Personalizing treatment for malignant pleural mesothelioma

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CHAPTER 2

2

Emerging Therapies for Malignant Pleural Mesothelioma

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Abstract

Malignant pleural mesothelioma continues to challenge clinicians and scientists, since its incidence is rising and prognosis is far from favourable. Currently, the standard treatment consists of a combination of cisplatin and pemetrexed. The role of surgery and multimodality treatment remains controversial, while new treatment approaches, such as immunotherapy and targeted therapies, ad promising and interesting options. This review provides a comprehensive evaluation of emerging therapies and predictive biomarkers that are being tested.

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumour posing major treatment challenges. Its widespread distribution on the pleural surface (see figure 1) does not easily permit an adequate resection: a radical resection inevitably compromises a large amount of normal lung tissue. Furthermore, MPM is resistant to the vast majority of systemic anticancer drugs.

The development of novel therapeutic strategies is hampered by several factors. Assessment of disease extent is complicated as is illustrated by the various staging systems for MPM (1). Due to this variability in staging, patient cohorts in trials are not entirely comparable, leading to heterogeneous study outcomes. To address this problem, the International Association for the Study of Lung Cancer (IASLC) and the International Mesothelioma Interest Group (IMIG) initiated the Prospective Staging Project in Malignant Pleural Mesothelioma. Recommendations are expected by January 2014.

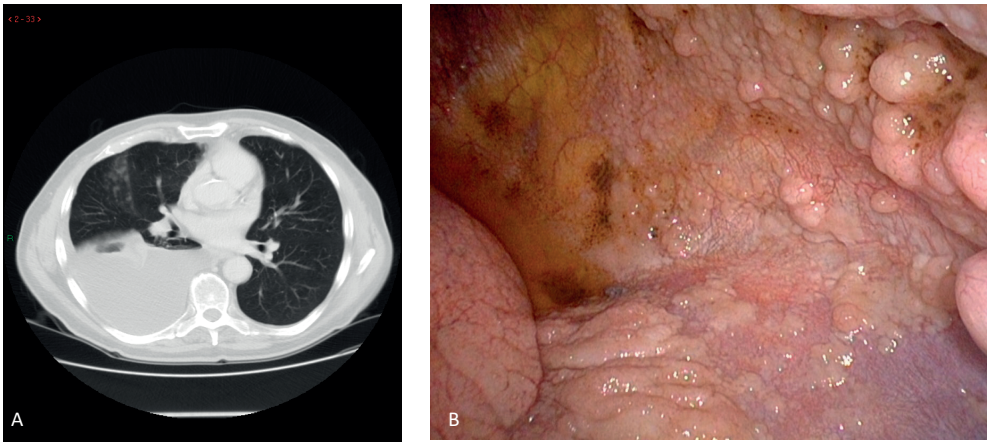

Fig. 1. (**A**) CT scan of a patient with mesothelioma showing right sided pleural fluid. (**B**) Thoracoscopic view of a patient with mesothelioma showing widespread distribution of tumor nodules on the pleural surface.

The modification of RECIST improved response evaluation, but still lacks sensitivity for adequate response assessment (2). Especially for thin tumor rinds, measurements are unreliable. Use of volumetric assessment is under investigation and seems promising for improving both staging and response evaluation (3-5).

Furthermore, MPM is a relatively rare and heterogeneous disease. The tumor comprises different histological subtypes: epitheloid, sarcomatoid and mixed (or biphasic), each of which are prognostically different. Recent pathologic studies have identified new prognostic factors like the pleiomorphic type, which is considered a subtype of epitheloid

mesothelioma, but has a prognosis similar to that of sarcomatoid MPM (6). Furthermore, stratification for nuclear grade, determined by nuclear atypia and mitotic count, enabled discrimination between 3 prognostic groups in a series of 323 MPM cases (7). Predictive biomarkers on the contrary, have not been identified. To date, no biomarker has proven to be sufficiently robust to apply in routine clinical practice. All of the above complicate validation of new therapeutic strategies in adequately powered randomized clinical trials.

In this review, we provide a comprehensive overview of current treatment options and the research that is ongoing in MPM with a focus on predictive biomarkers.

Surgery

The role of surgery in MPM has been the subject of debate for many years. Cao et al. systematically reviewed all literature on extrapleural pneumonectomy (EPP) up to 2010 and concluded that EPP as part of multimodality treatment, may improve survival in a group of highly selected patients ((8). However, only few trials have addressed this issue prospectively (9, 10) and retrospective trials typically suffer from selection bias. Two recent major publications assessed feasibility of multimodality treatment in early stage MPM. The MARS trial had patients undergo platinum-based induction chemotherapy and, if no signs of progression had occurred, randomized them to EPP followed by radiotherapy of the hemithorax, or to no EPP (11, 12). The primary endpoint, feasibility of randomizing 50 patients within one year, was not met. Patients were accrued in a three year time period. Only 45% of patients were eligible for randomisation and only 33% of the randomized patients were able to complete the full trimodality treatment. Median overall survival (OS) in the EPP group was 18 months (calculated from start of chemotherapy) versus 23.1 months in the no EPP group. Toxicity was higher in the EPP group and quality of life was lower. In the EORTC phase II multicentre trial on trimodality therapy, “success of treatment” was the primary endpoint. This was defined as undergoing the full protocol treatment within defined time-frames and still being alive 90 days after end of treatment, progression-free and without grade 3 or 4 toxicity (13). Only 42.1% of patients fulfilled these criteria. Median OS of the whole group was 18.4 months, but in those who completed trimodality therapy, it was as high as 33 months. Ninety-day mortality was 6.5%. Despite an encouraging 33 months’ median survival, neither study favours EPP in MPM patients.

Pleurectomy/decortication (P/D) on the contrary, may play a role in MPM treatment. Flores et al reported an improved survival in patients who underwent P/D, compared to those treated with EPP (14). However, this study was retrospective and selection bias is likely. In addition, the definition and surgical techniques of pleurectomy and decortication, vary

amongst different centers (15). Prospective trials with a uniform definition of lung sparing surgery for MPM are required to establish its role.

Chemotherapy

Since 2003, chemotherapy consisting of cisplatin and the anti-folate pemetrexed is considered standard of care in MPM patients with an adequate performance status. Vogelzang et al. reported in their landmark study a response rate of 41% in patients treated with this combination (16). Compared to cisplatin monotherapy, the combination arm demonstrated a survival benefit of approximately 3 months, leading to a 12 months median survival time. To reduce the haematologic toxicity of pemetrexed, supplementation of vitamin B12 and folic acid has proven its value (17). Van Meerbeeck et al. reported similar progression-free survival (PFS) and OS results with raltitrexed, another anti-folate tested in a large randomized phase III EORTC trial combined with cisplatin (18). Response rate however, did not equal the cisplatin-pemetrexed combination (24% vs 41%). Registration of raltitrexed for this indication has therefore been limited to a few European countries.
Carboplatin may be a reasonable substitute for cisplatin in MPM treatment. Ceresoli et al. reported a time to progression (TTP) of 6.5 months and median OS of 12.7 months in chemotherapy naïve patients treated with carboplatin and pemetrexed (19).

Thymidylate synthase (TS), an enzyme involved in folate metabolism, was identified as a predictive biomarker for pemetrexed therapy. Righi et al. noted that low protein expression of TS predicted for better outcome in pemetrexed treated MPM patients (TTP 17.9 vs 7.9 months and OS 30 vs 16.7 months). In order to confirm these retrospective data, a prospective randomized trial should be conducted. However, this is not feasible since approximately 1700 patients would be required per study arm to power such a trial. High expression of the excision repair cross-complementation group 1 (ERCC1) protein in this group of patients, was a prognostic but not a predictive marker (20).

Anti-tumour activity of the gemcitabine-cisplatin combination was assessed in several phase II trials showing response rates between 12% and 48% (21-24) Although never tested in a randomized phase III trial, this regimen demonstrated survival outcomes similar to the pemetrexed-cisplatin combination in a retrospective study by Lee and coworkers (25).

Second and further lines of treatment

Studies in second line treatment have yielded response rates between 10% and 20% with doxorubicin (26), pemetrexed alone (27, 28) pemetrexed in combination with carboplatin

(28), vinorelbine (29) or cisplatin in combination with irinotecan and mitomycin (30). A retrospective analysis of post-study treatment (PST) of patients included in the landmark study by Vogelzang, indicated that PST was associated with a better survival, regardless of the choice of chemotherapy (31). This may suggest a benefit of second or further lines of treatment in a subset of patients, although a clear survival benefit was not seen in any randomized trial (32). Retreatment with a pemetrexed-based regimen seems to be a valid option. A response rate of 19% has been noted in an observational study concerning patients that displayed an objective response or stable disease lasting for at least three months after first line pemetrexed-based chemotherapy (33). A similar response rate was observed in a second line phase II trial of patients receiving biweekly gemcitabine and docetaxel (34). With addition of granulocyte colony-stimulating factor (GCSF) to limit hematologic toxicity, this regimen proved to be well tolerated. Clinical activity of single agent taxanes however, is lacking (35). Surprisingly, gemcitabine combined with cisplatin did not elicit any objective responses in second line setting in another phase II study. Disease control rate was 67%, but toxicity was substantial with 35% of patients having grade 3 neutropenia and 47% having grade 3 or 4 trombocytopenia (36).

Maintenance therapy

Only few studies have addressed the subject of maintenance therapy in MPM. A small single arm phase II study by Van den Bogaert et al. reported pemetrexed maintenance therapy to be feasible and capable of evoking an ongoing response after induction chemotherapy (37). The Cancer And Leukemia Group B (CALGB) currently runs a randomized phase II study, comparing maintenance pemetrexed to placebo in non-progressive patients after first-line chemotherapy, consisting of pemetrexed and cisplatin/carboplatin. Progression-free survival was defined as the primary endpoint (data collection to be completed by January 2012) (38). The histone deacetylase (HDAC) inhibitor vorinostat was investigated in maintenance setting and is discussed further on in this manuscript.

Targeted therapies

In recent years, research has focused on exploring the molecular pathways involved in growth and progression of MPM. Several drugs that target these pathways, are being tested to define their role in MPM treatment (Table 1).

Histone deacetylase inhibitors

Epigenetic modifications such as hypermethylation and histone regulation, play an important role in tumorigenesis. Histones are packaging proteins, clustering DNA to form chromatin. Gene transcription can only occur after decondensation of chromatin. Histone

Table 1. Summary of drugs tested in MPM. n.a. = not assessed

Compound	Target	Phase	Line of treatment	Single agent/ combination therapy	Patients (no.)	RR (%)	PFS (months)	OS (months)	Biomarker tested	Predictive/ prognostic	Reference
Belinostat	HDAC I&II	II	2	Single agent	13	0	1	5	None		38
Vorinostat	HDAC	III	2	Single agent	660	0.3	1.6	7.7	Ongoing		39
Valproate	HDAC	II	2	doxorubicin	46	16	2.5	6.7	None		40
Bevacizumab	VEGF	II	1	cisplatin gemcitabine	108	25	6.9	15.6	VEGF	prognostic	43
Bevacizumab	VEGF	II	2	erlotinib	24	0	2.2	5.8	None		44
Sorafenib	RAS/RAF/MEK VEGFR, C-kit	II	1 or 2	Single agent	50	6	3.6	9.7	p-ERK1/2	prognostic	46
Sunitinib	VEGFR PDGFR	II	2	Single agent	51	10	3.4	6.7	None		47
Cediranib	VEGFR PDGFR	II	1 or 2	Single agent	50	10	1.9	4.4	None		49
Thalidomide	VEGF FGF	III	maintenance	Single agent	220	n.a.	4	11	None		51
Bortezomib	proteasome	II	1 or 2	Single agent	23	5	2	5.8	NOXA	neither	62
Dasatinib	Src kinase PDGFR C-kit BCR-ABL	II	2	Single agent	46	0	2.1	5.2	ongoing		60
CBP501	G2 checkpoint	I	1	Single agent	8	38	n.a.	n.a.	ongoing		61
ADI-PEG 20	Arginine synthesis	II	1 or 2	Single agent	66	ongoing	ongoing	ongoing	ASS	predictive	64
Cetuximab	EGFR	II	1	Cis/carboplatin pemetrexed	18	ongoing	ongoing	ongoing	none		68
MORAb-009	mesothelin	I	2	Single agent	13	0	n.a.	n.a.			78
NGR-hTNF	h-TNF antivascular	II	2	Single agent	57	1.8	2.8	12.1	none		83

deacetylase (HDAC) inhibitors are a class of antitumor agents that modulate chromatin structure, thereby regulating gene transcription leading to apoptosis, inhibition of angiogenesis and cell cycle arrest. Preclinical data have suggested a promising role for these agents in MPM (39, 40). However, in a phase II study with HDAC inhibitor belinostat, no anti-tumour activity was noted (41). Recently, the results of a large randomized phase III trial comparing HDAC inhibitor vorinostat to placebo in pretreated patients, was presented at the ESMO conference in Stockholm. Despite encouraging response rates in an earlier phase I study (42), the randomized trial demonstrated only a minor improvement in PFS and no survival benefit at all (HR 0,98). (LBA L Krug oral presentation ESMO ECCO 2011) Valproic acid, another HDAC inhibitor, was tested in combination with doxorubicin in recurrent MPM (43). The response rate of 16% was higher than that of doxorubicin monotherapy (26). These data do not support the use of the currently tested HDAC inhibitors in routine clinical practice. The role of HDAC inhibitors in combination with chemotherapy needs further evaluation.

Anti-angiogenic agents

Angiogenesis, the process of new blood vessel formation, is essential for growth of solid tumours. Increase in angiogenesis, reflected by an increase in microvessel density (MVD) is a negative prognostic factor in MPM patients (44). Several regulators of angiogenesis, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor-2 (FGF-2) and transforming growth factor beta (TGF-β), may serve as targets for treatment. VEGF is the most potent regulator of growth, and expression in MPM tissue is high compared to that in benign mesothelial cells (45).

Bevacizumab, a monoclonal antibody that neutralizes VEGF, is being investigated in combination with several chemotherapeutic regimens. Previous phase II trials did not report clinical activity of bevacizumab when added to standard chemotherapy (46) or EGFR-TKI (47). Zalcman et al. described an increase in disease control rate in patients treated with bevacizumab and cisplatin and pemetrexed (73.5% vs 43.2% in placebo) in a phase II study in previously untreated patients (48). The final results of this and other trials have to be awaited to determine if bevacizumab has a role in the treatment of MPM.

Another method to block the VEGF pathway is to inhibit the tyrosine kinase activity of the VEGF receptor. Sorafenib targets the tyrosine kinase domain of both the VEGF- and PDGF-receptor and inhibits the RAS/RAF/MEK/ERK pathway. A phase II study of sorafenib as single agent in 50 chemotherapy naïve or pretreated MPM patients, showed a limited response rate of 6%. Median PFS and OS were 3.6 and 9.7 months, respectively. Low or negative phosphorylation status of ERK1/2 in tumor tissue was correlated with improved survival (49).

Sunitinib, another VEGF- and PDGF-receptor tyrosine kinase inhibitor (TKI), was tested in 53 previously treated MPM patients. Response rate was assessed by modified RECIST criteria

on CT-scan and by metabolic response on FDG-PET. The total response rate was 22%, with 10% of the responses confirmed by modified RECIST on CT (50). Metabolic response on FDG-PET may be a more accurate way than modified RECIST to assess response, but its clinical relevance remains to be proven. In this study however, the median TTP (3.4 months) and median OS (6.7 months) do not support the claim of modest activity. Furthermore, toxicity required dose reductions in 28% of patients. Another phase II study confirms the lack of clinical activity of sunitinib as single agent (51).

Campbell and coworkers presented their results of a phase II study involving Cediranib at the latest ASCO annual meeting. This tyrosine kinase inhibitor of VEGFR and PDGFR was poorly tolerated requiring dose reductions in 48% and discontinuation for toxicity in 26% of patients. The trial failed to meet its prespecified response endpoint with a response rate of 10% (52).

Thalidomide is an immunomodulating drug that also acts on promoter regions of growth factor genes such as VEGF and FGF-2 by intercalating into guanine (G) and cytosine (C) rich regions of DNA. Subsequently, VEGF and FGF expression levels decrease, thereby diminishing angiogenesis and tumor growth. After promising results from a phase I study in 40 MPM patients (53), a multicenter, randomized phase III study comparing thalidomide maintenance therapy to observation, was launched. In this large trial, 222 patients without disease progression after induction chemotherapy, were included. Despite only mild toxicity, there was no benefit of thalidomide in PFS or OS (54).

So far, clinical activity of anti-angiogenic drugs, is disappointing. Two major mechanisms of resistance to these drugs have been suggested by Bergers and Hanahan. Firstly, intrinsic resistance is determined by specific tumor microenvironment and secondly, evasive resistance is due to upregulation of alternative pro-angiogenic pathways (55). A strategy to combine anti-angiogenic drugs with targeted agents might be a way to move forward. For this we need predictive biomarkers for response or resistance. Furthermore, it is essential to get a better understanding of the processes that evolve during treatment. Therefore, we developed a study protocol with interim biopsy analysis for a randomized phase II trial combining cisplatin and pemetrexed with axitinib, a VEGFR and PDGFR TKI, or placebo (56). So far, patient accrual is satisfactory and performing a second thoracoscopy for interim biopsy analysis is feasible. Results of this study are awaited in 2012.

PI3K/AKT/mTOR pathway

The PI3K/AKT/mTOR pathway is involved in a number of cellular processes that regulate proliferation, survival and motility (57). In MPM this pathway is frequently dysregulated which makes it an interesting target for therapy (58). Several PI3K inhibitors are currently being developed and a randomized phase III study in recurrent MPM patients is in preparation.

The downstream effector of this pathway, mTOR can be inhibited by agents like sirolimus, temsirolimus and everolimus, currently used as immune suppressors in transplantation medicine. Everolimus is being tested in a phase II trial in MPM patients with disease recurrence. Loss of Merlin/NF2 will be evaluated as a biomarker to predict anti-tumour activity (59). The South West Oncology Group (SWOG) is also evaluating everolimus in recurrent MPM (60).

Other targeted agents

Bortezomib is a selective proteasome inhibitor that decreases nuclear factor-κB and upregulates proapoptotic BH3 proteins. A single agent phase II trial has evaluated efficacy of this drug in first and second line setting. As clinical activity is lacking, further investigation as monotherapy is not warranted (Fennell et al., submitted). The association of NOXA expression to response was assessed in this trial, showing that NOXA cannot be used as a predictive biomarker. Two trials regarding bortezomib are ongoing: one combining it to cisplatin (61) and the other to oxaliplatin (62).

Dasatinib a receptor TKI of Src family kinases, PDGFR, C-kit and BCR-ABL fusion protein, did not show activity in MPM and was poorly tolerated (63). Data on pre- and post-treatment plasma levels of several biomarkers will be available in due time.

Tumour cells that acquire DNA damage usually arrest cell cycles to repair damaged DNA. Most solid tumors have genetic alterations that disturb cell cycle checkpoint G1 which makes them dependent on checkpoint G2 for survival. CBP501 is a compound that abrogates the G2 checkpoint, resulting in tumor cell death. This compound has demonstrated promising activity in combination with cisplatin in patients with MPM and patients with ovarian cancer in a phase I trial. Three out of 8 MPM patients showed a response. In two of them, time to progression was more than 9 months. Dose limiting toxicity (DLT) consisted of a histamine-release syndrome (64). A phase II study with CBP501 in combination with cisplatin and pemetrexed is currently recruiting patients with MPM.

Arginine is an amino acid involved in tumor metabolism and essential for tumor growth. Arginine synthesis is regulated by the enzyme argininosuccinate synthetase (ASS) and is downregulated in a number of tumor types such as MPM, hepatocellular carcinoma, and melanoma. Loss of ASS results in dependence on extracellular arginine. In a study by Szlosarek et al, 63% of mesothelioma patients had reduced or absent levels of ASS (65). Pegylated arginine deiminase (ADI-PEG 20) is an arginine-depleting drug that has demonstrated interesting results in a phase I/II study in hepatocellular carcinoma and melanoma (66). A multicenter randomized phase II of single agent ADI-PEG 20TM was recently launched in MPM patients with ASS negative tumors (67). ASS expression may serve as a biomarker predictive for treatment response of ADI-PEG 20.

The epidermal growth factor receptor (EGFR) is overexpressed in more than 50% of MPM patients. Activating mutations in the EGF receptor however, are not prevalent in MPM (68). This is reflected by the lack of activity of EGFR-tyrosine kinase inhibitors gefitinib and erlotinib in patients with MPM (69, 70). Cetuximab is a monoclonal antibody binding to the EGF-receptor that has shown a survival benefit in non-small cell lung cancer (NSCLC) patients with high EGFR expression (71). A study exploring the role of cetuximab in combination with pemetrexed and cisplatin or carboplatin, is ongoing (72).

Immunotherapy

Immunotherapy may be an attractive treatment approach for MPM for several reasons. The large lymphocyte infiltrate present in many cases of mesothelioma, and the spontaneous regression, occasionally occurring in MPM, suggest a role for the immune system in controlling tumor growth. Furthermore, several tumour-stroma generated cytokines (eg., TGF-β) suppress the local immune system, as do the abundant regulatory T cells in MPM (73). In the past, various passive immunotherapeutic approaches with cytokines such as IL-2, IL-12, INF-β and INF-Ɣ, were tested in murine models (74, 75) and some even in phase I-II clinical trials but with limited success (76-78). Hegmans et al. previously demonstrated efficacy of active immunotherapy in a murine MPM model using tumor lysate-pulsed dendritic cell vaccination (79). Recently, the results of a phase I trial testing this dendritic cell-based (DC) immunotherapy, were published. Ten patients received three vaccinations after completing standard chemotherapy. DC immunotherapy is feasible, well-tolerated and capable of inducing an immunological response to mesothelioma cells (80). It seems most effective in patients with modest tumour load. Applying DC immunotherapy after surgical debulking, is an interesting approach for future studies. A trial combining DC immunotherapy with cyclophosphamide, inhibiting T-regulatory lymphocytes and thereby enhancing immunological responses, is currently recruiting patients (81).

Mesothelin is a glycoprotein normally expressed on the surface of mesothelial cells lining the pleural and peritoneal cavity. Expression is upregulated in many solid tumors including MPM. Mesothelin can bind to CA-125, a cell surface mucin expressed on several types of tumor cells, thereby mediating tumor metastasis within pleural and peritoneal cavities (82). At least two different antibodies that target mesothelin, were developed and tested in phase I trials. MORAb-009 is a chimeric monoclonal antibody to mesothelin that was well tolerated and induced disease stabilization in patients with mesothelin-expressing tumors (83). An open-label clinical trial of MORAb-009 in combination with pemetrexed-cisplatin in patients with MPM, has completed accrual and results are awaited (84). SS1P (CAT-5001) is a recombinant immunotoxin linking an exotoxin of *Pseudomonas Aeruginosa* to mesothelin. Tolerability was demonstrated previously in a phase I study (85). Currently it is being tested

in combination with cisplatin and pemetrexed in MPM patients (86). Another phase I study is combining SS1P with an immune-depleting regimen consisting of pentostatin and cyclophosphamide (87).

Tumor necrosis factor α (TNF-α) is a potent anti-tumour agent. Systemic use however, is limited by severe toxicity (88). Asparagine-Glycine-Arginine–Human Tumor Necrosis Factor-α (NGR-hTNF) is a fusion protein of human TNF-α and Asparagine-Glycine-Arginine, a peptide that targets aminopeptidase N/CD13. This aminopeptidase N/CD13 is overexpressed by endothelial cells of the majority of solid tumors (89). NGR-hTNF was tested as single agent in triweekly and weekly dosing in MPM patients with disease recurrence. NGR-hTNF was well tolerated with short-lived chills being the most common side effects. Progression-free survival was 2.8 months and OS 12.1 months (90). A randomized double-blind phase II maintenance study of NGR-hTNF versus placebo, is currently recruiting patients with advanced MPM (91). A phase III study is also initiated comparing NGR-hTNF plus chemotherapy (best investigators choice (BIC)) to placebo in combination with chemotherapy BIC in patients previously treated with pemetrexed (92).

Gene therapy

The purpose of gene therapy is to kill tumor cells by means of genetic modification. In general this implies that a therapeutic gene is inserted into tumor cells using a vector system. Several viruses such as adenovirus or vacciniavirus may serve as such. In MPM the vector can be administered locally via the pleural cavity. The inserted gene can either be a suicide or sensitivity gene (e.g. Herpes Simplex Virus thymidine kinase), an immune modulator (e.g. IL-6 or IFN-β) or a replacement for a tumor suppressor gene. Sterman et alI. recently published their results of intrapleural administration of an adenoviral vector expressing interferon β (93). Ten patients were treated with an intrapleural injection which was repeated after one week. Gene transfer was confirmed in the pleural fluid. One patient had a partial response and two patients disease stabilization. However, neutralizing antibodies were rapidly developed after the first dose, preventing effective gene transfer. An early second injection after three days is currently being tested.

Conclusion and future perspectives

Despite ceaseless efforts to improve outcome in patients with MPM, the prognosis remains grim. The standard of care consisting of cisplatin-pemetrexed chemotherapy has not changed since 2003. Surgery should not be advocated outside clinical trials and targeted therapies have not entered clinical practice yet, due to lack of activity. In order to improve

prognosis, several measures are necessary. Firstly, we have to reconsider our current classification based on epitheloid vs non-epitheloid histology. Secondly, an improved system for staging and response assessment is required. In addition, we need better criteria to select patients that may benefit from surgery. The same applies to patient selection for targeted therapies as biomarkers predicting for treatment response are urgently needed. Furthermore, preclinical data suggest that in approximately half of MPM cases, more than one pathway is activated (94). Therefore, combining targeted agents is a treatment strategy worth exploring. Finally, to get a better understanding of the pathways involved in tumorigenesis, we advocate combining clinical trials with translational research.

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