Soluble Mesothelin-Related Peptide as a Marker of Response to Platinum-Based Chemotherapy in Malignant Pleural Mesothelioma

Thesis

Submitted for partial fulfillment of the M.D. Degree
in Clinical Oncology and Nuclear Medicine

By

Mohamed Sobhi Ali Ali

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

Faculty of Medicine - Ain Shams University

Supervised by

Dr./ Hesham Mahmoud Hassan Elwakeil

Prof. of Clinical Oncology and Nuclear Medicine
Faculty of Medicine - Ain Shams University

Dr./ Mohammad Sabry El-kady

Assistant Prof. of Clinical Oncology and Nuclear Medicine
Faculty of Medicine - Ain Shams University

Dr./ Walid Abd El Moniem Bayomy

Assistant Prof. of clinical Oncology and Nuclear Medicine
Faculty of Medicine - Ain Shams University

Dr./ Mohamed Essam Salah

Lecturer of Clinical Oncology and Nuclear Medicine
Faculty of Medicine - Ain Shams University

Dr./ Wessam El Sayed Saad

Lecturer of Clinical Pathology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2017

سورة البقرة الآية: ٣٢

Acknowledgments

My thanks are submitted first and foremost to **ALLAH** *Who gave me the strength and ability to complete this work.*

I would like to express my thanks and appreciation to **Dr./ Hesham Mahmoud Hassan Elwakeil,** *Prof. of Clinical Oncology and Nuclear Medicine, Faculty of Medicine - Ain Shams University, for his candid opinions, timely feedback, insights and the effort and time he has devoted to the fulfillment of this work. I am indebted to his meticulous follow-up and constructive criticism.*

My sincere gratitude and appreciation are also due to **Dr./ Mohammad Sabry El-kady,** *Assistant Prof. of Clinical Oncology and Nuclear Medicine, Faculty of Medicine - Ain Shams University, for his kind help, constant encouragement, constructive criticism, and the time and effort he dedicated to this work.*

I can't forget to thank with all appreciation, **Dr./ Walid Abd El Moniem Bayomy,** *Assistant Prof. of clinical Oncology and Nuclear Medicine, Faculty of Medicine - Ain Shams University, for the efforts and time he has devoted to accomplish this work.*

I would like also to thank **Dr./ Mohamed Essam Salah,** *Lecturer of Clinical Oncology and Nuclear Medicine, Faculty of Medicine - Ain Shams University, for his greate help and support.*

I am really indebted to **Dr./ Wessam El Sayed Saad,** *Lecturer of Clinical Pathology, Faculty of Medicine - Ain Shams University, for his valuable role in the practical part of this work.*

Last but not least, this work is dedicated to all our **patients**, *without them, this work would have been of no value, and also to my* **colleagues,** *for their support and care in every step of my career.*

I can't forget to thank all members of my family, specially my **Parents,** *my* **Wife** *and my* **Son,** *for pushing me forward in every step in the journey of my life.*

Mohamed Sobhi Ali Ali

List of Contents

List of Abbreviations

Abbr.	Full-term
ADA	: Adenosine deaminase
APC	: Antigen-presenting cell
ARD	: Asbestos-related disease
ARF	: Alternative reading frame gene
AS	: Argininosuccinate synthase
ASC	: Active symptom control
ASC	: Active symptom control
ASS1	: Argininosuccinate synthetase
BAP1	: BRCA associated protein 1
BTS	: British Thoracic Society Standards of Care Committee
CALGB	: Cancer and Leukemia Group B
CDKN2A	: Cyclin dependent kinase inhibitor 2A
CEA	: Carcinoembryonic antigen
CK	: Cytokeratins
CT	: Computed tomography
CTV	: Clinical target volumes
DCR	: Disease control rate
DVH	: Dose–volume histograms
EAP	: Extended Access Program
EBUS	: Endo-bronchial ultrasonography
EFEMP1	: Epidermal growth factor containing fibulin-like extracellular matrix protein 1
EMA	: Epithelial membrane antigen
EORTC	: European Organization for Research and Treatment of Cancer
EPP	: Extra pleural pneumonectomy
ERCC1	: Excision repair cross-complementing 1

FAK : Focal adhesion kinase
FDG : Fluorine182fluoro2deoxydglucose
FEV1 : Forced expiratory volume in 1 second
FGPS : Folypoly-c-glutamate synthetase
FISH : Fluorescence in situ hybridization
FNA : Fine-needle aspiration
FR-a : Folate receptor a
HA : Hyaluronate
HCRT : Highly conformal RT
HDACs : Histone deacetylase
HM : Human mesothilal
HSP90 : Heat shock protein S90
IALCS : International Association for the Study of Lung Cancer
ICRU-83 : International Commission on Radiation Units and Measurements Report 83
IGFR : Insulin growth factor receptor
IHC : Immunohistochemistry
IMIG : International Mesothelioma Interest Group
IMRT : Intensity-modulated RT
LATS2 : Large tumor suppressor 2 gene
MARS1 : Mesothelioma and Radical Surgery 1
MARS2 : Mesothelioma and Radical Surgery 2
MHC : Major histocompatibility complex
MLD : Mean lung dose
mOS : Median Overall survival
mPFS : Median progression free survival
MPM : Malignant pleural mesothelioma
MRI : Magnetic resonance imaging
mTOR : Mammalian target of rapamycin
MVP : Mitomycin, vinblastine, and cisplatin

NCCN : The National Comprehensive Cancer Network
NCI : National Cancer Institute
NF2 : Neurofibromatosis type 2
NF2 : Neurofibromatosis type 2 gene
NSABP : National Surgical Adjuvant Breast Project
NSCLC : Non-small-cell lung cancer
OPN : Osteopontin
OS : Overall survival
P/D : Pleurectomy/decortication
PDGF : Platelet derived growth factor
PDGFR : Platelet derived growth factor receptor
PFTs : Pulmonary function tests
PI3K : Phosphoinositide3kinase
PS : Performance status
PTV : Planning target volume
QALY : Quality-adjusted life years
RECIST : Response evaluation criteria in solid tumor
RRM1 : Ribonucleotide reductase M1
RT : Radiation therapy
RT : Radiotherapy
SEER : Surveillance, Epidemiology and results
SMRP : Serum mesothelin-related peptide
SUV : Standard uptake value
SUV : Standarduptake value
SV-40 : Simian virus-40
TCR : T-cell receptor
TGFb : Transforming growth factor b
TK : Tyrosine kinase
TS : Thymidylate synthase
TTF-1 : Thyroid transcriptionfactor 1

UICC : Union for International Cancer Control
VAT : Video-assisted thoracoscopy
VATS : Video-assisted thoracic surgery
VEGF : Vascular endothelial growth factor
VEGFR : Vascular endothelial growth factor receptor
WHO : World HealthOrganization
WT-1 : Wilms' tumor antigen 1
3DCRT : 3D conformal RT

List of Tables

List of Figures

Abstract

In malignant pleura mesothelioma (MPM), radiologic assessment of disease status is confusing soluble mesothelin-related peptide (SMRP) has utility in distinguishing MPM from benign pleural disease. We evaluated SMRP as predictive marker in relation to the disease course of MPM.

Patients and Methods: Serial plasma samples from patients with unresectable stage IV MPM were prospectively collected before starting and after finishing 3 cycles of platinum-based pemetrexed regimen. SMRP levels were measured. Radiologic assessment by modified resist criteria across time showing disease progression, stability, or shrinkage were compared with corresponding changes in SMRP levels.

Results: From 40 patients (female: 16; male: 24), 80 samples were collected. At study entry, all patients had measurable disease and SMRP level in 40 patients showed that the median SMRP was 0.32 ng/ml (IQR = 0.25-1.01) before chemotherapy) and the median SMRP was 0.29 ng/ml (IQR = 0.2-0.86) after 3 cycle chemotherapy. Percentage change in SMRP more than 10% correlated with the radiologic assessment (*P* .001) by modified RECIST (*P*.001). SMRP level of all partial response group decreased ≥ 10% from baseline level and SMRP level of all progressive decease group increased ≥ 10% from baseline level. No significant difference was observed between the absolute difference of SMRP and different response groups (p 0.227). In addition, Percentage change in SMRP had a significant effect on both OS (p 0.013) and PFS (p 0.023).

Conclusion: Percentage changes rather than absolute change of SMRP levels, are a potentially useful predictive marker of disease course. These findings should be validated prospectively for a role as an objective adjunctive measure of disease course in both clinical trials and clinical practice.

Keywords: Malignant pleural mesothelioma (MPM), Soluble Mesothelin-Related Peptides (SMRP), overall survival (OS), progression free survival (PFS).