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Review

Biology and management of malignant pleural mesothelioma

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ABSTRACT

Malignant mesothelioma is an aggressive tumour, with a poor prognosis and an increasing incidence as a result of widespread exposure to asbestos. The results of the treatments available are poor. Surgery and radiotherapy have a limited role in highly selected patients and systemic therapy is the only potential treatment option for the majority of patients. Despite some definite activity of the novel antifolates such as pemetrexed and raltitrexed, the results, even in combination with platinating agents, are still modest, with a median survival of approximately one year. The better understanding of the biology of mesothelioma makes the assessment of a number of targeted agents particularly interesting. Unfortunately, the targeted agents imatinib, gefitinib, erlotinib and thalidomide have been shown to be ineffective in unselected patients. Studies with anti-angiogenesis agents are ongoing. An improvement of the knowledge of major molecular pathways involved in malignant mesothelioma is needed in order to define proper targets for the systemic treatment of this disease.

1. Introduction

Malignant mesothelioma (MM) is an aggressive tumour of serosal surfaces, such as the pleura, peritoneum and tunica vaginalis testis,[1] that usually has a poor prognosis. This tumour was once rare, but its incidence has been increasing in several countries as a result of widespread exposure to asbestos in the past, and it is predicted that it will increase in the next decades, especially in the developing countries where asbestos has not yet been banned for use.[2] Approximately 80% of MM can be attributed to asbestos fibre exposure; other potential carcinogenic factors are exposure to simian virus 40 (SV40), radiation and thorotrast.[3] Median survival of patients with MM is less than 1 year, and most of the patients are not amenable to radical surgery. Systemic therapy is the only potential treatment option for the majority of these patients, but their poor performance status, the advanced extension of disease at diagnosis, and the low chemo- and radio-sensitivity of this tumour induced in the past a nihilistic attitude about medical treatment. Although trials comparing chemotherapy and best supportive care (BSC) are still ongoing, some data suggest that chemotherapy is better than BSC in terms of survival and quality of life.[4] Presently, the combination of pemetrexed plus cisplatin is considered the standard of care as a front line chemotherapy in MM patients because it was shown to significantly improve response rates, time to progression, overall survival and quality of life when compared to cisplatin alone.[5]

In this review, we critically analyse the current knowledge in terms of biology and management of patients with malignant pleural mesothelioma (MPM).

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2. Biology

In recent years, several molecular alterations have been reported in MM, which may cause a number of pathological processes, such as disruption of the normal cell cycle, including inhibiting apoptosis, neoangiogenesis and many others. Some of these changes can be caused by the effect of asbestos fibres directly on mesothelial cells, hormones and cytokines released by the surrounding tissues in response to damage, virally encoded proteins and loss of normal protein function because of DNA damage.

2.1. *Tumourigenesis and asbestos*

MM development is linked to amphibole fibres with a high length-to-diameter ratio (crocidolite, amosite and tremolite). The exact mechanism whereby asbestos fibres can induce MM is unclear however. In tissue culture, asbestos fibres can cause mutagenic events, including DNA strand breaks and deletion mutations, through the production of hydroxyl radicals and superoxide anions, and alter chromosome morphology and ploidy by mechanically interfering with their segregation during mitosis. Furthermore, macrophages produce DNA-damaging oxyradicals following phagocytosis of asbestos fibres, as well as elaborate lymphokines, which may depress the host immune response. These fibres also induce cytokine and growth factor production due to an inflammatory response, resulting in mesothelial cell proliferation. Asbestos fibres can mediate transformation of monkey cells by exogenous plasmid DNA and similarly facilitate transformation of mouse cells by simian virus 40 (SV40).[6] In asbestos-induced MM in rats, it was shown that the glypican 3 gene (*GPC3*), an X-linked recessive overgrowth gene, is affected in MM and may encode a negative regulator of mesothelial cell growth.[7] In hamster tracheal epithelial cells, crocidolite fibres have caused an increase in the expression of the nuclear factor-kB (NFkB), a transcription factor that regulates gene expression and cellular proliferation.[8] Crocidolite also induces redox changes that lead to the activation of NFkB and upregulation of pro-inflammatory cytokines, such as interleukin-6, interleukin-8 and tumour necrosis factor-alpha.[9,10] The establishment of better human in vitro mesothelial cell model systems may help in investigating the mechanisms of asbestos-induced MM.

2.2. *Chromosomal aberrations*

The long time lag in MM development suggests that the accumulation of multiple genetic hits is required. Chromosomal damage may occur when asbestos fibres interact directly with the mitotic spindle apparatus or may act on cellular proliferation, which allows spontaneous genetic mutations to occur unchecked over time. Though no specific chromosome anomaly characterises MM, and despite the complexity of the numerical and structural karyotypic changes in MM, a number of recurrent anomalies have been found. These include monosomy for chromosome 4 and particularly for chromosome 22, polysomy for chromosomes 5, 7 and 20, and loss at 1p21–p22, 3p21, 6q15–q21, 9p21–p22 and 22q12,[11–15] suggesting that tumour suppressor genes critical to MM tumourigenesis may reside at these loci. The deletion of chromosome bands 9p13-p22 has been observed by cytogenetic analysis in 50% of MMs.[10] Three putative tumour suppressor genes (p14, p15 and p16) are located in this region. P16 was commonly found altered in MM cell lines (homozygous deletions in 85% of 40 cell lines), but less frequently in primary tumours (22% of 23 specimens).[16] Approximately 70% of 50 MMs showed a co-deletion of p15 and p16 by FISH analysis, which was 100% in the sarcomatoid cases (21 of 21).[17] The absence or alteration of p16 and p14 may be important in transformation and proliferation of MM cells: Cell cycle arrest was induced in MM cells transfected with either p16 or p14 constructs.[18,19] This finding strongly suggests that p14, p15 and p16 or other neighboring genes on chromosome 9p are important targets for the development of this tumour.

2.3. *Cellular pathways and angiogenesis*

Malignant mesothelioma cells show an increased or dysregulated growth. The cells produce and respond to many autocrine growth factors, such as hepatocyte growth factor (HGF),[20] epidermal growth factor (EGF),[21] platelet-derived growth factors (PDGF) A and B,[22,23] transforming growth factor [24,25] and angiogenic factors, such as vascular endothelial growth factor (VEGF).[26]

Over-expression of c-Met, a receptor tyrosine kinase, and its activating ligand HGF was found in paraffin-embedded MM tumour samples. This co-expression suggests a possible self-stimulation of tumour cells. The HGF-positive MM also had a significantly higher microvessel density compared with its HGF-negative counterpart.[20] HGF and c-Met play an important role in mesothelioma cell motility and invasion into extracellular stroma.

Over-expression of epidermal growth factor receptor (EGFR) has been observed in MM, especially in epithelial malignant mesothelioma. An important molecule involved in downstream signalling from the EGFR is the phosphoinositide-3-kinase (PI3K) pathway that has been shown to be active in mesothelioma cells lines.[27–30] The mammalian target of rapamycin (mTOR), a kinase downstream of Akt and PI3K, has been identified in overexpression studies in mice, where the mTOR pathway was found to account for the major survival effect of Akt.[31]

PDGF is a potent mitogen for connective tissue cells; in vitro, mesothelial cells proliferate in a dose-dependent manner when exogenous PDGF is administered. PDGF receptors are differentially expressed in MM cells compared with normal mesothelium. MM cell lines express PDGF-β receptors, while normal mesothelial cells express PDGF-α receptors. Transduction of a hammerhead ribozyme against PDGF-β mRNA in mesothelioma cell lines led to a significant reduction of cell growth and decreased expression of PDGF-β. Catalano *et al.* showed that c-Kit and its ligand stem cell factor (SCF) are upregulated in multidrug-resistant (MDR) MM cell lines. Interestingly, knocking down c-Kit expression increased sensitivity to chemotherapeutic agents in MDR sub-lines, and forced expression of SCF/c-Kit signal was sufficient to lead to MDR in parental cells.[32]

The data suggest the great importance of angiogenesis in mesothelioma. Interleukin 8, a potent kemokine with pro-angiogenesis function, has been shown to be an autocrine growth

factor for mesothelioma cell lines.[33] VEGF expression in mesothelioma correlates with microvessel density; high microvessel density is associated with poor survival.[34] The VEGF inhibition reduces mesothelioma growth in animal models.[35]

2.4. *Antiapoptotic processes*

The limited effectiveness of cytotoxic drugs and radiotherapy in mesothelioma may implicate an important functional defect in apoptosis signalling. Considering that mesothelioma cells commonly express wild-type p53, a central regulator of cell cycle and apoptosis, and that its re-expression is not sufficient to substantially enhance susceptibility to apoptosis, probably the resistance to apoptosis arises downstream of p53,[36] by functional inactivation by SV40 large T antigen, or deletion of the tumour suppressor p16, or both.[37–39]

Apoptosis resistance can arise from the inhibition of mitochondrial permeabilisation, or the suppression of caspases. Several mechanisms of natural inhibition of this process have been described in mesothelioma, including the stabilisation of the mitochondrial membrane, and the direct inhibition of caspases by the inhibitor of apoptosis protein (IAP) family. The long form of the BCL-2 homologue, BCL-XL, is a potent repressor of apoptosis, and is commonly expressed in mesothelioma cells. BCL-XL has been shown to repress permeabilisation of both the inner and outer mitochondrial membranes blocking the caspase activation. Survivin and IAP1 are overexpressed in MM. Antisense downregulation of survivin in mesothelioma cell lines enhances spontaneous apoptosis. The level of expression of IAP1 correlates with sensitivity to cisplatin-induced apoptosis, suggesting that IAP1 has a role in regulation of the apoptosis threshold in mesothelioma cells. Stable downregulation of IAP1 gene expression increases not only the occurrence of spontaneous apoptosis, but also susceptibility to cisplatin-induced apoptosis by about 20 times.[40]

2.5. *SV40*

The involvement of SV40, a potent oncogenic DNA virus, in the pathogenesis of MM still remains controversial and unproven.[41] However, SV40 induces mesotheliomas in hamsters, and 60% of human mesotheliomas contain and express SV40 sequences. Human population was probably infected through contaminated poliomyelitis vaccines between 1955 and 1963.[6] The oncoprotein of SV40, large T-antigen (Tag) is able to initiate the transformation of mesothelial cells into malignant cells by blocking tumour suppressor proteins such as p53 and the products of the retinoblastoma-susceptibility gene. These transformations can occur easily in rodent cells, but the conversion of human cells is more complex. Some data suggest that SV40 may only be a laboratory anomaly.[42]

3. Management

The diagnosis of MM mostly requires histology, and the staging is rather inaccurate. Computed tomography scanning, magnetic resonance imaging, positron emission tomography, and often thoracoscopy and mediastinoscopy should be considered as complementary to define the extension of disease, selecting the patients candidate to multimodality approach. However, the staging of MPM still remains difficult. At present, the recommended classification for clinical use is the International Mesothelioma Interest Group (IMIG) Classification,[43] based on a TNM modification (Table 1). A number of prognostic factors have been described and two prognostic scoring systems have been reported (Table 2).

3.1. *Chemotherapy*

Systemic therapy is the only potential treatment option for the majority of these patients. All chemotherapy studies using either single agents or combination regimens in the setting of small phase II trials reported poor response rates (less than 20%), without any substantial impact on survival.[46,47] In a meta-analysis of studies published between 1965 and 2001, cisplatin was found to be the most active single drug and combination chemotherapy has been associated with higher response rates, but not with longer survival.[48] Although trials comparing chemotherapy and best supportive care (BSC) are still ongoing, O'Brien *et al.* recently observed how the early *versus* delayed use of chemotherapy (MVP schedule) in the management of patients with stable symptoms after control of any pleural effusion provided an extended period of symptom control, and a trend to survival advantage.[4] Several new cytotoxic agents with definite activity in mesothelioma have recently been evaluated, including gemcitabine and the antifolates pemetrexed and raltitrexed. Two randomised controlled trials comparing cisplatin alone *versus* its combination with an antifolate were reported (Table 3). The pemetrexed/cisplatin combination significantly improved response rates, time to progression, overall survival and quality of life compared to cisplatin alone.[5] Furthermore, the raltitrexed/cisplatin combination also improved overall survival compared with cisplatin alone,[49] confirming that cisplatin with an antifolate should be the reference regimen in patients with MM. The magnitude of the survival benefit was similar in both studies: a 2.8-month increase in median survival in the pemetrexed study (from 9.3 to 12.1 months) and a 2.6 months increase in the raltitrexed study. However, in the pemetrexed trial this difference was statistically significant, while in the other study the survival improvement had borderline significance, probably due to the more limited sample size. Considering that many MPM patients are unfit to receive a cisplatin-based chemotherapy, a number of regimens used carboplatin, instead of cisplatin, in an attempt to reduce toxicity maintaining the same survival benefit.[50,51] The regimen cisplatin-pemetrexed has become standard in the treatment of first line MPM patients, after FDA and EMEA approval. Interestingly, after the approval of first line chemotherapy, even second line chemotherapy is being used increasingly. In a retrospective analysis of patients treated in the phase III pemetrexed trial, Manegold *et al.* observed a significantly prolonged survival in the groups treated with post-study chemotherapy (PSC); however, because PSC was not randomised, it is impossible to know whether the reduced risk of death was associated with PSC or whether patients who had prolonged survival tended to receive more PSC.[52] Several recent phase II trials have evaluated the effectiveness of chemotherapy in previously treated patients. The partial re-

Table 1 – International staging developed by the international mesothelioma interest group

Descriptor	Region involved	Characteristics
T1a	Limited to the ipsilateral parietal pleura, including the mediastinal and diaphragmatic pleurae	No involvement of the visceral pleura
T1b	Ipsilateral parietal pleura, including the mediastinal and diaphragmatic pleurae	Scattered tumour foci that also involve the visceral pleura
T2	Each ipsilateral pleural surface.	At least one of the following: (i) involvement of the diaphragmatic muscle; or (ii) a confluent visceral pleural tumour (including fissures) or tumour extension from the visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but potentially resected tumour (each ipsilateral pleural surface)	At least one of the following: (i) involvement of the endothoracic fascia; (ii) extension into mediastinal fat; (iii) a solitary, completely resectable focus of tumour that extends into the soft tissues of the chest wall; or (iv) non-transmural involvement of the pericardium
T4	Locally advanced, technically unresectable tumour (each ipsilateral pleural surface)	At least one of the following: (i) diffuse tumour extension or multiple tumour foci in the chest wall with or without associated rib destruction; (ii) direct transdiaphragmatic extension to the peritoneum; (iii) direct extension to the contralateral pleura; (iv) direct extension to the mediastinal organs; (v) direct extension to the spine; or (vi) extension to the internal surface of the pericardium with or without pericardial effusion or involvement of the myocardium
NX		Regional lymph nodes not assessable
N0		No regional lymph node metastases
N1		Metastases in ipsilateral bronchopulmonary or hilar lymph nodes
N2		Metastases in subcarinal or ipsilateral mediastinal lymph nodes, including ipsilateral internal mammary lymph nodes
N3		Metastases in contralateral mediastinal, contralateral internal mammary and ipsilateral or contralateral supraclavicular lymph nodes
MX		Distant metastases not assessable
M0		No distant metastases
M1		Distant metastases

Stage	Tumour	Node	Metastasis
Ia	T1a	N0	M0
Ib	T1b	N0	M0
II	T2	N0	M0
III	Any T3	Any N1 or N2	M0
IV	Any T4	Any N3	M1

sponses to a variety of agents and combinations ranged from 5% to 10%. Furthermore, the number of patients demonstrating benefit in the second-line setting seems to be steadily increasing.[52–54]

3.2. *Surgery and radiotherapy*

The roles of surgery and radiotherapy in MPM are still debated. The results of each individual treatment are difficult to interpret because of variable patient selection, the relatively small number of patients prospectively followed in studies, the lack of randomised trials, and often the addition of another treatment modality to each of them. In general, patients with stage I disease can be considered candidates for radical surgery. Pleurectomy (PL) and extrapleural pneumonectomy (EPP) are the two major types of operations. Parietal PL has not been shown to prolong survival but it is able to reduce the recurrence of pleural effusion better than talc pleurodesis.[55] EPP is a rather complex operation, which should be performed by skilled surgeons and in select centres. The operative mortality is 5–9% nowadays, but serious complications are seen in 25% of patients or more. Surgery alone has not been extensively tested, and the use of combined modality approaches has been better investigated.

Radiotherapy alone has probably no major role in disease control and survival. Radiotherapy is often used for palliation of pain, and it has often been added to surgery in an attempt to improve local control and reduce local failure.[56,57] However, the diffuse nature of the tumour, which often covers most of the lung and the interlobular fissures, is the principal limitation to radiotherapy. The recent improvements in radiation treatment techniques, such as intensity modulated radiation therapy (IMRT), have provided the potential to conform radiation doses tightly to target volumes reducing normal tissue toxicity.[58]

3.3. *Combined modality treatment*

Combined modality approaches including surgery have been attempted in order to reduce local recurrence and systemic

Table 2 – EORTC and CALGB prognostic scoring systems

Group	Description	mSurvival (month) (95% CI)	1-year Survival (%) (95% CI)	2-year survival (%) 95% CI
EORTC [44]				
Low risk (score $\leqslant$ 1.27)	WBC > 8.3×10^9/l (score: +0.55) PS:1 or 2 (score: +0.60) Histologic diagnosis (score: +0.52) Sarcomatoid histological subtype (score: +0.67) Male gender (score: +0.60)	10.8	40 (30–50)	14 (CI 6–22)
High risk (score > 1.27)	WBC > 8.3×10^9/l (score: +0.55) PS:1 or 2 (score: +0.60) Histologic diagnosis (score: +0.52) Sarcomatoid histological subtype (score: +0.67) Male gender (score: +0.60)	5.5	12 (4–20)	0
CALGB [45]				
1	PS:0, age < 49 year PS: 0, age $\geqslant$ 49 year, HGB $\geqslant$ 14.6 g/dl	13.9 (11.1–31.4)	63 (46–77)	38 (23–55)
2	PS: 1/2, WBC < 8.7×10^9/l, no chest pain	9.5 (6.9–14.7)	41 (26–57)	21 (10–37)
3	PS:0, age $\geqslant$ 49 year, HGB <14.6 g/dl PS:1/2, WBC < 15.6×10^9/l, chest pain, no weight loss, HGB $\geqslant$ 12.3g/dl. PS:1/2, $9.8 \leqslant$ WBC < 15.6×10^9/l, chest pain, weight loss, HGB $\geqslant$ 11.2 g/dl	9.2 (7.5–10.5)	30 (23–37)	10 (6–16)
4	PS: 1/2, $8.7 \leqslant$ WBC < 15.6×10^9/l, no chest pain	6.5 (3.7–9.4)	25 (14–42)	6 (2–17)
5	PS:1/2, WBC < 15.6×10^9/l, chest pain, no weight loss, HGB <12.3 g/dl. PS:1/2, $9.8 \leqslant$ WBC < 15.6×10^9/l, chest pain, weight loss, HGB <11.2 g/dl PS:1/2, WBC < 9.8×10^9/l, chest pain, weight loss.	4.4 (3.4–5.1)	7 (3–15)	0
6	PS: 1/2, WBC $\geqslant$ 15.6×10^9/l.	1.4 (0.5–0.36)	0	0

CI, confident interval; EORTC, European Organisation for Research and Treatment of Cancer; CALGB, Cancer and Leukaemia Group B; WBC, white blood cells; PS, performance status (ECOG); HGB, haemoglobin.

Table 3 – Results of randomised trials with cisplatin and anti-folates in MPM

Regimen	Patients	RR (%)	mTTP (months)	mSv (months)	1-yrSv (%)	References
Cisplatin	222	16.7	3.9	9.3	38	[5]
Cisplatin + pemetrexed	225	41.3	5.7	12.1	53	
		$P < 0.001$	$P = 0.001$	$P = 0.02$		
Cisplatin	124	14	4	8.8	39.6	[42]
Cisplatin + raltitrexed	126	24	5.3	11.4	46.2	
		$P = 0.06$	$P = 0.058$	$P = 0.048$		

RR, response rate; mTTP, median time to progression; mSv, median survival; 1-yrSv, 1 year survival rate.

spread. Surgery was employed in the form of PL or EPP in combination with various forms of radiation treatment and chemotherapy.[59–65] This approach, which is not supported by randomised trials and has to be performed by skilled surgeons and in select centres, is safe and offers improved survival only for certain subgroups of patients. In particular, patients with epithelial cell type, lack of extra-pleural nodal involvement and negative surgical margins have a median survival approaching 5 years.[65] The pattern of failure analysis of 46 patients treated with trimodality therapy showed that 54% of patients had recurrences and the site of recurrence was local in 35% of them.[66] This and other studies indicate that more effective strategies should be sought to increase local control. Moreover, better preoperative staging procedures should be developed.[67] Another interesting approach is the use of preoperative chemotherapy. In the neo-adjuvant setting, chemotherapy seems to improve the resectability rates and survival without altering the surgery mortality rates.[68,69]

3.4. *Target therapy*

A number of targeted agents have been tested in MM. However, none of these agents have been targeted to specific MM molecular alterations or to subgroups of MM.

Unfortunately, early studies testing imatinib mesilate and the EGFR tyrosine kinase inhibitors gefitinib and erlotinib have shown limited or no activity in MPM patients.[70–72] The poor expression of c-Kit and the lack of the common EGFR

mutations that confer sensitivity to gefitinib in non-small cell lung carcinoma could be an explanation of resistance to imatinib and EGFR tyrosine kinase inhibitors, respectively, in MM.[73,74] Garland *et al*. suggested that the lack of phosphorylation of AKT and lack of PTEN expression in the AKT pathway downstream of EGFR observed in an immuno-histochemical analysis of 64 patients treated with erlotinib may be a mechanism of clinical resistance in MPM.[70]

Mesothelioma patients have the highest VEGF levels of any solid tumour patients.[75] VEGF expression in mesothelioma correlates with microvessel density and high microvessel density is associated with poor survival.[34] Thus, several antiangiogenic agents that target the vascular VEGF pathway, such as PTK787, thalidomide, bevacizumab and BAY43-9006, were evaluated or are still under evaluation. A modest activity (response rate 6%, disease stabilisation in about half of the patients) has been reported with PTK787, an inhibitor of the PDGF/VEGF pathway, but survival outcomes have been disappointing. Thalidomide showed lack of activity,[76] while some activity was reported with SU5416, an inhibitor of the VEGF-R receptor flk-1, hampered by an excessive risk of thrombosis. Bevacizumab, a recombinant human anti-VEGF monoclonal antibody that blocks the binding of VEGF to its receptors, is under evaluation in a double-blind, placebo-controlled, randomised phase II trial in combination with cisplatin and gemcitabine. The accrual of the study is concluded, but data are still blinded.

4. Future directions

Inhibition of angiogenesis appears to have some promise, and while we are awaiting the results of bevacizumab, other therapeutic strategies have to be explored. The limited effectiveness of cytotoxic drugs and radiotherapy in MM implicates an important functional defect in apoptosis signalling. Re-induction of apoptosis manipulating its critical control points, such as the extrinsic death pathway, the mitochondrial regulation, and the post-mitochondrial regulation is an interesting field to develop new effective treatments.[77]

The extrinsic death pathway, that starts from death receptor activated by ligands such as tumour necrosis factor (TNF), TNF-related apoptosis-inducing ligand (TRAIL), and Fas ligand or as a result of blockade of growth factors, which leads to activation of the caspase death cascade, is an attractive target for the induction of apoptosis in mesothelioma cells and many other tumour types. Because caspase activation occurs downstream of receptor ligation, the extrinsic death pathway essentially provides a parallel death-signalling pathway that bypasses mitochondrial permeabilisation. A few preclinical studies have suggested that activation of death receptors can synergise with conventional cytotoxic drugs that rely on mitochondrial permeability in mesothelioma cells; such an approach could therefore be exploited to therapeutic benefit.[78] Tumour necrosis factor 10 (TNF10) death receptors are expressed on mesothelioma cells. TNF10 ligand has been shown to sensitise mesothelioma cells to chemotherapeutic drugs that include cisplatin, gemcitabine, doxorubicin and etoposide in vitro.[78] A TNF10-receptor-activating monoclonal antibody is now in phase I clinical investigation in advanced cancers in both the USA and the UK.

The histone deacetylase inhibitors induce apoptosis in mesothelioma cells by a mechanism that involves the down-regulation of BCL-XL, a potent regulator of mitochondrial permeability.[79] Vorinostat, a histone deacetylase inhibitor, produced two objective responses in 13 MPM patients on a phase I trial, and a phase III double-blind, placebo-controlled trial is underway.[80]

The proteasome inhibitors can reduce viability and cause apoptosis in neoplastic cells.[81,82] Moreover, their combination with several chemotherapeutic compounds has a synergistic effect in tumour cells.[83,84] Recently, it has been found that inhibition of the proteasome also counteracts angiogenesis.[85] Bortezomib (Velcade, PS-341) is the first proteasome inhibitor to be introduced in clinical practice, for its striking activity in multiple myeloma. It interferes with proliferation of tumour cells and angiogenesis and induces apoptosis in tumours via various pathways important for tumour progression, including p53 and the nuclear transcription factor, NFκB.[86–88] Sun *et al*. recently found that proteasome inhibitors reduced mesothelioma cell viability by inducing cell apoptosis, especially in the epithelial sub-type.[89]

5. Conclusions

MPM is an aggressive tumour, with a poor prognosis and an increasing incidence in many countries. In the past years, some therapeutic progress has been obtained with the use of cisplatin combined with an antifolate. However, the results of the available therapeutics are still modest. Several targeted agents have been investigated or are being actively pursued in this disease. An improvement of the knowledge of the molecular alterations that are specific for MM will allow the development and testing of novel targeted agents in this disease in the future.

Conflict of interest statement

None declared.

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