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State of the art in mesothelioma

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Introduction

Malignant pleural mesothelioma (MPM) still has a dismal prognosis, and in the next 35 years it is calculated that about one-quarter of a million deaths will occur as a result of this disease in Western Europe [1].

History of asbestos exposure is reported in ~70–80% of all cases of mesothelioma and lifetime risk for exposed individuals is up to 20% [2–4]. The two major species of asbestos, crocidolite and chrysotile, are both hazardous. The workers at extraction facilities are at the greatest risk of exposure and development of asbestos-related diseases, but asbestos-cement, insulation and shipyard workers are also at increased risk. Environmental exposure to asbestos can occur as a result of living in areas characterized by natural outcrops of asbestos or asbestos-related materials, or those close to asbestos-producing or -using plants.

The disease mainly occurs in the fifth to seventh decade of life, and in males more commonly than females (3.6:1).

Molecular biology

The molecular steps leading from asbestos within the parietal pleura to the development of malignant mesothelioma are mostly unknown and certainly numerous. However, it is well known that in normal and premalignant cells, asbestos activates or inactivates a variety of genes, including the epidermal growth factor receptor (EGFR), the insulin receptor and cell cycle regulatory genes such as *INK4a/ARF*, as well as *p16* and *NF2* genes [5]. Mutations of the *p53* and *ras* genes, which are frequently mutated in lung carcinomas, are rare in malignant mesotheliomas. In contrast, SV40 Tag sequences are frequently present but are absent in adjacent lung tissues and in lung carcinomas [6, 7]. The biological and clinical significance of this finding is not fully understood and, in addition, some authors believe that the finding is attributable to an underestimation of the contamination by common laboratory plasmids containing SV40 sequences leading to false-positive results [8].

Aberrant methylation of CpG islands in the promoter region of tumor suppressor genes is a frequent mechanism of gene silencing, but in malignant mesothelioma has received scant attention. Methylation of RASSF1A has been linked to malignant mesothelioma and correlates with poor outcome. Aberrant methylation was more commonly observed in the epithelial form of mesothelioma rather than in sarcomatous/mixed types. Intriguingly, methylation in association with the epithelial form of mesothelioma was found in patients whose tumors showed SV40 Tag sequences. A profile of aberrant methylation may help to distinguish between malignant mesotheliomas and lung adenocarcinomas. For example, methylation of adenomatous polyposis coli (APC) promoter 1A was completely absent in mesotheliomas, although it was the gene most frequently methylated in adenocarcinomas (52%) [9].

Pathology

Histologically, these tumors are composed of fibrous or epithelial elements, or both. The epithelial subtype occasionally causes confusion with peripheral adenocarcinoma of the lung or metastatic carcinomas. Attempts at diagnosis by cytology or needle biopsy of the pleura are often not contributive. Thoracoscopy can be valuable in obtaining adequate tissue specimens for diagnostic purposes. Immunohistochemistry has recently become an essential diagnostic tool to differentiate MPM from other types of cancer. Calretinin and keratin 5/6 are positive for malignant mesothelioma, whereas Ber-EP4, CEA and Leu1 are negative.

Mesothelin is a 40-kDa cell surface differentiation antigen present on normal mesothelial cells and overexpressed in several human tumors, including mesothelioma, ovarian and pancreatic adenocarcinomas [10]. However, mesothelin immunostaining has a low specificity for discriminating between epithelioid mesotheliomas and adenocarcinomas, and its use may be considered in those instances in which the results obtained with the standard panel of immunohistochemical markers used for the diagnosis of mesotheliomas are inconclusive. Because mesothelin is a highly sensitive positive marker for epithelioid mesotheliomas, a negative staining for this marker is an indication against such a diagnosis; however, because of its limited utility, it is not recommended for inclusion in the standard panel of immunohistochemical markers used in the distinction between mesotheliomas and adenocarcinomas.

Clinical presentation

Dull, aching chest pain sometimes accompanied by cough, dyspnea on exertion, fever, malaise and weight loss are the most common presenting symptoms. Dullness to percussion and decreased breathing sounds over the base of the affected lung are the most common physical examination findings.

Pleural and, in a later phase of the clinical history, peritoneal effusions represent major symptomatic problems for at least two-thirds of patients.

Death occurs after a median of 6–9 months as a result of combinations of severe dyspnea, chest wall pain, abdominal distention with ascites, intestinal obstruction, pericardial tamponade, cachexia or pneumonia.

Diagnosis and staging

Computed tomography (CT) is usually the primary imaging modality used for disease staging in patients who are being considered for surgery. CT is readily available and provides a significant amount of anatomic information. The results can be used to preclude surgery in patients with obviously unresectable tumors (e.g. diffuse extension of tumor into the chest wall, mediastinum or peritoneum, or distant metastasis). Magnetic resonance imaging (MRI) or positron emission tomography (PET) can then be used as the final preoperative radiological examination to complement CT, particularly in questionable cases. MRI with the use of different pulse sequences and gadolinium-based contrast material can improve the detection of tumor extension, especially to the chest wall and diaphragm. PET is useful for the detection of nodal involvement and occult metastasis. Correlation of all imaging findings is essential in directing exploration to areas of possible invasion and selecting those patients who may benefit from aggressive therapy.

In addition to its role in diagnosis and staging, [^{18}F]fluorodeoxyglucose (FDG) PET has several other advantages in the management of MPM. Patients with MPM may have diffuse pleural thickening but only focal areas of malignancy. Areas of pleural thickening may not necessarily correspond to areas of high metabolic activity, and the most appropriate biopsy site may not be apparent from CT findings. Because FDG PET can provide information about metabolically active areas when findings are correlated with anatomic imaging information, it may be used to help determine the most appropriate biopsy site for obtaining positive results. Moreover, PET may help predict prognosis in patients with MPM. A recent study showed that MPM with higher FDG uptake is associated with significantly shorter survival time. This information may be clinically useful in determining whether to pursue an aggressive therapeutic approach based on the biological features of the tumor.

A histological diagnosis is required once MPM is suspected radiologically. Neither cytological analysis of pleural fluid nor needle aspiration biopsy of a pleural mass is diagnostic, because it is extremely difficult to distinguish between cells of MPM, metastatic adenocarcinoma and severe atypia. In contrast, CT-guided core needle biopsy has been shown to improve diagnostic accuracy. Thoracoscopy or thoracotomy is sometimes necessary, especially when a large core of tissue is needed. Video-assisted thoracoscopic surgery has been shown to have a diagnostic rate of 98%. Thoracoscopic evaluation may also allow more accurate staging of MPM compared with non-invasive methods such as CT and MRI. However, video-assisted thoracoscopic surgery causes postprocedural chest wall seeding in up to one-half of patients. Local postoperative radiotherapy can prevent such seeding. In contrast, seeding caused by imaging-guided biopsy is seen in no more than 22% of patients.

Small amounts of mesothelin can be detected in the blood of some patients with mesothelin-positive cancers and measurement of mesothelin in the blood may be useful for the diagnosis and follow up of some of these patients. In a blinded study, serum samples from 44 patients with histologically proven mesothelioma, 68 matched healthy controls, 40 of whom had been exposed to asbestos, and 160 patients with other inflammatory or malignant lung and pleural diseases were tested for the presence of mesothelin-related proteins. Eighty-four per cent of 44 patients with mesothelioma had raised concentrations of mesothelin-related proteins, compared with three (2%) of 160 patients with other cancers or other inflammatory lung or pleural diseases, and none of 28 controls who had not been exposed to asbestos. Concentrations correlated with tumor size and increased during tumor progression. Seven of the 40 asbestos-exposed individuals had increased serum concentrations of mesothelin-related proteins; three of those seven developed mesothelioma and one developed lung carcinoma within 1–5 years. None of the 33 asbestos-exposed participants whose serum samples had normal concentrations of mesothelin-related proteins and who were followed up over 8 years developed mesothelioma. Consequently, serum mesothelin could be a useful marker for diagnosis of mesothelioma and to monitor disease progression, and might also prove helpful for screening asbestos-exposed individuals for early evidence of mesothelioma [11].

The new staging system from the International Mesothelioma Interest Group is a tumor–node–metastasis (TNM) system that was initially developed to categorize similar cases into homogeneous prognostic groups to aid evaluation of new treatment options (Tables 1–3) [12, 13]. This staging system emphasizes criteria used to determine the extent of local tumor and lymph node involvement, both of which factors have been shown to be related to the overall survival rate in MPM. With locally advanced tumors, it is important to distinguish between T3 (potentially resectable) and T4 (technically unresectable) disease. This distinction guides the choice of treatment options and implies significant differences in survival. The presence of N3 nodal disease or distant metastasis also precludes surgery. Although surgical staging is often required in patients with potentially resectable lesions, CT, MRI and PET can aid in choosing whether to treat MPM surgically, medically or both.

Prognosis

Performance status and weight loss are powerful prognostic factors in mesothelioma. Whereas male sex, older age, and high platelet and leucocyte count have also been validated as poor prognostic factors.

Table 1. Tumor descriptors for malignant pleural mesothelioma

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 tumor 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 tumor (including fissures) or tumor extension from the visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but potentially resected tumor (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 tumor that extends into the soft tissues of the chest wall; or (iv) non-transmural involvement of the pericardium
T4	Locally advanced, technically unresectable tumor (each ipsilateral pleural surface)	At least one of the following: (i) diffuse tumor extension or multiple tumor 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

Tumor-related prognostic factors involve the anatomical extent of the tumor, and histological and biological characteristics of the tumor. The oldest, most important biological marker of mesothelioma is the histology, a prognostic factor with a major impact on survival. The survival of patients with an epithelial type of mesothelioma might be twice the survival of patients with a mixed or sarcomatoid type. This difference is apparent in both surgical series and in patients who received a non-surgical treatment. The invasive growth pattern of sarcomatoid mesothelioma hampers surgical procedures and major surgery is therefore not recommended in these patients.

Prognostic scoring systems have been proposed by the European Organization for Research and Treatment of Cancer (EORTC) [14] and by the Cancer and Leukaemia Group B (CALGB) [15]. These systems were derived from statistical analysis of large series of patients within chemotherapy trials. Two EORTC risk groups were identified after multivariate analysis of prognostic variables from 204 patients entered into five consecutive trials. The factors included in the model were: white blood cell count $>8.3 \times 10^9$/l, Eastern Cooperative Oncology Group performance status ≥ 1, sarcomatoid tumor cell type, probable or possible histological diagnosis, and male sex. The high-risk group was defined by the presence of three or more of these factors. The CALGB system is more complex and derives from the analysis of 337 patients. A regression tree leads to 11 groups, of which those with similar survival characteristics are combined to form six prognostic groups.

Table 2. Node and metastasis descriptors for malignant pleural mesothelioma

Descriptor	Characteristics
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

Table 3. Tumor–node–metastasis stage classification for malignant pleural mesothelioma

Stage	Tumor	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	Any M1

Treatment

Many new therapeutic modalities for MPM have been investigated, either as single treatment approach or as combined therapy. To date, there is no cure for MPM and consensus is lacking on its best management. Physicians are faced with a huge volume of conflicting literature, advocating diverse options from palliation only to aggressive multimodality therapy.

Age and co-morbidity often prohibit aggressive therapeutic options in the individual patient. The median time lag between asbestos exposure and development of MPM is >30 years, hence most patients are relatively old at presentation. About 20% also have co-existing pulmonary fibrosis from asbestosis. In addition, many patients are smokers with limited cardiorespiratory reserve.

The number of MPM patients treated by surgery is still rather small. Various surgical procedures may be possible in selected patients, providing long-term survival without cure. Although some patients with early-stage disease experience long-term survival with aggressive treatment approaches including extensive surgery, adjuvant chemotherapy and radiotherapy, it remains unclear whether overall survival has been significantly altered by the different treatment modalities or by combinations of modalities. Extrapleural pneumonectomy in selected patients with early-stage disease may improve recurrence-free survival, but its impact on overall survival is unknown. Pleurectomy and decortication can provide palliative relief from symptomatic effusions, discomfort caused by tumor burden and pain caused by invasive tumor. Operative mortality from pleurectomy/decortication is <2%, while mortality from extrapleural pneumonectomy has been reported to range from 6% to 30%.

For patients undergoing surgery the main prognostic factors are male sex, high platelet count, and large preoperative and postcytoreduction tumor volumes [16].

The use of radiotherapy in pleural mesothelioma has been shown to alleviate pain in the majority of patients treated. However, the duration of symptom control is short-lived [17].

Chemotherapy has been disappointing. EORTC examined several cytotoxic drugs as mitoxantrone, epidoxorubicin, etoposide and paclitaxel, with no objective responses and median survivals ranging from 6.7 to 9 months [14].

Single-agent and combination chemotherapy have been evaluated in single and combined modality studies. Until recently, the most studied agent was doxorubicin, which has produced partial responses in $\sim$15–20% of treated patients. Some combination chemotherapy regimens have been reported to have higher response rates in small phase II trials; however, the toxicity reported is also higher, and there is no evidence that combination regimens result in longer survival or longer control of symptoms [18].

In MPM, gemcitabine and cisplatin, given as single agents, have shown response rates ranging from 7% to 14%, and *in vitro* studies have suggested a synergic interaction between these two compounds. A pivotal single institutional study reported a response rate of 48% with this two-drug regimen [19]. However, a larger phase II study by the same authors [20] and additional phase II studies [21] have documented a significantly lower level of efficacy.

Recently, pemetrexed has shown promising activity in MPM. Pemetrexed is a folate antimetabolite that primarily inhibits thymidylate synthase (TS). The penaglutamate form of pemetrexed is the predominant intracellular form, and is >60-fold more potent in its inhibition of TS. A phase I study of pemetrexed plus carboplatin in 27 patients with stage III and IV showed a response rate of 32% according to the strict criteria of response assessment by measuring the thickness of pleural tumor at three separate levels on transverse cuts on each thoracic CT scan. Median time to progression was 10 months and median survival 15 months [22].

In a large phase III study, the combination of cisplatin and pemetrexed was associated with significantly improved survival time and with overall greater antitumor activity compared with cisplatin alone. The regimen was well tolerated, particularly in patients who received low-dose folic acid and vitamin B_{12}. Vitamin supplementation reduced toxicity with no apparent adverse affect on efficacy [23].

Pharmacogenetic tests can contribute to elucidate which patients can respond to a specific chemotherapy combination. Overexpression of *TS* mRNA could correlate with resistance to pemetrexed, and overexpression of nucleotide excision repair genes such as *ERCC1* mRNA correlates with resistance to cisplatin or carboplatin.

Another antimetabolite, raltitrexed, was combined with oxaliplatin and tested in 70 (15 pretreated and 55 chemotherapy-naïve) patients with diffuse MPM. In the overall study population, 14 patients (20%) had a partial response and 32 patients (46%) had stable disease. The symptomatic response rates were as follows: shortness of breath, 36%; pain, 30%; activity, 23%; appetite, 21%; and asthenia, 20%. Median time to disease progression was 18 weeks and overall 1-year survival was 26%. The most common adverse events were asthenia, nausea/vomiting and paresthesia, and no treatment-related deaths were reported [24]. An EORTC phase III trial compared cisplatin plus raltitrexed versus cisplatin in 229 patients with advanced MPM. Preliminary data indicate a non-statistically significant superiority of the combination in terms of median survival time, but more mature data are needed [25].

Ranpirnase (Onconase®; p30 protein) is a novel RNAse derived from frogs' eggs. As ranpirnase treatment was associated with encouraging survival in certain subsets of patients and showed an acceptable toxicity in a phase II trial [26], a phase III study was designed. This study randomized 154 patients to receive either doxorubicin or ranpirnase. The median and 1-year survival rates were similar in both arms: 7.7 versus 8.2 months, and 30.7% versus 32% (ranpirnase versus doxorubicin). The authors assumed that these disappointing data were caused by an excess of poor prognosis patients in the ranpirnase versus the doxorubicin arm [27].

Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) appear to be important

autocrine growth factors for mesothelioma, and different strategies aimed at blocking the autocrine loops have been recently explored [28, 29]. Three VEGF inhibitors, SU5416, bevacizumab and thalidomide, are currently evaluated in phase II studies in mesothelioma patients. Imatinib mesilate and PTK787, two PDGF-associated tyrosine kinase inhibitors, are also under clinical investigation.

In addition, $\sim$70% of malignant mesotheliomas have high level of expression of EGFR, and a subset of cell lines derived from MPM patients express both EGFR and transforming growth factor-α, suggesting an autocrine role even for EGFR. However, two pivotal studies testing EGFR-tyrosine kinase inhibitors have shown only limited level of activity [30, 31].

Chemical or thoracoscopic (either medical or video-assisted) pleurodesis is useful in preventing fluid re-accumulation and should be performed as early as possible.

Intrapleural administration of drugs or photodynamic therapy allows direct delivery to the pleural surfaces, but therapy administered in this manner usually fails to adequately penetrate the tumor and underlying tissues.

With disease progression, trapped lung can occur with tumor involvement of the visceral pleura. Once trapped lung syndrome develops, pleurodesis is unlikely to be successful. Small catheter drainage may provide an alternative to in-patient pleurodesis, especially for patients with advanced disease, but carries the risk of tumor metastasis along the catheter tract. Pleuroperitoneal shunting is not recommended because of the potential risk of enhancing malignant spread to the peritoneal cavity.

If dyspnea does not improve after adequate management of the pleural effusion, supplementary oxygen and opioids may help to reduce breathlessness.

References

1. Peto J, Decarli A, La Vecchia C et al. The European mesothelioma epidemic. Br J Cancer 1999; 79: 666–672.
2. Ruffie P, Feld R, Minkin S et al. Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: a retrospective study of 332 patients. J Clin Oncol 1989; 7: 1157–1168.
3. Tammilehto L, Maasilta P, Kostiainen S et al. Diagnosis and prognostic factors in malignant pleural mesothelioma: a retrospective analysis of sixty-five patients. Respiration 1992; 59: 129–135.
4. Chailleux E, Dabouis G, Pioche D et al. Prognostic factors in diffuse malignant pleural mesothelioma: a study of 167 patients. Chest 1988; 93: 159–162.
5. Lee WC, Testa JR. Somatic genetic alterations in human malignant mesothelioma. Int J Oncol 1999; 14: 181–188.
6. Carbone M, Pass HI, Rizzo P et al. Simian virus 40-like DNA sequences in human pleural mesothelioma. Oncogene 1994; 9: 1781–1790.
7. Carbone M, Rizzo P, Pass H. Simian virus 40: the link with human malignant mesothelioma is well established. Anticancer Res 2000; 20: 875–877.
8. Lopez-Rios F, Illei PB, Rusch V et al. Evidence against a role for SV40 infection in human mesotheliomas and high risk of false-positive PCR results owing to presence of SV40 sequences in common laboratory plasmids. Lancet 2004; 364: 1157–1166.
9. Toyooka S, Pass I, Shivapurkar N et al. Aberrant methylation and Simian virus 40 Tag sequences in malignant mesothelioma. Cancer Res 2001; 61: 5727–5730.
10. Chang K, Pastan I. Molecular cloning of mesothelin, a differentiation antigen present on mesothelium, mesotheliomas and ovarian cancers. Proc Natl Acad Sci USA 1996; 93: 136–140.
11. Robinson BW, Creaney J, Lake R et al. Mesothelin-family proteins and diagnosis of mesothelioma. Lancet 2003; 362: 1612–1616.
12. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma: from the International Mesothelioma Interest Group. Chest 1995; 108: 1122–1128.
13. Patz EF Jr, Rusch VW, Heelan R. The proposed new international TNM staging system for malignant pleural mesothelioma: application to imaging. Am J Roentgenol 1996; 166: 323–327.
14. Curran D, Sahmoud T, Therasse P et al. Prognostic factors in patients with pleural mesothelioma: the European Organisation for Research and Treatment of Cancer Experience. J Clin Oncol 1998; 16: 145–152.
15. Herndon JE, Green MR, Chahinian AP et al. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest 1998; 113: 723–731.
16. Pass HI, Temeck BK, Kranda K et al. Preoperative tumor volume is associated with outcome in malignant pleural mesothelioma. J Thorac Cardiovasc Surg 1998; 115: 310–318.
17. Ball DL, Cruickshank DG. The treatment of malignant mesothelioma of the pleura: review of a 5-year experience, with special reference to radiotherapy. Am J Clin Oncol 1990; 13: 4–9.
18. Ong ST, Vogelzang NJ. Chemotherapy in malignant pleural mesothelioma: a review. J Clin Oncol 1996; 14: 1007–1017.
19. Byrne MJ, Davidson JA, Musk AW et al. Cisplatin and gemcitabine treatment for malignant mesothelioma: a phase II study. J Clin Oncol 1999; 17: 25–30.
20. Nowak AK, Byrne MJ, Williamson R et al. A multicenter phase II study of cisplatin and gemcitabine for malignant mesothelioma. Br J Cancer 2002; 87: 491–496.
21. Van Haarst, JW, Burgers, JA, Manegold, CH et al. Multicenter phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma (MPM). In: Program and Abstracts of the Ninth World Conference on Lung Cancer, 11–15 September 2000, Tokyo, Japan. Lung Cancer 2000; 29 (Suppl 1): 18 (Abstr 56).
22. Hughes A, Calvert, Azzobi A et al. Phase I clinical and pharmacokinetic study of pemetrexed and carboplatin in patients with malignant pleural mesothelioma. J Clin Oncol 2002; 20: 3533–3544.
23. Vogelzang NJ, Rusthoven JJ, Symanowski J et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003; 21: 2636–2644.
24. Fizazi K, Doubre H, Le Chevalier T et al. Combination of raltitrexed and oxaliplatin is an active regimen in malignant mesothelioma: results of a phase II study. J Clin Oncol 2003; 21: 349–354.
25. van Meerbeeck J, Manegold C, Gaafar R et al. A randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the EORTC Lung Cancer Group and NCIC. Proc Am Soc Clin Oncol 2004; 22: 622s (Abstr 7021).
26. Taub RN, Keohan ML, Vogelzang NJ et al. Phase II trial of Onconase® in patients (PTS) with advanced malignant mesothelioma (MM): analysis of survival. Proc Am Soc Clin Oncol 1999; 18: 524a (Abstr 2021).
27. Vogelzang N, Taub R, Shin D et al. Phase III randomized trial of Onconase versus doxorubicin in patients with unresectable malignant

mesothelioma. Analysis of survival. Proc Am Soc Clin Oncol 2000; 19: 577a (Abstr 2274).
28. Ohta Y, Shridhar V, Bright RK et al. VEGF and EGF type C play an important role in angiogenesis and lymphangiogenesis in human malignant mesothelioma tumours. Br J Cancer 1999; 81: 54–61.
29. Langerak AW, De Laat PAJM, Van-Der-Linden-Van Beurden CAJ et al. Expression of platelet-derived growth factor and receptors in human malignant mesothelioma in vitro and in vivo. J Pathol 1996; 178: 151–160.
30. Govindan R, Kratzke RA, Herndon JE et al. Gefitinib in patients with malignant mesothelioma. A phase II study by the Cancer and Leukemia Group B (CALGB 30101). Proc Am Soc Clin Oncol 2003; 21: 630 (Abstr 2535).
31. Garland L, Rankin C, Scott K et al. Molecular correlates of the EGFR signaling pathway in association with SWOG S0218: A phase II study of oral EGFR tyrosine kinase inhibitor OSI-774 in patients with malignant pleural mesothelioma. Proc Am Soc Clin Oncol 2004; 22: 196sa (Abstr 3007).