

# Treatment of malignant pleural mesothelioma: current status and future directions

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**ABSTRACT:** *Treatment of malignant pleural mesothelioma: current status and future directions. X. Dhalluin, A. Scherpereel.*

Previously considered to be rare, malignant pleural mesothelioma (MPM) is a highly aggressive tumour that has become a very important issue over recent years due to its poor prognosis and its increasing incidence mostly linked to previous asbestos exposure. An optimal treatment for MPM is not established yet; new therapies and predictive tools are still needed in the management of this cancer.

Thus the aim of this review is to provide clinicians clear and up-to-dated data on the latest therapeutic strategies for MPM patients in 2010. The guidelines recently proposed by the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) taskforce are summarized here. The authors also briefly reviewed the future directions in MPM treatment including targeted therapies, gene or cell therapies.

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## Introduction

Malignant pleural mesothelioma (MPM) is a rare but highly aggressive tumor with poor prognosis and an increasing incidence. An optimal treatment of MPM is not clearly defined yet, even if clear and up-to-date guidelines on management of MPM patients were recently proposed by the European Respiratory Society (ERS) in collaboration with the European Society of Thoracic Surgeons (ESTS) [1]. These guidelines and an overview of potential future therapies for this cancer are summarized in this review.

## Current status

### *Surgery for MPM*

Main surgical procedures for MPM are pleurectomy/decortication (P/D, debulking surgery), a partial macroscopic clearance of tumour performed by thoracotomy or by video assisted thoracoscopic surgery (VATS), and extrapleural pneumonectomy (EPP) considered as “radical” surgery. There is very limited evidence supporting P/D but VATS may provide good symptom control and have an impact on survival [2]. An ongoing study in United Kingdom is com-

paring VATS debulking with chemical pleurodesis (MesoVATS). Thus P/D should not be proposed in a curative intent but rather to symptomatic (breathless, pain) patients with entrapped lung syndrome who cannot benefit from talc pleurodesis (grade of recommendation: 2C). Pleural undwelled catheters are also an option in this case.

There is also limited data supporting “radical” surgery (EPP) for mesothelioma, and only for EPP as part of multimodal treatment [3-5]. Median survival of patients benefiting from such strategy was 18-24 months. EPP mortality is about 5% in experienced centres [5] while morbidity is up to 50%. Therefore it is recommended that EPP should be performed only in clinical trials, in specialized centres, as part of multimodal treatment [1].

### *Radiotherapy (RT) in MPM*

#### POST-OPERATIVE RADIOTHERAPY

As evidence were limited and came from retrospective studies, the ERS/ESTS experts recommended that RT should not be performed after P/D (1A).

Recurrence rate of post-EPP RT may vary from 13% to 50%, and local-only recurrence rate from 4% to 13% [4, 6]. RT technical issues may partly explain these discrepancies. This procedure

should only be realized in clinical trials in dedicated centres (1A). A randomized European (SAKK) study is ongoing to assess the efficacy and tolerance of post-EPP RT.

In fact large fields, complex target shape and proximity of organs at risk such may limit dose and efficacy of RT in MPM. Intensity-modulated radiotherapy (IMRT) seems to be a relevant alternative as it theoretically allows large irradiations of complex fields. Preliminary results of IMRT after EPP were promising but several cases of fatal pneumonitis have been described [7-10]. Therefore, post-operative RT, including IMRT, should be performed only in expert centres, as part of clinical trials [1].

#### PALLIATIVE OR PROPHYLACTIC RADIOTHERAPY

In case of painful chest wall infiltration or nodules, *palliative* RT may be a useful treatment [1].

An irradiation with 7 Gy/day for three consecutive days within four weeks after any pleural procedure has been established to prevent subcutaneous tumour seeding developing along drainage channels or thoracocentesis tracts [11]. However, a small recent randomised trial as well as the Cochrane Overview [12] did not support *prophylactic* RT. There was no difference for tract tumour seeding between the RT arm and the no-RT arm [13, 14]. Underpowered studies and suboptimal irradiation techniques may explain the inconsistency of these results. Thus, as the value of prophylactic RT is questionable, the ERS/ESTS experts were not able to propose any firm recommendation [1]. However, based on previous French Pulmonary Society guidelines [15, 16] and our own centre experience, we decided to continue to use prophylactic RT, a cheap, easy and efficient procedure till a new significant study on this issue.

#### **Chemotherapy (CT) of MPM**

Significant improvement in MPM management was obtained by the first two large, multicentric, prospective and randomised phase III trials [17, 18]. Previous trials were often little informative because they usually reported small series of patients in monocentric, non-randomised and/or retrospective studies [1, 19].

#### FIRST-LINE CT IN MPM: DOES IT WORTH? WHICH DRUG(S) TO BE USED?

Only one randomised study assessed the value of CT versus placebo in addition to best supportive care (BSC) [20]. No significant difference for survival was found between the two arms. However this trial had several major limits because it was prematurely stopped due to a poor recruitment, and the drugs were not the optimal ones in this indication. In fact, phase III randomised trials [17, 18] suggested that cisplatin combined with antifolate, i.e. pemetrexed (C/P, with supplementation by folic acid and B12 vitamin) or raltitrexed (C/R), could increase response rate (RR) and median survival time (MST) compared to cisplatin

alone (C/P: 12.1 months or C/R: 11.4 months vs 9.3 and 8.8 months for cisplatin alone arms, respectively). Therefore combination of platinum and pemetrexed or raltitrexed is recommended as standard first line chemotherapy for patients with good performance status (PS<3) (1B) [1].

#### OPTIMAL TIMING TO START FIRST LINE CT - DURATION OF TREATMENT

Some indirect evidences suggest starting CT immediately after the diagnosis. First, an initial adequate PS was predictive of a better survival for patients in phase III trials [17, 18]; and large tumors may be less sensitive to CT [21-23]. Moreover results of a small randomised trial supported immediate first line CT versus delayed treatment at the time of symptoms progression, with a time to symptomatic progression (25 versus 11 weeks, respectively) and MST (14 versus 10 months; 1-year 66% versus 36%, respectively), although the difference was not statistically significant (p=0,1) [24].

There are no data suggesting delivering more than 6 cycles in stable or responding patients (2C) or supporting maintenance treatment with CT or targeted therapies. CT should also be stopped in case of progressive disease, grade 3-4 toxicities, or cumulative toxic doses (1A) [1].

There were a few studies evaluating the value of intrapleural therapies in MPM. To date, this treatment exhibited limited efficiency and high toxicity. Therefore it should be only considered in clinical trials [25].

#### SECOND-LINE TREATMENT

Second line treatment seems a reasonable issue as many patients having progressive disease still fit to benefit from another treatment. Thus, in a retrospective analysis of study of Vogelzang *et al*, 42% of the patients received second line treatment [26]. Moreover post-study treatment (PST) was associated with a better survival whatever cytotoxic drugs were used.

An extensive review of the literature concluded that no drug or combination of drugs have been validated in second line CT [1]. However, the pemetrexed expanded access program (EAP) provided interesting data in this setting [27]. The treatment was well tolerated in 187 patients receiving pemetrexed alone ("P"; n=91) or in association with cisplatin ("C/P"; n=96). No direct comparison was done between the different treatments. But in 80 "C/P" vs 73 "P" assessable patients, RR was 32.5% vs 5.5%, disease control rate was 68.8% vs 41%, and overall survival (OS) was 7.1 months (95% CI; 6.5-11) vs 4.1 months (95% CI; 3.2- N/A), respectively. Moreover, in a phase III randomised trial comparing pemetrexed and BSC versus BSC alone, there was a benefit in the CT arm in terms of survival without disease progression, RR and time to progression (TTP) but not for OS [28]. Vinorelbine might also be a reasonable choice in second line treatment and has recently exhibited on a series of 63 patients a 16% RR and MST of 9.6 months in this setting [29]. To date, it is recommended that patients demonstrating pro-

longed symptomatic and objective response with first line CT may be treated again with the same regimen in the event of recurrence (2C). Other patients, in a good PS, should rather be proposed to participate to clinical trials (2C) [1].

#### TARGETED THERAPIES AND OTHER BIOTHERAPIES IN MPM

Immunomodulators such as interferons or interleukin-2 seemed not effective alone and are not recommended outside of a clinical trial. Preliminary results of *Mycobacterium vaccae* administration seemed interesting but need confirmation. Ranpirinase has not demonstrated its effectiveness in trials. Several targeted therapies were also tested in malignant mesothelioma but no positive clinical trial was published yet. Main drugs and results are summarized in the second part of the review. To date, immunomodulating agents, targeted treatments and other biotherapies should not be used in the treatment of MPM outside clinical trials (1C) [1].

#### WHAT ASSESSMENT CRITERIA SHOULD BE USED FOR PATIENTS MONITORING IN MPM?

The response to the treatment can be assessed on [1]:

- clinical criteria such as symptoms control and quality of life (modified version of the Lung Cancer Symptom Scale (LCSS) recommended) [30];
- imaging criteria: CT-scan is recommended for assessment and follow-up of MPM. If a patient has had pleurodesis, chest CT-scan should be performed again before starting chemotherapy in order to better evaluate the response to treatment (1B). The modified RECIST criteria [31-33] are the preferred method of measuring response to treatment (1B). Positron emission tomography (PET) combined CT-scan may allow a better response evaluation but is still not validated in routine in MPM;
- survival parameters (OS rather than TTP);
- biological markers are still under investigation for patients monitoring in MPM. However, serum mesothelin seems to be a promising biomarker according to recent reports and was already approved in the USA by the FDA for compassionate use [34, 35];
- reassessment of MPM by thoracoscopy was never published.

#### **Multimodal strategy**

As surgery alone is not curative in MPM because resection margins can be hardly obtained, it has been proposed to combine radiotherapy and/or chemotherapy to surgery. However, this strategy may improve the treatment efficacy but also cumulate specific toxicities. Therefore the value multimodal approach is still highly debated and patients who are potential candidates for this procedure need to previously undergo a thorough work-up. This work-up should include at least physical examination, pulmonary function tests and cardiac function assessment, and imaging procedures for tumour staging [1].

The following criteria are usually considered for potential EPP and multimodal treatment: histological proof of non-sarcomatoid MPM subtype, clinical and/or pathological stage T1-3, N0-1 ( $\leq N2$  for a few centres), M0 patient fit to have pneumonectomy and to receive neoadjuvant/adjuvant chemotherapy and adjuvant radical hemithorax irradiation [1].

There are limited and weak data available on the best combination treatment, and only recent studies included optimal chemotherapy. Moreover, multimodal approach including EPP is usually responsible for morbidity up to 70% and mortality rate  $\leq 7\%$  in specialized centres. In a Swiss study recruiting 61 patients with MPM  $\leq T3N2M0$  treated by 3 cycles of cisplatin-gemcitabine followed by EPP and limited radiation to high-risk sites, only 45 patients benefited from full treatment and exhibited a MST of 23 months [5]. The European phase II trial EORTC 08031 assessed in 58 patients with MPM  $\leq T3N1M0$  the feasibility of induction CT (3 cycles platinum-pemetrexed) followed in non-progressing subjects by EPP and postoperative RT (54 Gy, 30 fractions) [36]. Primary endpoint was “success of treatment” meaning that patients received full treating without grade 3-4 toxicity and did not progressed within 90 days post treatment. Only 24 patients (42%) met these criteria (one-sided 90% CI 0.36-1.00), having median OS of 18.4 months (95% CI 15.6-32.9) and PFS of 13.9 months (95% CI 10.9-17.2).

Finally the Mesothelioma and Radical Surgery (MARS) controlled trial randomized patients after platinum-based CT, if still eligible, to surgery (EPP) followed by radical hemithorax RT versus no surgery [37]. Only 50 patients out of 112 (45%) patients entering the evaluation and induction phase of the trial went on to be randomized. Thus randomization between surgery and no surgery was feasible but results were quite deceptive as previous studies. Therefore, as this approach is still not validated, that patients who are considered candidates for this multimodal strategy should be included in prospective randomised trials in dedicated centres [1].

#### **Future directions for systemic treatment of MPM**

New pathways identified in MPM pathogenesis led to new targets and innovative therapies. These targeted therapies and biotherapies, still under investigation, are summarized below.

#### ***Epidermal Growth Factor Receptor (EGFR)***

The tyrosine kinase (TK) EGF receptor pathway is involved in angiogenesis, proliferation, survival, and migration of tumor cells, and is over-expressed in MPM. Govindan *et al* evaluated the efficacy of the EGFR TK inhibitor gefitinib in 43 non-selected MPM patients for activating EGFR mutation [38]. The RR was low: one partial response (PR), one complete response (CR) and 21 stable disease (SD). Similar deceptive results were found with erlotinib in 63 unselected chemo-naïve

patients [39]. No objective response was observed if toxicity was acceptable.

### ***Vascular endothelial growth factor (VEGF) inhibitors and other anti-angiogenic drugs***

VEGF is an autocrine growth factor having a key role in tumor angiogenesis and lymphangiogenesis in mesothelioma [40, 41]. Moreover VEGF and VEGF receptors are highly expressed in MPM. Several anti-angiogenic drugs were tested alone or in combination with other agents in MPM.

In a phase II trial, no objective response was observed in 24 MPM patients treated by anti-VEGF antibodies bevacizumab (15 mg/kg/3 weeks) in combination with erlotinib 150 mg/day [42]. In a randomised phase II trial assessing cisplatin-gemcitabine with or without bevacizumab, the addition of bevacizumab did not result in improved response rate (25% versus 22%) nor survival rate (MST 15.6 months vs 14.7 months;  $p=0.91$ ) [43]. This may be partly due to second line CT by pemetrexed resulting in a response rate of 12.1% and SD in 46% of pre-treated patients, in one year survival rate of 54% and in median time to progression of 4.9 months. Interestingly, low initial serum VEGF level was associated with a better overall survival and PFS in all patients ( $p=0.008$ ). A French phase II randomised clinical trial "MAPS", evaluating first line CT combining pemetrexed-cisplatin (PC)  $\pm$  bevacizumab (PCB) in 111 patients, was just achieved on January 2010. Preliminary promising results were presented during 2010 ASCO meeting [44]. The PCB chemotherapy was well-tolerated and feasible. In the first 93 eligible patients, there were 27/47 patients (57.4%) with disease control (1 CR, 17 PR, 9 stable disease) in the PCB Arm vs. 21/46 (45.7%) in the PC arm ( $p=0.01$ ).

*Thalidomide*, another anti-angiogenic drug through inhibition of VEGF, bFGF, and TGF- $\alpha$ , was tested alone or in combination with chemotherapy [45, 46]. In a phase I/II trial testing thalidomide alone [46], there was no objective response but 11 patients/40 (27%) had a SD more than 6 months; MST was 11 months; TTP was 8 weeks. A smaller Australian study ( $n=22$ ) had similar results. Finally, in 16 chemo-naïve patients treated by cisplatin, gemcitabine and thalidomide, PR and SD rates were 14% and 55%, respectively; MST was 12 months; TTP was 17 weeks. Other trials with thalidomide are ongoing.

There are very limited clinical data on *multi-targets (TK) drugs* such as *sorafenib*, *vatalanib*, *pazopanib*, or *sunitinib* in MPM. Although some patients experienced objective response, endpoints of the different studies were never achieved, and new trials are ongoing. Phase II trials assessing *imatinib mesylate* in MPM were deceptive with no objective response (SD: 12-44%) [47-49]. VEGFR-2 inhibitor *semaxanib* seemed to be efficient (response rate 11%; MST 12.3 months) but was associated with an intolerable risk of thrombosis [50].

A phase II trial evaluated tetrathiomolybdate (TM), a potential anti-angiogenic and anti-VEGF drug through copper depletion and ceruleoplasmin decrease, starting 4 to 6 weeks after debulking surgery in 30 stage I-III patients compared to a historic series of 164 patients from the same group [51]. Toxicity was low and TM exhibited a potential value in stages I-II disease only, but methodological issues did not permit any firm conclusion.

### ***Ribonuclease inhibitors***

Ranpirnase is an enzyme degrading tRNA in the Golgi system resulting in inhibition of proteins synthesis including proteins involved in cell replication and apoptosis. The role of ranpirnase in MPM, alone or in combination with doxorubicin, was evaluated through phases II and III trials with deceptive results [1].

### ***Histone deacetylase inhibitors (HDACi)***

HDAC are a large group of  $Zn^{2+}$ -dependent enzymes are potential targets in cancer because inhibition of histone deacetylation results, through acetylation of histone proteins, in expression of genes associated to cell cycle arrest, apoptosis and tumor suppression. Moreover HDACi lead to acetylation of nonhistone proteins leading to other anticancer effects such as inhibition of angiogenesis, motility and invasion of tumor cells [52]. Many class-specific or pan HDACi have been tested in different cancers. For example, HDACi such as vorinostat (SAHA), panobinostat or valproic acid (VPA) are evaluated in lung cancer patients in combination with chemotherapy [53-55]. Vorinostat is already FDA-approved in the treatment of cutaneous T-cell lymphoma

Vorinostat was tested in previously treated MPM patients. In a phase I study ( $n=13$ ), it appeared to be well-tolerated [56]. Then in a phase II, vorinostat was evaluated versus placebo. Despite unpublished results of this phase II study, a large randomised controlled phase III trial with the same design is ongoing.

Belinostat, a novel HDACi, was also tested in 13 MPM patients including 11 patients previously treated by pemetrexed-platinum [55]. The study was stopped because belinostat was considered as inefficient single agent: no objective response was found; MST was 1 month and OS was 5 months.

In a recent phase II study, the value and the safety of valproic acid (VPA) combined with doxorubicin was assessed in 45 MPM patients (PS 0-2) after at least one chemotherapy line [57]. RR was 16% (95% CI 3-25%), disease control rate was 36% (95% CI 22-51%); OS was 6.7 months (95% CI 4.9-8.5 months). Toxicity was acceptable as severe neurological toxicity was seen, main toxicity was leuco-neutropenia induced by doxorubicin.

This was the first phase II suggesting clearly an anti-tumor effect of HDACi in mesothelioma, associated with an improvement of survival.

### Immunomodulators

*Interferons and interleukins* were tested in MPM with some success. But doses, method of administration (intrapleural or systemic), drugs and disease stage varied highly from one study to another. Therefore these results must be cautiously analyzed and, to date, monotherapy with interferons or interleukin-2 seemed not effective and are not recommended outside of a clinical trial [1].

Interesting preliminary results were observed after administration of *Mycobacterium vaccae* in a limited number of patients. This needs to be confirmed before recommend the use of this treatment.

*Gene therapy* has shown promising results in mesothelioma in pre-clinical models. Anti-tumor response in MPM was demonstrated in murine models and in patients during phase I trial when injecting intra-pleurally adenoviral vectors (Ad) with thymidine kinase gene (associated with ganciclovir IV) or IFN- $\beta$  gene [58, 59]. CD4+ and CD8+ tumor-specific T cells appeared as key effector cells for tumor inhibition [60], suggesting a potential benefit to associate cell therapy to this strategy. Significant tumor inhibition was also shown in animal models, but not in humans so far, by transfection of p53, Bak, p14<sup>arf</sup>, or CD40 ligand genes, or using antisense oligonucleotides (ODN) to block the expression of some genes such as growth factors (PDGF  $\alpha$  et  $\beta$ , IGF I, TGF- $\beta$ ...) [61, 62].

*Cell therapy* seems to be another interesting treatment in MPM [63-65]. In fact, if chemotherapy may increase RR to treatment and survival in non-resectable patients, there are always some resistant tumor cells that may inactivate the immune system. Thus it is necessary to stimulate and to "educate" antigen presenting cells (dendritic cells...) and immune effector cells (natural killer (NK) cells, cytotoxic T cells) to eliminate these tumor cells. Associated to other standard therapies (chemotherapy...), this vaccine strategy may improve the treatment of MPM patients. Encouraging results were recently published of a phase I trial assessing in 10 MPM patients the safety and immunological response induced by the intradermally and intravenously administration of tumor lysate-pulsed dendritic cells (DC) at two-week intervals after CT [65]. No grade 3 or 4 toxicities or any evidence of autoimmunity were observed. Interestingly, local accumulations of infiltrating T cells were found at the site of vaccination. Immunological response to tumor cells was detected in a subgroup of mesothelioma patients.

### Conclusion

Significant improvement has been achieved recently in the management of MPM, reflected by the guidelines from European scientific societies [1]. However many questions about MPM treatment, in particular about second line treatment and the role of targeted therapies, remain without clear and validated answer. Moreover the overall sur-

vival of mesothelioma patients is still poor. These facts should stimulate clinicians to recruit these patients as much as possible in prospective and randomised clinical trials to improve the treatment of mesothelioma.

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