

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

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سَبَّحْتَكَ لَا أَعْلَمُ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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List of Abbreviations

<i>Abbr.</i>	<i>Full-term</i>
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 Health Organization
WT-1	: Wilms' tumor antigen 1
3DCRT	: 3D conformal RT

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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 $\geq 10\%$ from baseline level and SMRP level of all progressive disease group increased $\geq 10\%$ 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).