

Advances In the Systemic Therapy of Malignant Pleural Mesothelioma

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Summary and Introduction

Summary

Malignant pleural mesothelioma is an aggressive thoracic malignancy associated with exposure to asbestos, and its incidence is anticipated to increase during the first half of this century. Chemotherapy is the mainstay of treatment, yet sufficiently robust evidence to substantiate the current standard of care has emerged only in the past 5 years. This Review summarizes the evidence supporting the clinical activity of chemotherapy, discusses the use of end points for its assessment and examines the influence of clinical and biochemical prognostic factors on the natural history of malignant pleural mesothelioma. Early-phase clinical trials of second-line and novel agents are emerging from an increased understanding of mesothelioma cell biology. Coupled with high-quality translational research, such developments have real potential to improve the outlook of patients at a time of increasing incidence.

Introduction

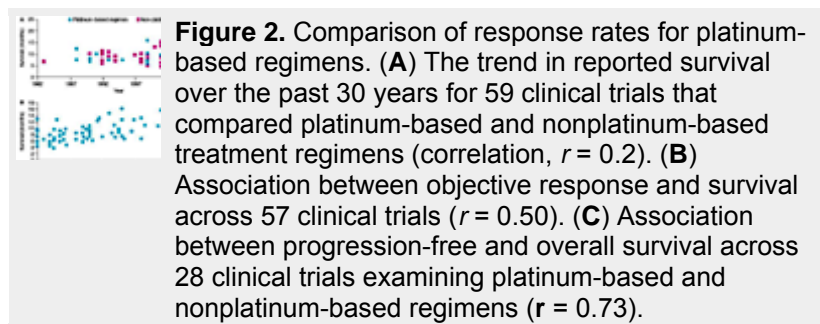
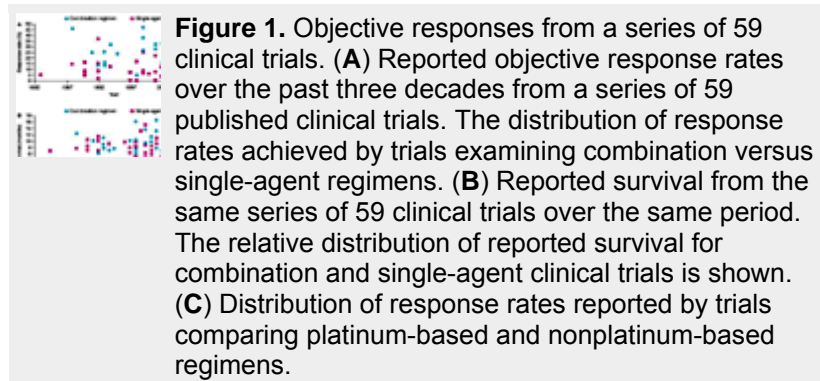
The incidence of malignant pleural mesothelioma (MPM) is anticipated to increase over the next 10 years in both Europe and the developing nations.^[1] Although the outcome for patients remains poor, recent advances in the systemic treatment of this disease have emerged. The principal goals of this Review are to summarize the role of chemotherapy in treating MPM, discuss the determinants of prognosis and outline the novel therapeutic approaches in development.

Chemotherapeutic Efficacy

The majority of patients with MPM present with stage III or IV disease, which is usually detected by PET imaging. For example, in a recent CT-PETstaged series 3% of patients had stage I disease, 9% of patients had stage II disease, 48% of patients had stage III disease and 40% of patients had stage IV disease.^[2] Approximately 85-90% of patients with MPM present with unresectable disease at diagnosis and such patients rely on palliative treatment. The efficacy of chemotherapy for MPM has been evaluated predominantly in single-arm, uncontrolled trials in which the objective response rate can be classified as low (<10%), moderate (10-15%) or high (>20%), as shown in [Table 1](#).

The results of older studies require cautious interpretation, however, because they differ widely in trial design, patient selection, response criteria, sample size and power. These are factors that might affect the outcome significantly. Nevertheless, a number of conclusions can be drawn from these series, which have been subjected to meta-analyses.^[3,4] Most single agents exhibit low intrinsic activity, with the exception of cisplatin.^[3,4] Patient response rates have essentially remained below 50%, which is consistent with intrinsic drug resistance. The response rate and survival are generally greater for combination than single-agent regimens, as illustrated in [Figure 1A](#), which summarizes the response rate of 59 first-line clinical trials. Moreover, two phase III trials showed that responses were generally higher for combination versus single-agent trials (26% versus 8%, respectively; $P < 0.001$).^[5,6] Interestingly, the improvement in median survival with combination therapy versus singleagent therapy was less impressive across this series of trials (i.e. 10 vs 8.1 months, respectively; [Figure 1B](#)). Platinum-containing regimens have a greater activity than nonplatinum-containing combinations, with cisplatin and doxorubicin showing the

highest reported response rates.^[3] Figure 1C shows the distribution and greater response rates for platinum-containing versus nonplatinum-containing regimens in the same series of 59 published trials (24% vs 8%, respectively). The effect of platinum-containing regimens on survival seems to be modest, as indicated by meta-analyses that compared the median survival times of patients receiving platinum-based regimens with those of patients receiving nonplatinum regimens (8.6 vs 9.6 months, respectively; Figure 2A). Three-drug chemotherapy combinations were found to be no more active than two-drug combinations. Finally, the meta-analyses revealed that the activity of agents was consistently higher when CT scanning was used to measure the response. This outcome is due to the high sensitivity of CT scanning for detecting a response in the type of disease that has a rind-like pleural thickening and pleural fluid masking the measurable target lesions.



End Points for Efficacy Evaluation

Adequate response evaluation is a cornerstone for the identification of active drugs. The average response rate across 59 published trials conducted over 30 years was 15.7%. Over this time interval, however, the response rate reached a plateau, reflecting the underlying chemoresistant phenotype of MPM.^[7] Nevertheless, the suggestion of a positive correlation (r) between activity and survival ($r = 0.50$), as shown in Figure 2B, provides a rationale for development of novel chemosensitization strategies.

Response assessment typically employs a modified set of RECIST (Response, Evaluation, Criteria In Solid Tumors) criteria that are based on measurement of tumor thickness rather than its maximum diameter.^[8] The change in tumor volume required to achieve a partial response is smaller for models of MPM geometry than for spherical tumor models. Volume changes associated with a partial response according to the RECIST criteria were much smaller than volume changes associated with a partial response according to different criteria.^[9] It is still unclear whether an objective response rate determined by radiology is sufficiently predictive for MPM, and this could be particularly relevant in emerging trials of novel targeted compounds, which function primarily to stabilize growth rather than induce tumor shrinkage.

Progression-free survival (PFS) reported for 29 trials over the past 30 years demonstrates only a minor upward trend in this outcome measure ($r = 0.2$); however, there is a relatively strong correlation between PFS and survival ($r = 0.73$), suggesting predictive value of this end point (Figure 2C). Furthermore, patients who received platinum-based combinations had longer PFS than patients who received nonplatinum singleagent therapy (6.8 vs 4 months; Figure 2C). The European Organisation for Research and Treatment of Cancer (EORTC) has analyzed the

relationship between PFS and activity through meta-analysis of 10 trials (523 patients).^[10] Three groups with insufficient, moderate, or good activity were defined by the distribution of PFS rates at 3, 4, 5 and 6 months, supporting the use of PFS as an end point for evaluation of clinical activity, particularly if stabilization rather than tumor shrinkage is anticipated.

Timing of Chemotherapy

The optimum timing of chemotherapy treatment according to the natural history of the disease has only been addressed recently. A pilot study randomized 43 patients with a good performance status and stable symptoms to either immediate or delayed chemotherapy with mitomycin-vindesine and cisplatin.^[11] The median time to delayed treatment was 17 weeks. Trends towards worse survival (14 vs 10 months; $P = 0.1$), PFS (25 vs 11 weeks; $P = 0.1$) and quality of life were determined in the group receiving delayed chemotherapy. Although this is a very small randomized study, one interpretation might be that early therapy for MPM does not adversely affect the natural history of the disease.

Third-Generation Antifolates

Although there is little doubt among investigators about the potential benefit of chemotherapy over best supportive care—also called ‘active symptom control’ (ASC)—no randomized data support this approach. Following a feasibility trial to establish whether patients could be randomized to ASC,^[12] a three-armed randomized phase III study was conducted in the UK to evaluate the efficacy of chemotherapy—mitomycin, vinblastine and cisplatin^[13] or vinorelbine^[14]—compared with ASC. Since the initiation of this study, however, data from two pivotal randomized trials have provided evidence to suggest that a platinum-based doublet containing a third-generation antifolate is superior to platinum alone.^[5,6]

Pemetrexed and raltitrexed are thought to be concentrated within MPM cells and to specifically inhibit one or several of the key enzymes involved in the synthesis of purines and pyrimidines. On the basis of the moderate-to-high activity observed with these agents either alone or in combination with platinum, investigators compared them in randomized trials using cisplatin as a comparator drug. Vogelzang *et al.* were the first to report the improved efficacy of the combination of cisplatin and pemetrexed (Table 2).^[6] This chemotherapy combination was unexpectedly toxic and resulted in several treatment-related deaths; this outcome was also observed in several previous phase II studies. Toxicity was due to interference with homocysteine metabolism, and could be prevented by the prophylactic use of vitamin B₁₂ and folate, although the outcome in the subgroup of vitamin-substituted patients was not significantly better than those who did not receive prophylactic vitamin B₁₂ and folate. This outcome is possibly because of the small sample size of the subgroup, although doubt about a possible detrimental effect of vitamin substitution on efficacy cannot be completely excluded. On the basis of the results of this trial, pemetrexed has been licensed for the treatment of MPM in several countries.^[15]

The EORTC Lung Cancer Group reported the results of a randomized trial that compared cisplatin and raltitrexed with cisplatin only;^[5] significant improvements in efficacy and disease-related symptoms (pain and dyspnea) were observed with raltitrexed and cisplatin.^[16] Although the increased increments in overall survival were numerically smaller than in the phase III trial that compared pemetrexed and cisplatin with cisplatin alone, the outcome is considered equivalent in the absence of a head-to-head comparison. Of note, no significant serious additional toxicity was observed with the raltitrexed-cisplatin combination.

From these two pivotal randomized trials, it can be concluded that modern chemotherapy improves symptoms and has no deleterious effect on quality of life, despite the associated toxicity.^[16] Response and PFS were borderline improved with the raltitrexed-cisplatin regimen compared with cisplatin alone (5.3 months PFS for the combination vs 4 months for cisplatin; $P = 0.058$). By contrast the pemetrexed-cisplatin regimen produced significantly better PFS than cisplatin alone (3.7 vs 5.7 months; $P = 0.001$). Survival in the cisplatin-only arm of both of these phase III trials was similar, enabling some comparison between them. A combination of cisplatin with pemetrexed improves the outcome, as measured by symptomatic and objective response rates, overall survival and PFS. The pooled observed reduction in the risk of death at 1 year is 10%, corresponding to an estimated increase in median survival of 6–8 weeks (J van Meerbeeck, unpublished data). Currently, the cisplatin and antifolate combination is to be regarded as the standard chemotherapy regimen in patients with good performance and unresectable disease and should be administered for a median of four to six cycles, unless progression or severe toxicity occurs. The results cannot be extrapolated to subgroups that have been insufficiently studied, such as patients with a moderate or poor performance status, the elderly (those >75 years of age) and patients with the sarcomatous histologic subtype. The

relative activity of platinum-antimetabolite combinations compared with other platinum doublets has not been addressed in phase III studies.

Recent observations in phase II trials regarding the equivalent efficacy of three-drug regimens, novel agent-platinum regimens, nonplatinum combinations, maintenance treatment with a single agent and carboplatin-based instead of cisplatin-based regimens are speculative, and such claims cannot be adequately addressed in the absence of large comparative series or meta-analyses. Patients unable to receive third-generation antifolates, therefore, are treated according to drug availability, toxicity, ease of administration and their physician's personal experience.

Multimodality Therapy

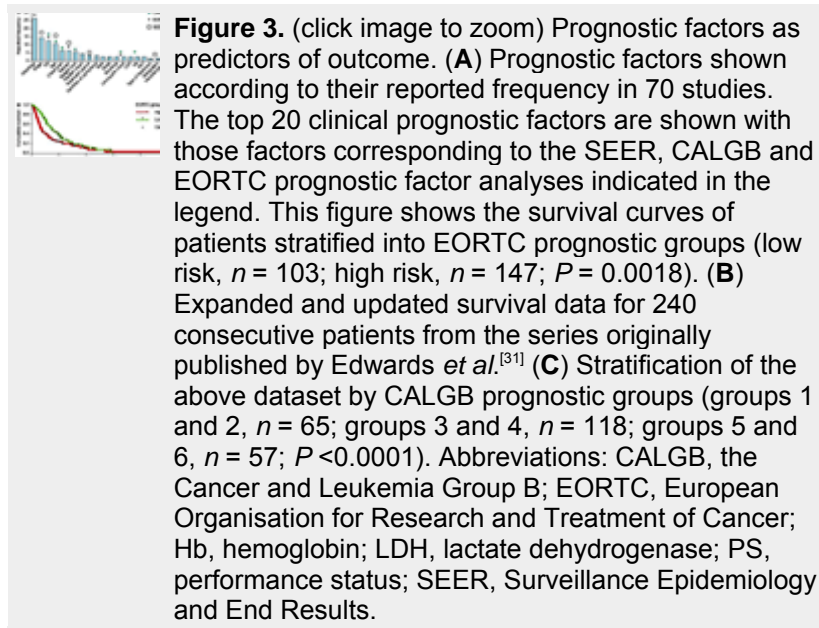
The development of active drug combinations has led to their use as part of combined-modality treatments, with sequential surgery and/or radiotherapy. Weder *et al.* were the first to report on the use of gemcitabine and cisplatin as induction therapy preceding an extrapleural pneumonectomy (EPP).^[17] Although currently not regarded as the induction regimen of choice, the promising results of this trial paved the way for the use of cisplatin-pemetrexed in several similar ongoing phase II studies. Trimodality therapy, involving adjuvant chemotherapy and radiotherapy, was investigated in a single-arm study of 183 patients with early-stage disease who underwent EPP followed by radiotherapy.^[18] The mortality rate was 3.8%, the morbidity rate was 50%; and median overall survival was 19 months. In a subgroup of 31 patients with epithelial histology, negative resection margins and no evidence of extrapleural nodal involvement, median survival was 51 months.^[18] To date, no randomized trials evaluating the net benefit of EPP have been reported; one UK study is currently enrolling patients into a clinical trial designed to address this issue.^[19]

Second-Line Therapy

Second-line therapy of MPM might have an important role in increasing overall survival; however, no standard has been defined in this setting, partly because of a paucity of reported studies.^[20] Despite this limitation, there is increasing evidence from single-arm studies that chemotherapy in the second-line setting is not only feasible, but also active.^[21-24] Recently, the efficacies of single-agent pemetrexed therapy and pemetrexed and carboplatin following platinum-based therapy without pemetrexed have been reported.^[25] Patients received an average of six cycles of therapy, and the response rates for the monotherapy and doublet arms, were 21% and 18%, respectively. PFS and overall survival were 21 and 32 weeks, and 42 and 39 weeks, respectively. A recent phase III trial that randomized patients in the second-line setting to either pemetrexed, vitamin supplementation and best supportive care or to best supportive care alone showed no survival advantage for the combination arm.^[26] Despite an increase in the response rate and PFS, overall survival was not increased significantly. The authors suggested that this might have been owing to poststudy therapy in the control arm.

Determinants of Clinical Outcome

Reliable prognostic and predictive factors can facilitate treatment planning. The Surveillance, Epidemiology and End Results Program review (published in 1988) is a landmark study of prognostic factors in MPM. This study included 1,475 patients with histologically confirmed MPM and demonstrated that age, gender, tumor stage, treatment and geographic area of residence are important predictors of patient survival.^[27] This result led to the evaluation of prognostic factors as predictors of outcome following treatment of patients in clinical trials (Figure 3A). The Cancer and Leukemia Group B^[28] and EORTC^[29] developed prognostic scoring systems that discriminated between patients with good and poor outlooks receiving systemic treatment. The Cancer and Leukemia Group B prognostic tree uses data on performance status, age, hemoglobin, whiteblood-cell count, the presence of chest pain and weight loss to define six patient groups with significantly different survival experiences. The different patient groups defined by this scoring system have different median survival times, ranging from 1.4 months in the worst group to 13.9 months in the best group.^[28]



The EORTC system divided patients into two groups according to gender, performance status, white-blood-cell count, histologic subtype and probability of histologic diagnosis. The median survival of the low-risk group (i.e. patients with two or fewer poor prognostic factors) was 10.8 months, compared with 5.5 months in the high-risk group.^[29] A subsequent retrospective analysis of 145 patients included in three phase II studies validated the EORTC scoring system.^[30] Both systems have been shown to be applicable to a general hospital population (Figures 3B,C).^[31] The impact of clinical prognostic factors on outcome underscores the potential for considerable bias in single-arm phase II trials.

Functional Imaging as a Predictive Tool

Although the role of PET-CT imaging in the diagnostic evaluation of MPM remains to be defined, there is emerging evidence that high accumulation of [¹⁸F]fluorodeoxyglucose (FDG) in the tumor, as measured by the standardized uptake value (SUV), before treatment is associated with resistance to chemotherapy and a poor outcome.^[32,33] PET imaging was used to assess 137 patients before surgery.^[32] A PET SUV of 10 was used as the cutoff point between high and low values. Following a median follow-up period of 24 months for all surviving patients, median survival in the high-SUV group was 9 months compared with 21 months in the low-SUV group. Multivariable analysis revealed that tumors with a high SUV were associated with a considerably greater risk of death than tumors with a low SUV.^[32]

There is controversy as to whether the tumor response evaluated by CT imaging criteria predicts patient survival following systemic chemotherapy for MPM. Nonetheless, there is growing evidence that therapy-induced changes in tumor FDG uptake might predict response and patient outcome early in the course of treatment. In a study of 22 patients evaluated by FDG-PET and CT imaging at baseline and after 2 cycles of therapy, 8 out of 20 evaluable patients showed a decrease of 25% or more in tumor FDG uptake (as measured by SUV) and were defined as having a metabolic response. Metabolic response correlated to PFS, which was 14 months in responders and 7 months in nonresponders. By contrast, no correlation was found between PFS and the radiologic response evaluated by CT imaging. Patients with a metabolic response had a trend towards a longer overall survival.^[33] Taken together these findings indicate that FDG-PET imaging could be useful in the early assessment of treatment efficacy.

Biological Prognostic Factors

Several retrospective studies have reported novel biomarkers of MPM, but no biomarker has been successfully translated into the clinic as a useful predictive or prognostic tool. An underlying problem is how to define a patient subpopulation in which single or multiple biological variables accurately predict sensitivity to therapy and prognosis by significantly adding to, or supplanting, clinical variables.^[34] Many biomarkers have indicated associations between certain biochemical pathways and clinical outcome, and provide a useful hypothesis generator for novel, early clinical trials.

Proteins involved in regulating the angiogenic process have been implicated in the prognosis of MPM and can be indirectly assessed using immunohistochemistry and microvessel counting. Studies have indicated that increased microvessel density is associated with a poor outcome.^[35,36] VEGF, the VEGF receptors (VEGFRs) flt1 (VEGFR1), KDR (VEGFR2), and VEGFC and its cognate receptor VEGFR3 have been shown to be co-expressed in MPM.^[37,38] Both VEGF and VEGFC function as autocrine growth factors for the development of MPM. Other angiogenic growth factors expressed in this disease include transforming growth factor β , fibroblast growth factor (FGF) 1, FGF2, thrombospondin 1, methionine aminopeptidases, interleukin (IL)-6 and IL-8. High levels of VEGF and FGF2 or co-expression of TGF β , VEGF, FGF1 and FGF2 have been found to be associated with a poor outcome.^[39] MPM exhibits high levels of expression of the surrogate marker of hypoxia, hypoxia-inducible factor 1 α .^[40] Tumor hypoxia contributes directly to chemoresistance; for example, through downregulation of BAX.^[41] The reduced level of this tumor suppressor has been associated with a poor outcome.^[42] Despite the expression of multiple antiapoptotic BCL2 family members,^[43,44] expression of these proteins does not predict an outcome consistent with findings *in vitro*.^[45,46]

Global gene-expression analysis has identified a four-gene signature comprising KIAA097, GDP-dissociation inhibitor 1 (GDIA1), cytosolic thyroid hormone-binding protein (CTHBP) and an expressed sequence tag similar to the L6 tumor antigen, which correctly classified a training sample into good and poor prognostic groups.^[47] This gene signature was subsequently tested on 29 samples and predicted the correct outcome in a significant number of cases. This signature was also validated in a subsequent study, supporting the identification of novel disease-specific and treatment-specific prognostic molecular marker candidates.^[48] A further study by Pass and coauthors used two different methods of microarray analysis to identify a common subset of 27 genes that could be used to predict both survival and progression of MPM.^[49] Despite the potentially useful data that have resulted from genearray studies, the clinical applicability of this technology remains unclear.

An analysis of primary tumors and metastases from transgenic mouse models of prostate cancer and cancer patients has identified an 11-gene, oncogene-driven-pathway signature that consistently has a stem-cell-like expression profile. The presence of this 11-gene profile is associated with a poor prognosis in patients with MPM.^[50] A large gene-expression analysis has identified and validated aurora kinases as predictive of outcome. This study also identified increased expression of regulators of mitosis and cell-cycle control in more-aggressive cancers,^[34] supporting several previous studies that have reported mitosis or proliferation, diploidy and S-phase fraction as indices of significance.

Novel Therapeutic Strategies

Angiogenesis and Survival Pathways

Deregulated expression of growth factors or proteins involved in downstream signaling pathways has an important role in malignant transformation of mesothelial cells. Autocrine circuits of activation have been identified in MPM for VEGF,^[37,51] insulin-like growth factors I and II,^[52] platelet-derived growth factor receptor β (PDGFR β),^[53] hepatocyte growth factor (HGF) receptor-Met^[54] and epidermal growth factor (erbB) receptor family receptors.^[55] Expression of c-Kit in MPM cells has been associated with chemoresistance in mesothelial cells.^[56] These receptors activate the PI3K-Akt pathway, which has a crucial role in MPM cell survival^[57-60] and contributes to the antiapoptotic phenotype.^[7] Indirect inhibition of Akt by abrogation of PDGFR β activity has been shown to increase the chemosensitivity of MPM cells.^[61] This has led to a pilot, stratified phase II trial, with the PDGFR β inhibitor imatinib mesylate combined with gemcitabine in both the chemorefractory and second-line settings.

Angiogenesis is a validated target for anticancer therapy, as shown by the activity of anti-VEGF-targeted therapy in other solid tumors.^[62] Bevacizumab is a recombinant humanized IgG monoclonal antibody against VEGF and its

use is being explored in phase II trials with pemetrexed and carboplatin or cisplatin. Data from a recent randomized phase II trial failed to demonstrate an increase in survival when bevacizumab was given in addition to gemcitabine-carboplatin therapy.^[63] AZD2171, a pan-VEGFR inhibitor,^[64] has demonstrated activity in patients with glioblastoma and is being evaluated in a phase II trial of patients with MPM in the second-line setting.

Inhibition of tyrosine kinase activity can disrupt survival pathways. The multikinase inhibitor sorafenib (Nexavar®, Bayer Aktiengesellschaft, Leverkusen-Bayerwerk, Germany) inhibits the Ras/Raf/MEK/ERK and p38 signaling pathways, VEGFR2 and VEGFR3, and members of the PDGF receptor family, PDGFR β and c-Kit.^[65] First-line and second-line phase II clinical trials are currently enrolling patients with MPM. Sunitinib malate (Sutent® Pharmacia & Upjohn Company, North Peapack, NJ) that acts on several targets, such as VEGFRs, PDGFR β and c-Kit, has shown promising activity in phase III trials enrolling patients with renal cell carcinoma and gastrointestinal stromal tumors.^[66-68] A firstline phase II trial with sunitinib in patients with inoperable MPM has been recently approved.

Proteome-Modifying Strategies

Methylation of tumor-suppressor promoters in MPM results in inhibition of gene expression and might contribute to chemoresistance and tumor aggressiveness through specific alterations of the proteome.^[69] Histone deacetylase (HDAC) inhibitors derepress methylated genes, leading to apoptotic cell death, and are associated with Bcl-xL downregulation and antiproliferating activity, which warrants their evaluation in MPM and other cancers.^[70] PXD101 is a novel HDAC inhibitor being explored in a phase II study of patients with unresectable MPM. A placebo-controlled phase III trial of the HDAC inhibitor suberoylanilide hydroxamic acid is also currently enrolling patients. Decitabine is a novel agent that induces promoter hypomethylation and is being explored in combination with the HDAC inhibitor depsipeptide in a phase I trial. Depsipeptide causes dose-dependent inhibition of growth and apoptosis of MPM cells and synergizes with the cyclin-dependent kinase inhibitor flavopiridol.^[70] In light of these findings, a phase I trial of depsipeptide and flavopiridol in patients with refractory MPM has been initiated.

Argininosuccinate synthetase has a key role in the metabolism of arginine and is frequently methylated in malignant MPM cells, leading to loss of expression *in vivo*. As a consequence, MPM cells are frequently auxotrophic for exogenous arginine and argininosuccinyl synthetase-negative cells that lack this amino acid exhibit BAX activation and loss of viability.^[71] On the basis of preclinical results, an arginine-lowering drug (ADI-PEG 20), which has been approved by the FDA, will be evaluated in a stratified phase II trial in chemo-naïve patients with inoperable disease who are unfit for platinum-based, antifolate-containing doublet therapy.

Regulation of protein degradation by the ubiquitin proteasome is altered in cancers, including peritoneal MPM.^[72] Bortezomib inhibits nuclear factor-kappa B and upregulates proapoptotic BH3 proteins.^[73] Proteasome inhibition induces apoptosis of mesothelioma cells *in vivo* and *in vitro*.^[74,75] On the basis of promising preclinical data, two phase II trials of bortezomib have been initiated in Europe. One trial is exploring single-agent activity in the second-line setting and in patients with a performance status of 2 in the first-line setting. The second trial, conducted by the EORTC, is exploring the use of this agent in a combination regimen with cisplatin in the first-line setting.^[76]

Immune-Activation Strategies

Mesothelin, a membrane-bound glycosyl phosphatidylinositol-anchored glycoprotein, is overexpressed on the surface of MPM, ovarian and pancreatic cells and can elicit a humoral immune response in patients with MPM.^[77,78] Two phase I clinical trials examining the use of antimesothelin monoclonal antibodies in patients with recurrent or refractory MPM have been initiated on the basis of the restricted expression and immunogenicity of this antigen. Gene-delivery strategies offer an alternative strategy for immune activation. For example, intratumoral delivery of a recombinant adenovirus encoding the CD40 ligand can stimulate and recruit MPM-specific CD8⁺ T cells in immunocompetent mice, leading to antitumor effects.^[79] Delivery of an adenovirus expressing interferon β achieves similar effects in *nu/nu* immunodeficient mice,^[80] and these approaches are, therefore, currently being tested in phase I clinical trials. A pilot phase II secondline clinical trial is currently evaluating the efficacy of cyclophosphamide and a vaccine against MPM cells treated with interferon α followed by granulocyte-macrophage colony-stimulating factor,^[81] in promoting an immune response. In summary, a considerable number of trials of novel agents are now ongoing, some of which are moving beyond early-phase evaluations.

Conclusions

The past 5 years have seen major advances in the first-line therapy of inoperable MPM. The most important of these have undoubtedly been the positive results of two randomized trials. These benchmark studies have now established the use of antifolate-platinum doublets as a widely adopted standard, supporting the evidence from meta-analyses for the superior activity of platinum-based combinations. The once nihilistic perception of second-line therapy for mesothelioma has now been supplanted by early evidence showing clinical activity in this setting. This body of evidence is likely to grow in the near future. Clinical prognostic scores provide tools for *a priori* identification of patients likely to do better or worse following a diagnosis of MPM; however, good predictive biomarkers that can reliably identify chemoresistant subgroups are yet to be translated into routine clinical practice. Having now entered the era in which translational research is considered a standard component of the design process of clinical trials, it is possible that tailored therapy for MPM could become a reality in routine practice. Finally, new preclinical research is shedding light on the underlying cell biology of MPM. It is the translation of this knowledge that will ultimately help to develop therapies for MPM that progress beyond the existing therapeutic plateau.

Key Points

- Malignant pleural mesothelioma remains a highly lethal cancer, which is increasing in incidence in several countries
- Chemotherapy is the mainstay of treatment for the majority of patients presenting as inoperable
- Despite the therapeutic plateau of the past 20 years, randomized trials have now confirmed that combining antifolates with platinum-based therapy confers a survival benefit
- No standard therapy has yet been defined in the second-line setting
- New approaches for treating this disease are arising from a better understanding of the underlying biology and are beginning to be translated into the clinical setting

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Tables

Table 1. Response Rate Outcomes of Phase III Trials

Medscape®		www.medscape.com	
Study type or regimen	Number of studies	Number of patients	Intention to treat response rate % (95% CI)
Single agent			
Long-term alkylating agents	7	194	4.6 (1.8–7.5)
Anthracyclines, liposomal anthracyclines or mitoxantrone	10	319	6.1 (3.6–8.7)
Taxanes	4	111	5.1 (1.2–9.1)
Vinca alkaloids	5	115	3.6 (0.4–6.8)
Gemcitabine	3	72	6.7 (1.2–12.2)
Antimetabolites	8	319	9.0 (6.0–11.9)
Topoisomerase inhibitors	4	117	4.9 (1.0–8.8)
Cisplatin	5	108	20.0 (12.8–27.2)
Carboplatin	3	89	10.1 (3.9–16.3)
Other experimental agents	12	376	4.0 (2.0–5.9)
Combination regimens			
Platinum-based	19	790	24.9 (22.0–27.9)
Cisplatin- but not anthracycline-containing	20	547	23.2 (19.7–26.8)
Anthracycline- and nonplatinum-based	8	213	11.3 (7.0–15.5)
Cisplatin- and anthracycline-containing	6	151	28.5 (21.3–35.7)
Nonplatinum- and nonanthracycline-based	54	409	11.6 (10.0–13.3)

The data were originally published in references 1 and 3.

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Table 2. Characteristics of Phase III Trials

Medscape®		www.medscape.com		
Reference	Vogelzang <i>et al.</i> (2003) ⁶		van Meerbeeck <i>et al.</i> (2005) ⁵	
Study arms	Cisplatin	Pemetrexed–cisplatin	Cisplatin	Raltitrexed–cisplatin
Number of patients	222	226	124	126
Drug dosage	C: 75 mg/m ² once every 3 weeks	P: 500 mg/m ² C: 75 mg/m ² Both: once every 3 weeks	C: 80 mg/m ² Once every 3 weeks	R: 3 mg/m ² C: 80 mg/m ² Both: once every 3 weeks
Median number of cycles given	4	6	4	5
% Response rate with 95% CI	17 (12–22)	41 (35–48)	14 (7–20)	24 (16–32)
<i>P</i> value	<0.001		0.056	
Overall survival				
Median (months)	9.3	12.1	8.8	11.4
1 year (%)	38	50	40	46
2 year (%)	17	22	10	19
Hazard ratio (95% CI)	1	0.77 (0.60–0.90)	1	0.76 (0.58–1.00)
<i>P</i> value (log rank)	0.002		0.048	
PFS/TTP				
Median	3.9	5.7	4.0	5.3
Hazard ratio	1	0.68	1	0.78
<i>P</i> value (log rank)	0.001		0.058	

The data were originally published from references 5 and 6. Abbreviations: C, cisplatin; P, pemetrexed; PFS, progression-free survival; R, raltitrexed; TTP, time to progression.

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