

Malignant pleural mesothelioma: current and future perspectives

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ABSTRACT

Mesothelioma still remains an occupational related cancer with severe outcome. It is usually diagnosed at advanced stage since it does not demonstrate early symptoms. Several efforts have been made towards removing all materials inducing mesothelioma in the work setting and new work protection measures have been applied. Although we have new targeted treatments and radical surgery as arrows in the quiver, the type of mesothelioma and early diagnosis still remain the best treatment approach. Novel treatment modalities have been explored and several others are already on the way. In the current review we will present current data for mesothelioma and future perspectives.

KEY WORDS

Mesothelioma; pathogenesis; diagnosis; treatment; targeted treatment

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Introduction

Malignant pleural mesothelioma (MPM) represents a common malignant disease. It is an aggressive tumor arising from the mesothelial cells lining the pleura (1). There is an extremely poor prognosis and a vast majority of MPM patients are diagnosed in an advanced stage. Rapid progression of the disease, no effective therapeutic approach and resistance to chemotherapy and radiotherapy resulted in a median survival time of less than 12 months (2).

Exposure to airborne asbestos fibers is mainly associated with the development of MPM (3). Incidences of MPM reach 100 cases/million/year in occupationally exposed populations opposed to 1 case/million/year in the general population (4). Wagner and his colleagues were the first to describe the relationship between asbestos and MPM in 1960 when he

published a series of MPM cases in asbestos mine workers from South Africa (5). Western Europe (6,7), United States (8), Japan (9), Australia (10), India (11), China, Indonesia and Vietnam (12) include countries where the incidents of MPM are expected to increase. This prediction is supported by the extensive use of asbestos in developed countries since 1950s and the continuing use in developing countries considering that the incubation period between initial exposure to asbestos and MPM diagnosis is 20 to 50 years (13). However, radiation, exposure to other mineral fibers such as erionite, simian virus 40 and genetic predisposition (14-16) include also causative agents for the development of MPM.

Although 50 years have passed since the discovery of the first incidence of MPM, an optimal strategy has not been yet established, as the diagnosis, staging and treatment of the disease remains difficult and complex. Recent advances in the field of genetic and molecular biology of cancer as well as in immunohistochemistry techniques have led to an improved identification and understanding of the tumor phenotypes. This individual approach is generally termed as 'personalized medicine' (17). However, to date there are no established indicators of clinical significance in MPM. In the present review, we will summarize the existing knowledge of the MPM management reporting the most clinically useful and promising prognostic factors of MPM.

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Pathogenesis and diagnosis

Due to occupational exposure, MPM is more common in men than in women (5:1 ratio) (18) and more frequent in advanced ages as a result of the long latency period. The most common symptoms are shortness of breath and pain (90%) while others include tiredness (36%), worry (29%), cough (22%), sweating (22%) and constipation (22%) (19).

MPM is divided into three major histological sub-types: sarcomatoid biphasic and epithelioid. Epithelioid is the most common sub-type among patients with MPM (<50%), associated also with the best prognosis (20). Diagnostic procedures can be either non-invasive such as Chest X-ray, CT, FDG-PET or invasive such as image-guided (CT or US) pleural biopsy, extrapleural pneumonectomy (EPP) or laparoscopy (20). Video-assisted thoracoscopy is the best biopsy technique (accuracy of 98%) and cytology, a reliable diagnostic tool for experienced cytopathologists, can offer additional tissue confirmation. Thus, several immunohistochemical panels are proposed to distinguish between sub-types of mesothelioma, secondary carcinoma and other malignant tumors metastatic to serosal membranes (21). Calretinin is the most commonly used antibody, positive for mesothelioma with a reported sensitivity of 95% and specificity of 87% (22). Other useful antibodies include thrombomodulin, mesothelin and cytokeratin 5 (22). It is recommended by the International Mesothelioma Interest Group that the immunohistochemical markers have either sensitivity or specificity greater than 80% (23). However, as no mesothelial marker has 100% sensitivity and specificity for mesothelioma diagnosis, the need to identify new panels is crucial. To date, no tissue or serum marker has been shown to have sufficient specificity, consistency and reproducibility (21). Also, given that the disease is infrequent and only a few pathologists have extensive experience with mesothelioma, make the diagnosis more difficult.

Molecular genetic analysis has revealed three key genetic alterations that can lead to the development of new diagnostic tools and new target therapies. Cyclin-dependent kinase inhibitor 2A/alternative reading frame (CDKN2A/ARF), neurofibromatosis type 2 (NF2) and BRCA1-associated protein-1 (BAP1) genes are the most frequently mutated tumor suppressor genes that can be detected in malignant mesothelioma cells (24).

Up to date, several staging systems for mesothelioma have been used but were proven inadequate to improve therapeutic outcomes. The most practical and most commonly used system is the tumor-node-metastasis system developed by the International Mesothelioma Interest Group (23). Other staging systems include the Butchart system which is the oldest one and the Brigham system which is currently not used (25).

Treatment

Treatment of MPM can be classified into radical procedures such as surgery and into palliative measures which concern the removal of pleural effusions and the preventing of their recurrence in order to relieve the symptoms such as dyspnea and chest pain. Some researchers suggested that the radical procedures had a better prognosis (26), however, later studies could not confirm this suggestion (27,28). Today, once the diagnosis is made there are no accepted or published guidelines to establish a standard surgical approach. It is a fact that surgery is not an option for the majority of the patients due to the diffuse spreading growth of this neoplasm (29).

Apart from the controversy on whether surgery increases survival, another issue is the lack of evidence in comparing the commonly used techniques such as EPP and pleurectomy/decortication (P/D) in multi-institutional, randomized-controlled trials (30). Nevertheless, according to Mesothelioma and Radical Surgery (MARS), a multicentre randomised controlled trial (28), MPM patients treated with P/D had an equal to better outcome than those treated with EPP which raised a question whether performing a P/D with perioperative chemotherapy would have better outcome with a lower operative mortality than EPP and perioperative chemotherapy (31,32). However, these techniques are not suitable for the majority of the patients due to locally advanced or unresectable disease (33). Several factors should be taken into account concerning the choice of surgery treatment such as disease stage, the patient's cardiopulmonary reserve, surgeon's experience and the extent of planned adjuvant therapy (30). Another surgical approach includes lung-sparing cytoreductive surgery which is usually combined with chemotherapy and radiation (trimodality treatment) (34). In a systematic review conducted by The *et al.*, results of 1,270 patients from 26 studies were analyzed (34). The authors suggested that more controlled trials would lead to further consideration of lung-sparing cytoreductive surgery.

However, since the role of surgery as single-modality therapy in MPM remains controversial, the management of MPM consists of combinations between platinum-based chemotherapy, surgery and radiation. Similarly to surgical treatment, there is also no evidence of survival benefit concerning radical radiotherapy of the hemithorax when compared to best supportive care (35). Radiotherapy is mainly applied as adjuvant treatment or for symptom relief (36). Hence, radiotherapy has proven to be a disappointment in the management of MPM.

Currently, multimodality strategies include EPP or pleurectomy combined with adjunctive therapies such as immunotherapy, chemotherapy and radiotherapy which are used on a case by case basis, however, frequently the only choice available is palliative treatment (37). As far as immunotherapy is concerned, in spite of favorable results *in vitro* and *in vivo* in

Table 1. High lightened studies of platinum based chemotherapy as first line treatment of malignant pleural mesothelioma, (EAP, International Expanded Access Program).

First name, year, ref	Phase/study	n	Chemotherapy regimen	Response rates (RR)	Median progression-free survival (PFS) months	Median overall survival (OS) months	Outcome
Vogelzang, 2003 (45)	III	226	Cisplatin + pemetrexed	41.3%	5.7	12.1	Satisfactory, superior to cisplatin
Van Meerbeeck, 2005 (45)	III	126	Cisplatin + raltitrexed	23.6%	–	11.4	Satisfactory, superior to cisplatin alone
Ceresoli <i>et al.</i> 2006 (46)	II	102	Carboplatin plus pemetrexed	18.6%	6.5	12.7	Satisfactory, combination active and well tolerated
Obasaju, 2007 (47)	EAP	728	Cisplatin + pemetrexed	21%	–	10.8	Satisfactory, MPM patients experience a response or stable disease
Santoro, 2008 (48)	EAP	861	Cisplatin + pemetrexed	22%	–	–	Satisfactory, 1-year survival rates
Hillerdal, 2008 (49)	II	173	Carboplatin + gemcitabine + liposomal doxorubicin	33%	–	13	Satisfactory, high number of responses and long survival, and a low toxicity

animal models (38-40), in clinical trials limited success was achieved (41-43).

Chemotherapy in MPM patients includes an option for resectable and unresectable tumors. However, MPM patients appear to be resistant to chemotherapy due to epigenetic errors leading to inadequate gene expression in tumor cells, consequently novel strategies are expected to arise concerning epigenetic therapies (44).

Chemotherapy in MPM patients is given either as single agent treatment or in most cases combination of drugs which has shown improved response rates and survival. Vogelzang *et al.* conducted a phase III clinical trial of 456 MPM patients comparing cisplatin plus pemetrexed to cisplatin alone reporting superior survival time of 2.8 months, time to progression and response rates for the combination (45) (Table 1). After the results of this study, cisplatin in combination with pemetrexed has been established as standard first-line treatment for MPM patients in advanced stage disease (50). However, this combination confers a median progression-free survival (PFS) of 5.7 months and there is no alternative when MPM patients fail this treatment option (51).

Other efforts which reported promising results include studies which combined carboplatin with pemetrexed in MPM (46-48,52). The use of gemcitabine, another antitumor agent, has been limited in rather small size clinical trials and its efficacy in cancer as a single-agent has shown to be either unsatisfactory (53,54) or sufficient in combination with cisplatin (55-57).

Furthermore, a phase II clinical trial concluded that

raltitrexed, a thymidine synthase inhibitor as a single agent had activity in MPM patients (58). Similarly, in a more recent phase III trial, it was demonstrated a 2.6-month improvement in OS, 11.4 months for the combination of raltitrexed and cisplatin, compared to 8.8 months for cisplatin alone (50).

To date, there is no standard second-line treatment for MPM. Phase III clinical trials reported feasible results, when pemetrexed alone or combined with cisplatin was compared in patients who had previously received systemic chemotherapy (59,60). More recently, Bearz *et al.* concluded that if a patient had a long-lasting benefit from previous treatment with pemetrexed combined with a cisplatin compound, the same treatment should be offered at progression (61).

Another drug that has been investigated in clinical trials of MPM is vinorelbine which has already shown satisfactory results in breast cancer (62) and non-small cell lung carcinoma (NSCLC) (63). In a phase II clinical trial it was suggested that due to the relatively low toxicity of vinorelbine, the combination of this drug with other agents should be feasible (64). Moreover, Muers *et al.* conducted a multicenter randomized trial (MS01) in which active symptom control (ASC) with or without chemotherapy in the treatment of patients with MPM was analyzed (19). The researchers concluded that the addition of chemotherapy to ASC offered no significant benefits in terms of OS or quality of life, but exploratory analyses suggested that vinorelbine merited further investigation.

More recently, Sorensen *et al.* reported that cisplatin and intravenous vinorelbine was a highly active regimen in MPM

with a response rate and survival comparable to the most active regimens so far reported (65) while Stebbing *et al.* evaluated the efficacy and safety of weekly vinorelbine in relapsed MPM patients reporting a reasonable response rate with an acceptable toxicity profile in the second-line treatment of MPM (66).

Despite the positive results regarding the combination of doxorubicin, an active drug for MPM patients, with cisplatin during phase II studies, long-term use is not an option due to its toxicity profile (67-69). In contrast, liposomal doxorubicin (LD), an agent with different toxicity profile was evaluated in phase II trials in combination with cisplatin (70) or with carboplatin and gemcitabine (49). The authors identified them as active combinations for MPM treatment with acceptable toxicity profile. However, phase III trials should be conducted to compare LD plus cisplatin to cisplatin/pemetrexed or cisplatin/raltitrexed for the determination of standard first line treatment.

Currently, the most aggressive multimodality treatment includes chemotherapy, post-operative radiotherapy and surgery. Recent studies demonstrated that patients completing trimodality treatment had a median survival of 29 months (71,72). However, the European Organisation for Research and Treatment of Cancer (EORTC; protocol 08031) phase II trial investigated the feasibility of trimodality therapy consisting of induction chemotherapy (cisplatin + pemetrexed) followed by EPP and post-operative radiotherapy in MPM patients (27). Although the results were positive, trimodality therapy was not completed within the strictly defined timelines of this protocol and adjustments were necessary. A similar approach which was conducted in a small study of 36 patients (73) failed to show any survival benefit. Thus, there are limited results regarding the trimodality treatment, applicable only at a very early stage of MPM patients with a good performance status (71). Therefore, more data from multicenter randomized clinical trials are needed.

Targeted treatments and biomarkers

MPM treatment is guided mainly by clinical stage and patient characteristics and not by histological or molecular features of the tumor. Moreover, platinum based chemotherapies and available treatments have failed to show improvements in survival benefits and there are no other approved regimens for relapsed or refractory MPM. However, the expanding knowledge on molecular mechanisms has led to the identification of several novel targets and biomarkers. Molecular pathways that have been identified in MPM include cell cycle regulation, apoptosis, growth factor pathways and angiogenesis (74).

More specifically, up-regulation of epidermal growth factor receptor (EGFR) is an important part of MPM development, thus, EGFR-tyrosine kinase inhibitors (TKIs) such as ZD1839 (gefitinib) and OSI-774 (erlotinib) might represent novel therapeutic options. *In vitro* studies have shown that gefitinib

inhibited MPM cell growth and survival preventing EGF-dependent activation of ERK1/2 pathway by blocking EGFR-TK phosphorylation and stabilizing inactive EGFR dimers (75,76).

Furthermore, recent studies have identified that the presence of specific EGFR mutations was predictive of response to therapy and cancer outcome in NSCLC (77). Similarly, EGFR activating mutations in mesothelioma were recently identified for the first time appearing to share same 'relative' improved clinical outcome like mutant EGFR-NSCLC (78).

Vascular endothelial growth factor (VEGF) signaling also plays a very important role in MPM. Several angiogenesis inhibitors have been used in clinical trials such as bevacizumab (Avastin; Genentech, South San Francisco, CA), a recombinant humanized monoclonal antibody, or other antiangiogenic agents SU5416, vatalanib, thalidomide and sorafenib which have shown modest activity as single-agent treatments; Thus, further research is needed to conduct comparisons with other agents (79).

In a recent multicenter randomized phase II trial, the addition of bevacizumab to gemcitabine/cisplatin was evaluated but it did not manage to improve significantly PFS or OS in malignant mesothelioma patients (80) (Table 2). Currently, several studies of bevacizumab in combination with pemetrexed and cisplatin are ongoing (<http://www.clinicaltrials.gov>) and it is expected that antiangiogenic therapy could benefit subgroups of MPM patients (84).

Recently, Nascreen *et al.* in their review included receptor EphA2 as a novel potential molecular target in MPM (18). Other inhibitors include histone deacetylase (HDAC) inhibitor which plays a role in cellular differentiation and malignant transformation of MPM. HDAC has shown a partial response in a phase I trial (85). Met signaling pathway is also a very promising target of MPM for patients expressing both Met and HGF, as selective small molecular inhibitors of c-Met kinase were shown to be effective *in vitro* and *in vivo* experiments (86). Another promising drug is ranpirnase, a ribonuclease (RNase) isolated from early embryos of the Northern Leopard Frog (87), which proved to have disease-modifying activity against malignant mesothelioma (88). A potent antitumor agent is vandetanib which markedly enhanced pemetrexed and carboplatin activity against established MPM cell lines (89).

In addition, a phase II study of asparagine-glycine-arginine-human tumor necrosis factor alpha (NGR-hTNF), a selective vascular targeting agent, in previously treated patients with MPM found modest results warranting additional evaluation (81). Modest results were shown in a phase II trial (82) for BNC105P, an inhibitor of tubulin polymerization that has vascular disrupting and antiproliferative effects (90), as second line therapy in MPM after first line pemetrexed/platinum chemotherapy.

According to reports extracellular signal-regulated kinase 5 ERK5 inhibition in combination with chemotherapeutic drugs is a beneficial strategy for combination therapy in patients

Table 2. High lightened studies of targeted treatment and possible biomarkers of malignant pleural mesothelioma.

First name, year, ref	Phase/study	n	Chemotherapy regimens	Targeted treatment/ biomarker investigated	Response rates (RR)	Median progression-free survival (PFS) months	Median overall survival (OS) months	Outcome
Gregorc, 2010 (81)	II	57	Pemetrexed	Human tumor necrosis factor alpha	44-46%	2.8	12.1	Warrant additional evaluation
Kindler, 2012 (80)	II	108	Gemcitabine/ Cisplatin	Bevacizumab	24.5%	6.9	15.6	Addition of bevacizumab did not significantly improve PFS or OS
Nowak, 2013 (82)	II	30	Pemetrexed/ Platinum	Vascular Disrupting Agent BNC105P	43%	1.5	8.2	Insufficient
O'Brien, 2013 (83)	II	82	Cisplatin and bortezomib	-	28.4%	5.1	13.5	PFS rate at 18 weeks as strong predictor of survival

Table 3. Biomarkers for malignant pleural mesothelioma.

Biomarker	Information, references
Mesothelin	A 40 kDa cell surface glycoprotein on normal mesothelial cells, levels of serum mesothelin as a biomarker (93-95)
N-ERC/mesothelin index	Predicts chemotherapeutic response and prognosis
Osteopontin	Glycoprotein on normal mesothelial cells, a negative predictor of MPM survival (96,97)
ERCC1, MLH1, MSH2, MSH6, and β III-Tubulin	Resistance proteins involved in DNA repair mechanisms for "tailoring" platinum-based chemotherapy (98)
VEGF serum concentration	Useful prognostic factor (99,100)
Modified Glasgow Prognostic Score (mGPS) and neutrophil-to-lymphocyte ratio (NLR)	Validated prognostic indices (101)
Neutrophil-to-lymphocyte ratio	Predictor of longer survival (102,103)
CD24 immunoreactivity	Differentiating malignant mesothelioma from pulmonary adenocarcinoma (104)
Serum levels of HMGB1	Prognostic marker (105)
miR-126 in association with SMRPs	A marker for early detection (106)
miR-625-3p	Promising novel diagnostic marker (107)

with malignant mesothelioma (91). Another study combined negative ERCC1 and class III β -tubulin immunostaining to be associated with significantly prolonged PFS and OS in MPM patients receiving cisplatin-vinorelbine therapy (92).

In a prospective phase II study of cisplatin and bortezomib (CB) a protease inhibitor, as first line treatment of MPM was investigated. The researchers reported validation of progression free survival rate at 18 weeks (PFSR-18) as primary end-point which was confirmed as a strong predictor of survival (83).

The lack of established biomarkers in MPM makes difficult to achieve positive outcomes of targeted agents in clinical trials, however, several efforts have been reported (Table 3). The first

study to suggest serum mesothelin (a cell surface glycoprotein on normal mesothelial cells) as a biomarker of mesothelioma was reported in 2003 by Robinson *et al.* (93) using an enzyme-linked immunosorbent assay (ELISA) which was later commercialized as Mesomark (Fujirebio Diagnostics, Malvern, PA) and was approved in 2007 by the US Food and Drug Administration (94). However, the main limitation of mesothelin is its poor sensitivity, which makes difficult to achieve early diagnosis (95). Furthermore, N-ERC/mesothelin (N-ERC) index is considered to be a useful biomarker for predicting not only the chemotherapeutic response but also the prognosis in patients with advanced MPM (108). Another glycoprotein is osteopontin whose baseline levels

were proven to be an independent negative predictor of MPM survival, however, they were less associated to the disease than mesothelin serum levels (96). A similar study also demonstrated that osteopontin had a lower diagnostic accuracy than mesothelin in patients suspected of MPM (97).

Resistance proteins involved in DNA repair mechanisms such as ERCC1, MLH1, MSH2, MSH6, and β III-Tubulin are found to be associated with response and outcome to platinum-based chemotherapy in MPM patients (98). Thus, these enzymes could be used as biomarkers for “tailoring” platinum-based chemotherapy for MPM patients who may expect the largest clinical benefit.

VEGF serum concentration could also be a useful prognostic factor, as suggested in recent studies (99,100). More specifically, 51 MPM patients were found with significantly higher serum levels of VEGF when compared to 42 individuals with benign asbestos-related diseases (asbestosis or pleural plaques) or who were healthy despite asbestos exposure (100). Similarly, in another study it was demonstrated that patients with MPM had significantly higher pleural effusion VEGF levels than a population with non-malignant pleuritis or lung cancer involving malignant pleural effusion (99).

It is known that chronic inflammation plays a key role in the pathogenesis of MPM and recently the inflammation-based prognostic scores such as modified Glasgow Prognostic Score (mGPS) and neutrophil-to-lymphocyte ratio (NLR) were found to be externally validated prognostic indices in 171 MPM patients (101). NLR was also suggested as an independent predictor of longer survival for patients with MM undergoing systemic therapy (102) or as a poor prognostic factor in patients undergoing EPP (104).

Recently, CD24 immunoreactivity was identified as potential new marker in differentiating malignant mesothelioma from pulmonary adenocarcinoma (104). Other researchers investigated serum levels of HMGB1 in MPM patients comparing them with a population previously exposed to asbestos without developing MPM (105), suggesting it as prognostic marker for MPM. As soluble mesothelin-related peptides (SMRPs) have been suggested as promising biomarkers for MPM (109) and microRNAs (miRNAs) have shown to be involved in cancer (110) and malignant mesothelioma (111), Santarelli *et al.* proposed miR-126 in association with SMRPs, as a marker for early detection of MPM (106). Moreover, another study suggested miR-625-3p as a promising novel diagnostic marker for MPM (107).

Other researchers evaluated a new combined therapy consisting of ascorbate/epigallocatechin-3-gallate/gemcitabine mixture (called AND, for Active Nutrients/Drug). The authors concluded that this combination was synergistic *in vitro* on MPM cells, and blocked *in vivo* tumor progression and metastasization in REN-based xenografts (112). Despite the

amount of biomarkers that are being presently investigated, the biological heterogeneity of MPM effects the identification of clinically validated prognostics factors.

Conclusions

In summary, the increasing MPM incidents are a fact, making the need of novel treatments more demanding. Surgery, radiotherapy, and chemotherapy have failed as single modality therapies and first-line standard chemotherapy of MPM, the combination of cisplatin and pemetrexed offers no further improvements in survival. Furthermore, the lack of randomized trials is added to the lack of efficient treatment. Thus, novel therapeutic strategies such as multimodality treatment, targeted agents and improved biomarkers include the on-going research to prolong patient's survival and quality of life. It is crucial that large clinical trials should be implemented so that efficient and practical serum biomarkers can be identified for the prediction and evolution of the disease.

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