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Mesothelioma

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Malignant pleural mesothelioma continues to be a clinical challenge. The disease is associated with asbestos exposure; its incidence will continue to increase in regions even though the commercial use of asbestos has been banned, and is certain to continue to contribute to cancer mortality in regions of the word lacking worker protection and persisting with its commercial use. It will depend on political actions and the will of governments to change this situation [1]. Once diagnosed with pleural mesothelioma, patients nearly invariably die of the disease. Advances have been made in the immunohistochemical diagnosis of the disease allowing a firm diagnosis in most patients. While some benefit of chemotherapy for advanced disease has been established, many other aspects of treatment continue to be controversial, in particular in regard to surgery and radiotherapy. However, the best survival data are reported from groups using multimodality treatment including neo- or adjuvant chemotherapy and extrapleural pneumonectomy (EPP). Over the past few years several review articles have dealt with pleural mesothelioma [2–5] and recently the new European Respiratory Society/European Society of Thoracic Surgeons guidelines have been published [6].

epidemiology

In Europe, where commercial use of asbestos has been banned for many years, a first analysis predicted that male mesothelioma deaths will to continue to increase and peak in the year 2020 [7]. More recent models indicate that the increase may already be levelling off and the peak should occur earlier at around 2015 [8, 9]. These estimates have taken into consideration a certain latency period and the ban on commercial asbestos exposure in the early 1990s. However, recent data from the Italian Mesothelioma Registry demonstrated an even longer median latency than expected. The median latency was 44.6 years and increasing over time in a linear fashion [10]. Environmental asbestos exposure is common in some villages in Turkey. Here the rate of mesothelioma mortality can be >100-fold higher than in control villages [11].

molecular pathology

Although mesothelioma development is linked to asbestos fibers such as crocidolite, amosite and tremolite, the exact mechanism of mesothelioma development is unclear. The pleura is the target for the carcinogenic activity of asbestos probably because asbestos can translocate from the lung to the pleural space and then concentrate in the parietal pleura at the sites of lymphatic drainage [12].

To get insight on genes relevant to pathology, chromosomal aberrations have been investigated. Cytogenetic studies have revealed highly complex karyotypic changes involving all chromosomes with chromosomal losses more frequent than chromosomal gain [13]. A number of recurrent abnormalities have been found, among those deletion of 9p21 and 22q12. The single most consistent numerical chromosomal change concerns chromosome 22. The tumor suppressor merlin is encoded by the neurofibromatosis type 2 gene (*NF2*), which is located on chromosome 22q12, and mutations in this gene have been found in 40% of mesotheliomas [14–16]. Re-expression of *NF2* inhibits invasiveness of mesothelioma cells [17]. Mesotheliomas develop at higher frequency in mice with only one *NF2* allele compared with the wild type when experimentally exposed to asbestos fibers [18]. In addition, in asbestos-induced tumors the remaining *NF2* allele is lost, indicating that the *NF2* gene has a key role as 'gatekeeper' in asbestos-induced mesothelioma [18]. Additional characterization of this model led to the discovery that loss of the remaining allele was accompanied by loss of *INK4a/ARF* [19]. The *INK4a/ARF* locus is located at the 9p21 region and encodes two distinct proteins translated from alternatively spliced mRNA: p16 and ARF. p16 inhibits cyclin-dependent kinase-4/6, thereby controlling retinoblastoma phosphorylation, hence cell cycle arrest in G_1. ARF promotes MDM2 degradation preventing MDM2-mediated degradation of p53. Mesotheliomas lack expression of both p16 and ARF proteins [20, 21] due to gene deletion [22–24] or methylation [25–27]. In experimental animal models, targeted inactivation of *NF2* by adeno-Cre infection of the mesothelial cells lining the thoracic cavity rarely results in mesothelioma. However, concomitant loss of *INK4a/ARF* strongly accelerates mesothelioma development [28], indicating that functional inactivation of NF2 leads to tumor development in a 'permissive' (*INK4a/ARF* deficient) background. If this animal model is representative of key pathways for mesothelioma development in humans, one may ask the question why mutations in this gene have been found 'only' in 40% of mesothelioma [14–16]. One of the reasons could be that *NF2* might be inactivated by other ways than deletion.

The human *NF2* gene consists of 17 exons and spans ~95 kb of DNA. *NF2* transcripts undergo alternative splicing,

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generating multiple isoforms [29]. Isoform I, missing exon 16, and isoform II, containing all 17 exons, are the two predominant species. As the result of alternative splicing, isoform I encodes a 595-amino-acid protein. Isoform II differs from isoform I only at the C terminus. Insertion of exon 16 into the mRNA provides a new stop codon, resulting in a 590-amino-acid protein that is identical to isoform I over the first 579 residues. Other less abundant variants such as delE2, missing exon 2, delE3, missing exon 3, and delE2/3, missing exons 2 and 3, have been described [29–32]. Only isoform I functions as a tumor suppressor and this activity is phosphorylation dependent [33, 34]. Phosphorylation of Ser518 by PKA or PAK inactivates merlin by disrupting the intramolecular self-association. Myosin phosphatase MYPT1-PP1δ dephosphorylates Ser518 and thereby activates merlin. PP1δ docks on merlin through binding of its targeting subunit, MYPT1 and a missense mutation (L339F) found in brain tumors ablates its binding to MYPT1, indicating that disruption of NF2 function indeed happens also by avoiding dephosphorylation [35]. This is further supported by the observation that protein kinase C-potentiated phosphatase inhibitor of 17 kDa (CPI-17), a cellular inhibitor of MYPT1, induces neoplastic transformation *in vitro* by inactivating NF2/merlin [36].

No data are available yet on NF2 isoforms expressed in mesothelioma and their phosphorylation status, but the recent findings of NF2/merlin inactivation in DU145 prostate cancer cells by PAK-mediated constitutive phosphorylation [37] indicate that this possibility might have clinical relevance. Phosphorylation of residues other than Ser518 inhibits NF2/merlin function in a different way. Indeed, Akt-driven phosphorylation on Thr230 and Ser515 leads to NF2/merlin ubiquitination and degradation [38]. This indicates that in tumors expressing an intact NF2/merlin, an active PI3K pathway would also result in NF2 functional inactivation. Malignant mesothelioma tumor specimens demonstrate high levels of phosphorylated Akt expression [39] and this may be linked to overexpression of autocrine growth factors such as hepatocyte growth factor and its receptor c-Met [39, 40]. Activated PI3K generates a lipid second messenger, which is essential for translocation of Akt to the plasma membrane, where it is phosphorylated and activated by phosphoinositide-dependent kinase 1. Phosphorylated Akt then conveys downstream signals, promoting cellular proliferation and survival over apoptosis. Activity of the PI3K/Akt pathway is negatively regulated by the phosphatase and tensin analogue (PTEN) tumor suppressor gene, and overexpression of PTEN in mesothelioma cells induced hypophosphorylation of Akt and apoptosis [41]. In addition poor survival of malignant pleural mesothelioma patients lacking PTEN expression has been observed [42].

If inactivation of NF2 in an *INK4a/ARF*-deficient background triggers the development of malignant mesothelioma one could ask how and why these genes could act as 'gatekeeper' and 'caretaker'. The answers to these questions can be inferred from the fact that NF2/merlin is required for the assembly but not the maintenance of apico-lateral junctional complexes [43], which means that NF2 loss will be mostly important when it occurs in dividing cells, e.g. during tissue repair. This might be one of the reasons why it is disrupted in mesothelioma, which is thought to result from chronic mesothelium injury by asbestos fibers [44]. Cells that cannot form apico-lateral junctional complexes will be unable to form a well-organized tissue and will be resistant to contact-dependent growth arrest. Chronic injury stimulates tissue repair by activating stem cells [45] and mesothelioma carcinogenesis could proceed by misappropriating homeostatic mechanisms that govern tissue repair and stem cell self-renewal. This concept is supported by the observation that the Wnt-dependent stem cell signaling pathway is dysregulated in mesothelioma. Indeed, there is a significant transcriptional downregulation of the secreted frizzled-related proteins (sFRPs) in malignant pleural mesothelioma primary tissues and cell lines [46]. sFRPs, a family of five secreted glycoproteins, have been identified as possible dominant-negative modulators of the Wnt signal transduction pathway. Transfection of the SFRP gene construct into MPM cell lines lacking sFRP expression resulted in apoptosis and growth suppression [46].

The idea of mesothelioma as one of the chronic inflammation-related cancers is reinforced by the recent observation that inflammation-associated transcription factor NF-κB is constitutively active in various mesothelioma cell lines [47]. This results in activation of anti-apoptotic mechanisms as frequently observed in mesothelioma [48].

As mentioned in the Diagnosis section below, during mesothelioma development epithelial cells undergo epithelial to mesenchymal transition and another gene, p15, also located in the 9p21 locus, seems to be involved. Indeed on the one hand, p15 is often silenced by methylation in mesothelioma [27] and on the other hand, in an experimental animal model, combined deficiency of p16 and p15 results in a different type of soft tissue sarcoma composed of mixed cell types and showing biphasic differentiation [49].

diagnosis

Morphologically, pleural mesothelioma presents most often as epithelioid and less commonly as mixed disease or especially as a pure sarcomatoid form. Even less common is the well-differentiated papillary mesothelioma of the pleura. This disease was initially described in the peritoneum of young women without a history of asbestos exposure. A case series from France described the pleural variant of this disease, which is characterized by lack of deep invasion and association with a more indolent course; however, in some cases with evaluation to pleural mesothelioma. It occurs equally in men and women and a history of asbestos exposure has been identified in half of the cases [50].

The morphological diagnosis of pleural mesothelioma is generally made by a pleural biopsy, preferentially by thoracoscopy. Immunohistochemical staining has a central role in the diagnostic process. Markers indicative of the diagnosis of mesothelioma are calretinin, D2-40, WT1, cytokeratin 5/6 and podoplanin, while epithelial membrane antigen (EMA), carcino-embryonic antigen (CEA) and thyroid transcription factor 1 (TTF1-1) are indicative of the diagnosis of adenocarcinoma, the latter in particular of adenocarcinoma of lung origin [51–53]. In contrast to these markers, staining for

mesothelin is less useful for the diagnosis of mesothelioma [54]. The distinction between sarcomatous mesothelioma and true sarcoma or the rare sarcomatoid carcinoma of the lung can also be a challenge. Here, a recent publication recommended the use of cytokeratin antibodies together with WT1 [55].

The identification of mesothelin-related proteins as serum markers of mesothelioma has raised great hopes of their potential to monitor the disease under therapy and their investigation for the screening of individuals exposed to asbestos [56]. Since, several investigators have examined the potential clinical role of mesothelin. Mesothelin serum levels were found to be elevated in patients with mesothelioma and ovarian cancer [57]. Serum levels were higher in patients with mesothelioma than in patients with lung cancer and in one study differed significantly between stage I and higher stages of mesothelioma [58, 59]. The discriminating power to distinguish between non-small-cell lung cancer and mesothelioma was increased by combining serum CEA and mesothelin measurements [60].

surgery

The role of surgery in pleural mesothelioma continues to be a matter of debate. The procedures used for the treatment of mesothelioma are thoracoscopy and pleurodesis for diagnosis and pleural effusion control, pleurectomy with tumor decortication of the lungs for debulking and major cytoreduction and especially EPP as the most radical resection. A systematic review based on the literature from 1985 to 2004 could not determine whether the use of EPP improves survival or effectively palliates symptoms of pleural mesothelioma [61]. Some centers advise pleurectomy and decortication for patients with compromised cardiac or pulmonary function, advanced age or certain disease distributions, in particular with early disease, in order to remove the bulk of the tumor while sparing lung function. When comparing their results with EPP with video-assisted thoracoscopic pleurectomy and decortication in patients >65 years of age, the group in Leicester (UK) documented a reduced 30-day mortality with the VATS procedure with a similar survival outcome (11.5 months for EPP and 14 months for pleurectomy and decortication) [62]. In some series the outcome after EPP was worse in patients with N2 disease [63, 64] as investigated in a case–control study comparing the outcome in patients with N2 disease between EPP and open radical pleurectomy and decortication. The two groups did not differ in stage, but differed in age with older patients undergoing pleurectomy and decortication. With 15 and 16 months, there was no difference in survival [65]. Combing the experience of three large centers in the United States, the outcome of 663 patients treated between 1990 and 2006 was analyzed retrospectively [66]. The median survival for the entire group was 14 months with a small advantage for pleurectomy and decortication. Operative mortality was 7% for EPP and 4% for pleurectomy and decortication. A multivariate analysis demonstrated a hazard ratio for EPP of 1.4. A difference was noted in the site of first recurrence. Local recurrence occurred in 33% versus 65%, distant recurrence in 66% versus 35% in patients undergoing EPP versus pleurectomy and decortication. However, because of biases in patient selection for a certain procedure and the retrospective nature of the analysis, no firm conclusions can be made until the question is addressed in a controlled prospective trial.

multimodality therapy including neoadjuvant chemotherapy and EPP

The largest published experience with EPP in conjunction with adjuvant chemotherapy and radiotherapy was published from the Boston group. An update from this group included 183 patients intended for the trimodality approach [63]. Median survival in the 176 patients alive after surgery was 19 months. The availability of more effective chemotherapy regimens and the experience of neoadjuvant chemotherapy in stage IIIA non-small-cell lung cancer prompted us to explore the role of neoadjuvant chemotherapy and EPP in pleural mesothelioma. In a pilot study on 19 patients treated at the University Hospital of Zürich, the response to neoadjuvant cisplatin and gemcitabine was 31%, and 16 patients underwent EPP with no perioperative mortality. The median survival of all patients was 23 months, and two of these patients remained disease free for 6 years after surgery [67]. These results were confirmed in a prospective multicenter phase II trial in Switzerland. Sixty-one patients with T1–localized T3 and N01–N2 disease and including all histologies received three cycles of neoadjuvant cisplatin and gemcitabine [68]. Extrapleural pneumonectomy was performed in 45 (74%) and complete resection was felt to be achieved in 37 (61%) patients. Operative mortality was 2.2%. The median survival by intent to treat was 19.8 months, the median survival for patients undergoing EPP was 23 months. Quality of life measurements were performed. Psychological distress showed only minor variation over time with distress above the cut-off score indicating no morbidity in 82% at baseline and 76% at 3 months after surgery. These results compare favourably with the series from Boston with a median survival after EPP of 19 months [69], a series from the Mayo Clinic with a median survival after EPP of 12 months [70] and a series from the MD Anderson Cancer Center with a median survival after EPP and intensity-modulated radiotherapy of 10.2 months [71].

Based on the results of a landmark trial [72] demonstrating the survival benefit of a combination chemotherapy of cisplatin with pemetrexed over cisplatin alone this combination has been adopted for a neoadjuvant approach by most centers. While the published results and reviews [73] so far are indicative that radical surgery may indeed be associated with longer survival than chemotherapy alone, final proof of this concept will only come from a randomized study. These data will hopefully be forthcoming from the MARS (mesothelioma and radical surgery) trial initiated in the UK.

While the rate of operative mortality after EPP is now <5% in experienced centers, EPP is associated with significant operative morbidity requiring the attention of a dedicated team. Three recent series have analyzed their operative complications. The group in Boston reported minor and major complications in 60% of patients operated on and overall mortality was 3.4% [74]. The group from Leicester reported significant morbidity in 63% and an overall mortality of 6.7% [75]. Risk factors for perioperative morbidity were induction chemotherapy for

acute lung injury and symptomatic mediastinal shift, right-sided procedures and prolonged operations for technical complications such as dehiscence of the diaphragmatic patch, chylothorax or fistulae. Our group in Zürich reported postoperative complications in 62% and mortality in 3.1% [76]. Most frequent complications included postoperative empyema in 16%, bronchopulmonary fistula in 10%, chylothorax in 8% and patch failure in 6%. All could be successfully managed.

radiotherapy

Radiotherapy can be effective for local palliation and has been suggested to be of benefit for the prevention of malignant seeding after invasive procedures [77, 78]; however, this has recently been thrown into doubt by other reports and is no longer recommended [79, 80].

After EPP most patients have tumor recurrence in the ipsilateral chest. The rate of local relapse reported from the Boston group was 35.% [81]. A phase II trial from the Memorial Sloan-Kettering Cancer Center indicated a reduced rate (6%) of local failure after EPP with high-dose postoperative radiotherapy [82]. This was confirmed in a study of intensity-modulated radiation therapy from the MD Anderson Cancer Center, demonstrating local failure in 13% with distant failure of 54% [71]. Intensity-modulated radiotherapy after extrapleural pneumotectomy can be associated with severe or lethal pulmonary toxicity. A series of 13 patients treated in Boston reported the development of fatal pneumonitis in six patients, the most likely explanation being dose–volume effects on the contralateral lung [83]. The author suggested specific metric techniques to avoid this toxicity [84]. The rate of lethal pulmonary toxicity was much lower in patients of the MD Anderson Cancer Center series where in a retrospective analysis the importance of low V_{20} was emphazised [85]. The impact of high-dose hemithoracic radiation on toxicity and local failure after neoadjuvant chemotherapy and extrapleural pneumonecty is the subject of an ongoing prospective randomized study of the Swiss Group for Clinical Cancer Research.

imaging

The role of imaging in pleural mesothelioma has been examined in two recent reviews [86, 87]. The role of 2-[fluorine-18]fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) and PET–CT for staging and selection of patients for surgery has been investigated in smaller series. A first report on PET demonstrated increased uptake of pleural mesothelioma in 62 of 63 patients and identification of six patients with N3 or M1 disease subsequently confirmed by other means. However, the sensitivity of PET in identifying the 21 patients with surgical T4 status was only 19% and the nine patients with surgical N2 only 11% [88]. Using integrated PET–CT for the staging of potentially resectable pleural mesothelioma, extrathoracic disease that was not identified by conventional staging was found in 7 of 29 patients, but tumor stage was correctly identified in only 15 of 24 and nodal stage only in 6 of 17 [89]. Thus, based on these studies, the major role of PET and PET–CT lies in the identification of extrathoracic disease and not in the determination of T and N stage. FDG-PET cannot be used for assessment of local disease in patients who underwent talc pleurodesis, since this procedure can lead to persistant pleural FDG uptake [90].

Response assessment in malignant mesothelioma remains difficult; however, the adoption of modified RECIST criteria by most investigators has improved the situation somewhat. They were developed because of the nature of pleural mesothelioma to grow as a rind and are reported as the difference in the sum of two measurements perpendicular to the chest wall at three different levels. Response according to these criteria predicted for survival and forced vital capacity [91]. While modified RECIST is the standard currently used in assessing response in pleural mesothelioma, more sophisticated methods such as computerized analysis of CT scans [92] and total glycolytic volume determined in PET–CT have been developed and await clinical validation. FDG-PET might have a role in the assessment of tumor response. A study on a group of 22 patients reported an association of early metabolic response with time to progression, while no such association was found using CT-based criteria [93]. A second study on 23 patients found an association of an early reduction in the total glycolytic volume with survival [94].

systemic chemotherapy

The palliative effect of combination chemotherapy for patients with pleural mesothelioma has been documented in a study from the UK. An update of the experience from the Royal Marsden Hospital focused on the palliative benefits of mitomycin C, vinblastine and cisplatin. While the rate of objective response was only 13.5% and the median survival only 7 months, 69% of patients reported an improvement of symptoms. The symptoms best responding to treatment were pain in 71%, cough in 62% and dyspnoea in 50% [95].

Two large randomized trials have proved the benefit of the addition of a folate antagonist to cisplatin. A large prospective trial including 456 patients comparing cisplatin alone with cisplatin and pemetrexed demonstrated a significantly better response (17% versus 41%) and median survival (9.3 months versus 12.1 months) with the cisplatin–pemetrexed combination over cisplatin alone [72]. A post-study analysis on the use of second-line chemotherapy supports the assumption that this survival effect is not the result of second-line chemotherapy [96]. The EORTC study, which included 250 patients to examine the addition of raltitrexed to cisplatin, also proved superioritiy of the combination chemotherapy for response (14% versus 24%) and median survival (8.8 months versus 11.1 months) [97]. Based on the registration of pemetrexed and the trial results, the combination of cisplatin and pemetrexed has since become the preferred chemotherapy regimen for patients with pleural mesothelioma.

Pemetrexed in combination with carboplatin has been explored in two large phase II studies. They reported response rates of 19% and 21% and median survival of 12.7 and 14 months. Non-hematological toxicity was negligible and febrile neutropenia occurred in only one study at a rate of 1% of patients [98, 99]. Based on the activity of both agents in

mesothelioma, the combination of pemetrexed and gemcitabine has been investigated in a phase II study. The authors concluded that the efficacy was not better than expected with pemetrexed alone and inferior to the platin–pemetrexed combinations [100].

The effect of early or delayed chemotherapy in symptomatically stable patients was explored in a small randomized trial also using mitomycin C, vinblastine and cisplatin chemotherapy [101]. Twenty were in the early chemotherapy group and 22 in the delayed chemotherapy group, of which 17 eventually received chemotherapy. The median time to symptomatic progression was significantly better in the early chemotherapy group as compared with the late chemotherapy group with 25 weeks as compared with 11 weeks. There was a trend to better survival in the early chemotherapy group with 14 as compared with 10 months.

The role of second-line chemotherapy in pleural mesothelioma needs to be defined. Pemetrexed alone or in combination with carboplatin has yielded objective responses of ~20% in a small series of patients with disease progression after cisplatin chemotherapy [102]. Recently a prospective randomized phase III study enrolling 243 patients examined the role of pemetrexed versus best supportive care [103]. This study demonstrated a better disease control rate for the pemetrexed arm (59% versus 19%); however, there was no significant survival benefit. The survival results might have been influenced by post-discontinuation chemotherapy, which was given to 28% of patients in the pemetrexed group and 51% of patients in the best supportive care group. The question of how to treat patients with progression after cisplatin and pemetrexed is unanswered. Vinorelbine has demonstrated activity when used in first-line therapy and might be a reasonable choice [104]. Vinflunine, a new microtubule inhibitor, has recently been demonstrated to have clinical activity when used in first line [105].

new approaches

Despite the expression of epidermal growth factor receptor in pleural mesothelioma and promising preclinical data, single-agent gefitinib and erlotinib were found to have no significant clinical activity [106, 107]. Because platelet-derived growth factor was thought to be an important factor in the pathogenesis of mesothelioma and c-kit expression was reported to be present in one-third of mesotheliomas in one small series, the activity of single-agent imatinib has been examined in two phase II studies. No objective responses were seen [108, 109]. In contrast, clinical signals with objective responses were reported in abstract form with multitargeted tyrosine kinase inhibitors vatalanib and sorafenib, both including vascular endothelial growth factor (VEGF)-2 as target [110, 111], prompting further clinical studies with this group of agents.

The potential role of the anti-VEGF antibody bevacizumab in mesothelioma has been explored in a large randomized phase II study in combination with cisplatin and gemcitabine. The result has been presented and failed to show a survival benefit for bevacizumab in this combination [112]. A first report on the potential of thalidomide demonstrated disease stabilization in 27% of 40 patients [113], a firm conclusion, however, can only be drawn after the completion of a prospective phase III trial on thalidomide maintenance that is currently being conducted in the Netherlands.

Preclinical studies with the proteosome inhibitor bortezomib have demonstrated activity and synergy with cisplatin in mesothelioma cell lines and clinical phase II studies with this agent in pleural mesothelioma have been initiated [114]. Histone deacetylase inhibitors are also under investigation. In a phase I study with the suberoylanilide hydroxamic acid in advanced cancer unconfirmed responses have been reported in 3 of 13 patients with mesothelioma, prompting further investigations into this disease in a prospective randomized phase III study in second line [115]. As reviewed by Fenell [5] other histone deacetylase inhibitors being explored in early clinical trials in mesothelioma are belonistat [116] and desipeptide in combination with flavopiridol, the latter combination having demonstrated cytotoxicity in mesothelioma cells [116]. The potential dependence of mesothelioma cells on external arginine because of loss of expression of argininosuccinate has led to the investigation of a pegylated form of arginine deiminase [117, 118].

Mesothelin might not only serve as diagnostic marker in serum or tissue, but also represent a target for therapy of mesothelioma [119]. Patients with mesothelioma and other tumors expressing mesothelin have been treated in a phase I study with a recombinant anti-mesothelin immunotoxin. Despite transient pleuritis as dose-limiting toxicity, treatment was otherwise well tolerated and clinical activity has been observed [120]. A chimeric anti-mesothelin antibody has been developed, which is now undergoing clinical testing [121].

Other targeted strategies have been elucidated in preclinical studies that might lead to new therapeutic approaches. These include targeting the apoptotic pathway with antisense oligonucleotides to survivin or inducing apoptosis with the TRAIL antibodies mapatumumab or lexatumumab, both approaches enhancing the effect of cisplatin on mesothelioma cells [122, 123]. Inhibition of the met receptor with tyrosine kinase inhibitors and inhibition of activated c-src by desatinib both decreased the growth of mesothelioma cell lines [124, 125]. A humanized antibody to CD26 has been shown to induce antibody-dependent cellular cytotoxicity against mesothelioma cell lines and to inhibit mesothelioma cell growth in a xenograft system [126].

disclosure

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