Vascularity Impact on the Treatment Outcome in Malignant Pleural Mesothelioma

A thesis

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Candidate

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List of Abbreviations

Abbr.	Full-term

BerEp4 : Tumor glycoprotein
bFGF : Basic fibroblast growth factor
CALGB : Cancer and Leukemia Group B
CDK : Cyclin-dependent kinase
CEA : Carcinoembryonic antigen
CK : Cytokeratin
CNS : Central nervous system
CT : Computed tomography
EGFR : Epidermal growth factor receptor
EMA : Epithelial membrane antigen
EMT : Epithelial to mesenchymal transition
EORTC : Organisation for Research and Treatment of Cancer
EPP : Extrapleural pneumonectomy
GCSF : Granulocyte colony stimulating factor
HIF-1 : Hypoxia-inducible factor 1
HLA : Human leuckocyte associated Ag
HMFG-2 : Human milk fat globule protein-2
IGF : Insulin-like growth factor
IHC : Immunohistochemistry
IL1 : Interleukin 1
IMRT : Intensity modulated radiotherapy
LDH : Lactate dehydrogenase
MIF : Macrophage migration inhibitory factor
MOC-31 : Tumor glycoprotein

List of Abbreviations (Cont.)

Abbr.	Full-term
MPE	: Malignant pleural effusions
MPM	: Malignant pleural mesothelioma
MRI	: Magnetic resonance imaging
NCI	: National Cancer Institute
NF2	: Neurofibromatosis type 2
OS	: Overall survival
P/D	: Pleurectomy/decortications
PDGF	: Platelet-derived growth factor
PET	: FDG18- Positron-emission tomography
PFS	: Progression free survival
PGE2	: Prostaglandin E2
PGF	: Placental growth factor
PIT	: Prophylactic irradiation to intervention tracts
ROS	: Reactive oxygen species
SV40	: Simian virus 40
T2DM	: Type 2 Diabetes mellitus
TGF	: Transforming growth factor
TKIs	: Tyrosin kinase inhibiters
TNF	: Tumor necrosis factor
TTF-1	: Thyroid transcription factor-1
UICC	: Union for International cancer control European
VEGF	: Vascular endothelial growth factor
VHL	: Von Hippel-Lindau
WT	: Wilms tumour gene protein

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Introduction

Malignant mesothelioma is a rare aggressive tumour arising from mesothelial cells of the pleural, peritoneal cavity, pericardium and tunica vaginalis of the testis ***(Tischoff et al., 2011).***

Mesothelioma is estimated to occur in approximately 2500 people in the United States every year, malignant pleural mesothelioma occur mainly in older men (median age of 72 years), median overall survival is approximately 1 year ***(David et al., 2014).***

There are prominent differences in incidence of malignant pleural mesothelioma (MPM) reported from different countries worldwide varying from to 7 per million (Japan) to 40 per million (Australia) inhabitants per year, In Europe the incidence is around 20 per million with large intercountry variation, It is reasonable to accept that these differences are mainly due to differences in historical asbestos import and consumption ***(van Meerbeecke et al., 2011).***

Malignant pleural mesothelioma is most common (MPM), whereas malignant peritoneal mesothelioma accounts only for 6-10%, Infrequent sites of origin are the pericardium and tunica vaginalis in 1-2%, malignant mesothelioma shows either diffuse growth pattern or occurs

as a localized tumour mass, Diffuse type represents an aggressive tumour with poor prognosis and is incurable in most cases ***(Tischoff et al., 2011).*** There are three major types: epithelioid type, sarcomatoid type and biphasic type and the proportion of each is approximately 60, 20 and 20%, respectively. The desmoplastic type is rare probably 1–2% ***(Inai, 2008).***

A lot of data indicate a relationship between mesothelioma and asbestos, the latency periods elapsing between first exposure to asbestos and development of mesothelioma are mostly longer than 40Years, Some recent studies show that the risk increases with the duration of exposure, Possible co-factors in the pathogenesis of asbestos-related mesothelioma include genetic predisposition, diets poor in fruit and vegetables, viruses, immune impairment, recurrent serosal inflammation ***(Bianchi et al., 2007).***

Although the mechanism of carcinogenesis is not fully understood, Several molecular pathways involved in malignant pleural mesothelioma have been identified**;** these include cell cycle regulation, apoptosis, growth factor pathways, and angiogenesis, ***(Zucalia et al., 2011).***

Hallmarks of asbestos fibres inhalation included early and sustained inflammation causally attributed to initial accumulation of alveolar macrophages promoting the

subsequent generation of reactive oxygen species (ROS) that cause DNA damage and induce cells to proliferate in a chronic inflammatory milieu, that induce mesothelial cells transcription and production of cytokine which critical to the initiation of injury, fibrosis and tumor Thus, the oxidants and growth factors seem to be responsible for both dysregulation of mitogenic signaling and loss of tumor suppressor proteins that may govern malignant mesothelioma pathogenesis ***(Comar et al., 2014).***

The tumours require the continuous formation of new blood vessels in order to grow. Malignant mesothelioma cells produce angiogenic factors, such as vascular endothelial growth factor (VEGF**)** ***(Robinson and Lake, 2005).*** Macrophage migration inhibitory factor (MIF) and its receptor CD74 found to be associated with angiogenic activity ***(McClelland et al., 2009).***

Vascular endothelial growth factors (VEGFs) belong to the platelet-derived growth factor supergene family ***(Shibuya, 2013),*** Vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) have crucial roles in both physiological and pathological angiogenesis ***(Akahashi, 2011).*** The blockage of this pathway is a promising therapeutic strategy for inhibiting angiogenesis and tumour growth ***(Moreira et al., 2007).***

The expression of receptor-ligand pair in associated with the angiogenic activity that macrophage migration inhibitory factor(MIF) induces expression of angiogenic CXC chemokines by tumour-associated monocytes and that MIF-dependent expression of angiogenic CXCchemokines is one of several major pathways by which cancer tumoursinduce an angiogenic environment ***(McClelland et al., 2009).***

Malignant pleural mesothelioma clinically manifests after decades of initial exposure to etiologic agents, such as asbestos, and presents with nonspecific symptoms such as dyspnea, pain, or weight loss ***(Ramalingam and Belani, 2008).*** The definite diagnosis can only be established by diagnostic laparoscopy or open surgery along with biopsy to obtain histological examination and immunocytochemical analysis ***(Ahmed et al., 2013).*** The type of mesotheliomas and stage at diagnosis remain the cornerstone for treatment approach ***(Propodisk et al., 2013).***

Factors associated with poor prognosis in patients with MPM include:

Old age, poor performance status (PS), advance disease stage, chest pain thrombocytosis, weight loss, asbestos exposure and long duration of symptoms ***(Shuko Nojir et al., 2011)*** .

National guidelines recommend that patients with MPM be managed by a multidisciplinary team with experience in MPM, Treatment options for patients with MPM include surgery, radiotherapy, and/or chemotherapy ***(David et al., 2014).*** Currently, malignant pleural mesothelioma therapy is guided by clinical stage and patient characteristics rather than by the histological or molecular features of the tumor ***(Zucalia et al., 2011).***

The aim of radical surgery for malignant pleural mesothelioma (MPM) is to achieve greater survival ***(Nakas and Waller, 2014).***

This disease is largely unresponsive to conventional chemotherapy or radiotherapy, and most patients die within 10–17 months of their first symptoms ***(Zucalia et al., 2011).***

Targeted therapy used in MPM such as antiangiogesis agents, immunotherapy, signaling pathway inhibitors ***(Shukla and Shukla, 2014)***, still has an important role in mesothelioma in controlling the symptom and improve quality of life ***(Lang-Lazdunskil, 2014).***