	: Megakaryocyte Potentiating Factor
MPM	: Malignant Pleural Mesothelioma
MRI	: Magnetic Resonance Imaging
MRP	: Multi Drug Resistance Associated Protein
NCI	: National Cancer Institute
ng	: Nano gram
NK	: Natural Killer
nM/L	: Nano Mole/ Litre
NSCLC	: Non Small Cell Lung Cancer
OPN	: Osteopontin
OV569	: Ovarian monoclonal antibody
P 32	: Radioactive Phosphorus 32
PA	: Postero-Anterior
PAS	: Periodic Acid Schiff
PDGF	: Platelet Derived Growth Factor
PDT	: Photo Dynamic Therapy
PET	: Positron Emission Tomography
RB	: Retinoblastoma
ROC	: Receiver Operating Characteristic
RPCI	: Ross Well Park Center Institute
Rt	: Right
RT	: Radiotherapy
SIBLING	: Small Intgrin-Binding Ligand; N-Linked Glycoprotein
SMRP	: Soluble Mesothelin Related Protein
SPSS	: Statistical Package for Social Science
SV 40	: Simian Virus 40
TAG	: T Antigen
TB	: Tuberculosis
TNM	: Tumor, Node, and Metastasis
USA	: United States Of America
VATS	: Video Assisted Thoracoscopy Surgery
VEGF	: Vascular Endotelial Growth Factor
Vp 16	: Vepsid
VS	: Versus
WHO	: World Health Organization

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INTRODUCTION

Malignant mesothelioma was a rare tumor but it became common especially in areas where asbestos exposure was common either in the environment or in the workplaces, it tended to be an aggressive tumor that arised from the serosal surface cells lining the pleura, peritoneum and pericardium ***(Price and Ware, 2004).***

Despite of decreasing or even preventing industries using asbestos, the incidence of malignant mesothelioma is increasing, which may be due to the delay in the patient's complaint or the long latency period between the exposure and the developing of mesothelioma, as up to 99% of asbestos associated cases have latency period more than 15 years from first exposure to death due to the disease with median latent period being found to be 32 years ***(Lanphear and Buncher, 1992).***

Asbestos exposure is the primary etiological factor known for mesothelioma and association to occupational asbestos exposure has been documented in 80% of mesothelioma cases. The majority of mesotheliomas occur with amphibole fibers exposure. In general a much smaller fibers burden is associated with mesothelioma induced by amphibole ($1/400^{th}$ asbestos burden) compared with chrysolite. Males are

at a much higher risk for mesothelioma than females due to occupational exposure (plumbers, pipe fitters, insulation installers, and shipyard workers) ***(Puntoni et al., 2003).***

During the past several decades, cytogenetic studies have been performed in an attempt to identify specific non-random alterations that may prove to be of diagnostic value. Despite these efforts, karyotyping of mesotheliomas did not provide specific diagnostic anomalies. Evolving of molecular techniques, such as tumor suppressor gene methylation and micro-array gene profiling have yielded insight into mesothelioma oncogenesis, diagnosis, prognosis and potential therapy ***(Kettunen et al., 2001).***

Sensitive, specific and less invasive markers can facilitate early diagnosis of malignant mesothelioma, and early therapeutic intervention in patients with mesothelioma is more likely to be beneficial than late intervention. Thus, simple specific and sensitive markers for early detection of malignant mesothelioma could lead to more effective treatment. Mesothelin is a 40 kDa glycoprotein that is attached to the cell surface by phosphatidylinositol and is thought to have a role in cell-adhesion and possibly in cell-to-cell recognition and signaling, it is synthesized as a precursor 69 kDa protein and forms two proteins, the membrane-bound mesothelin and a

soluble protein megakaryocyte potentiating factor (MPF) ***(Urwin and Lake, 2000).***

A third member of the mesothelin / MPF family was identified by its ability to bind to OV569 here, it is referred to any soluble molecule related to mesothelin / MPF that is recognized by OV569 as soluble mesothelin related. Increased concentrations of soluble mesothelin related proteins (SMRP) have been detected in serum samples of patients with ovarian carcinoma and in a few patients with other carcinomas ***(Robinson et al., 2003).***

Since most mesotheliomas retain some mesothelial differentiation characteristics, raised concentrations of SMRP usually occur in the serum of patients with mesothelioma ***(Scholler et al., 1999).***

The sure diagnosis of any malignant disease is the tissue biopsy from the tumor, but with the use of new markers which have a very high specificity which reaches 100% and high sensitivity which reaches about 84% ***(Robinson et al., 2003)***, they may be very helpful in the diagnosis of the disease and it may be very beneficial in the early detection of the disease in the exposed persons who are at risk of developing of malignant mesothelioma and their relatives who are exposed to the same pollutants in the areas of inhabitants or dealing with worker's

clothes which are carrying the asbestos fibers to the worker's homes.

A significantly higher concentration of osteopontin was detected in patients with diagnosed cases of mesothelioma compared to subjects with asbestos exposure. The levels of osteopontin were not significantly different in unexposed control subjects versus those subjects exposed to asbestos. Nearly 78% of mesothelioma patients showed elevated osteopontin levels. In over 85% of cases osteopontin levels differentiated patients with mesothelioma versus benign lung conditions ***(Pass et al., 2005) (A).***

AIM OF THE WORK

The aim of this work is to determine the level of Soluble Mesothelin Related Protein (Mesomark) and Osteopontin in serum to evaluate their specificity and sensitivity as new and less invasive markers in diagnosis of malignant pleural mesothelioma comparing them with pleural biopsy.