A phase II trial of low-dose gemcitabine in a prolonged infusion and cisplatin for malignant pleural mesothelioma

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After a favorable experience with gemcitabine at a low dose in a prolonged infusion in combination with cisplatin for advanced non-small-cell lung cancer, here, we present the results from a phase II trial for patients with malignant pleural mesothelioma. Eligible patients had biopsy-proven malignant pleural mesothelioma, were chemo-naive, Eastern Cooperative Oncology Group performance status 0–2, had normal hematopoietic liver and renal function, and gave informed consent. Treatment consisted of gemcitabine 250 mg/m^2 in a 6-h infusion on days 1 and 8 and cisplatin at 75 mg/m^2 on day 2 of a 3-week cycle for four cycles, followed by two additional cycles without cisplatin. Seventy-eight patients (58 men, 20 women; age 33–82 years, median 58) were recruited into the trial. The histologic types were as follows: epitheloid 56 (71.8%); four sarcomatoid (5.1%); mixed 15 (19.2%); and mesothelioma, three not otherwise specified (3.8%). Grades 3–4 toxicity included two (2.6%) patients with anemia, 18 (23.1%) with neutropenia, and one with nausea/vomiting. Reversible thrombocytosis with platelets over 1000–10^9/l was recorded in 10 (12.8%) patients and grade 2 alopecia in 60 (76.9%). Four (5.1%) patients showed a complete response and 35 (44.9%) showed a partial response with a response rate of 39/78 (50%). Minimal response or stable disease was seen in 35 (44.9%), whereas only four (5.1%) patients progressed during treatment. Most patients reported symptomatic improvement with a higher or a stable quality of life score in 70 (89.7%) cases. The median progression-free survival was 8.0 months (confidence interval 6.9–9.0). The median overall survival was 17.0 months (confidence interval 14.7–19.2). One-year, two-year, and three-year survival rates were 67.3, 32.7, and 19.8%, respectively. Epitheloid histological type was the only statistically significant favorable prognostic factor for progression-free survival and overall survival. Because of the acceptable toxicity, remarkable activity, and reasonable cost, this treatment should be further explored. *Anti-Cancer Drugs* **23:230–238**

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Introduction

Malignant mesothelioma is a rare tumor whose incidence has been increasing worldwide. Following a clear recognition of the role of asbestos in the pathogenesis of mesothelioma, most countries have implemented severe restrictions on the production and use of asbestos. Nevertheless, due to the long latency between exposure and development of mesothelioma, its incidence will continue to increase, especially in the older population [1–3].

Because of its aggressive local growth and only modest sensitivity to modern anticancer treatment, malignant mesothelioma is among the most difficult challenges of thoracic oncology. Selected patients of low clinical stage, medically operable, and with good performance status are candidates for multimodality therapy with a curative intent [4]. Most patients are treated with chemotherapy, which may lead to a short-term remission. Despite all efforts, over 90% of patients will die from the disease [5].

Before the pemetrexed era, the doublet of gemcitabine and cisplatin or carboplatin was the most widely used systemic treatment for mesothelioma. Seven studies with a total of 254 patients have been published [6–12]. Pooled data lead to an estimated median survival of 11.7 months, a figure that is clearly superior to that obtained with older drugs. Although gemcitabine was never specifically registered for mesothelioma, there should be no doubt about its activity.

Although gemcitabine is usually applied at a relatively high dose in a brief infusion, very interesting data on pharmacokinetics and on the clinical use of gemcitabine in a prolonged infusion have been published. For the usual 30-min infusion (dose rate 40 mg/m^2/min) and for the moderately prolonged infusion at a dose rate of 10 mg/m^2/min, the maximal tolerated dose (MTD) is 1500 mg/m^2 or even higher [13–15]. With lower dose rates, MTD decreases significantly. With infusions lasting for 3, 6, or 24 h, MTD decreases to 450, 250, and 180 mg/m^2, respectively [16–19]. This phenomenon may be attributed

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to the saturation of deoxycytidine kinase, the enzyme needed for the conversion of gemcitabine into its active gemcitabine–triphosphate form. Although a short infusion leaves most of the drug unmetabolized, a prolonged infusion leads to higher serum and intracellular concentrations of the active metabolite [18,20–22]. Because of the much higher conversion rate, a long infusion of gemcitabine leads to different pharmacokinetics, significantly lower MTD, different toxicity profile (including, e.g. alopecia), and an apparently different spectrum of antitumor activity [18,19]. Over the past two decades, several trials of low-dose gemcitabine in a prolonged infusion have been published and have reported a promising experience for non-small-cell lung cancer (NSCLC), sarcomas, heavily pretreated Hodgkin's disease, and breast, pancreatic, and bladder cancer [23–29].

In our previous clinical trials for NSCLC [30–32], gemcitabine at a low dose in a prolonged infusion was combined with cisplatin, the primary constituent of most doublets used for the treatment of lung cancer and a spectrum of other malignancies [33]. When designing this particular doublet, a 6-h infusion of gemcitabine was applied on days 1 and 8, and cisplatin (with proper hydration and antiemetics) on day 2, to make the schedule feasible also on an outpatient basis. This minor modification of the timing of the cytotoxic drugs proved to be easily tolerated. Neutropenia and thrombocytopenia were rare. Most toxicity was related to cisplatin and increased over the course of the treatment: due to nausea/vomiting and anemia, cisplatin often had to be excluded after four cycles of the doublet. We therefore adopted the policy of limiting cisplatin to the first four cycles, followed by a short-term 'maintenance' with single-agent gemcitabine during cycles 5 and 6.

Our favorable experience with gemcitabine at a low dose in a prolonged infusion and cisplatin for NSCLC [30–32] led us to a phase II trial for patients with mesothelioma. Our hypothesis was that low-dose gemcitabine in a long infusion in combination with cisplatin would lead to at least equal activity when compared with the published experience with gemcitabine at standard doses.

Patients and methods

Patients

Eligibility criteria included biopsy-proven malignant mesothelioma; no history of another cancer during the past 5 years or breast cancer ever; no previous irradiation to the chest; Eastern Cooperative Oncology Group performance status 0–2; and adequate hematopoietic, cardiac, liver, and renal function to receive cisplatin-based chemotherapy. In addition, there was a discussion on all patients at the multidisciplinary thoracic oncology tumor board and considered inoperable due to tumor extent, limited pulmonary function, other comorbidity, or patients' reluctance to undergo major surgery. Before registration, all patients were fully informed about the trial and signed an informed consent.

Exposure to asbestos was classified as heavy for persons working with asbestos for more than 5 years; as light for those with shorter or occasional exposure to asbestos; and as environmental for persons living within 10 km from a large asbestos factory in Anhovo. Although the production of asbestos at this site closed in 1996, pollution of the environment remains a serious health hazard.

Tumor extension was classified according to the TNM malignant tumors classification [34] on the basis of results from chest and upper abdominal computed tomography (CT) scan and thoracoscopy. For comparison with subsequent scanning, the thickness of the tumor on three CT levels was recorded. During most of the study period, MRI was not routinely used and PET-CT scanning was not available.

Study treatment

Treatment schedule

Treatment started with gemcitabine at a dose of 250 mg/m^2 in a 6-h infusion on days 1 and 8, and cisplatin at 75 mg/m^2 on day 2 of a 3-weekly cycle. After four cycles, patients not showing progression and without serious toxicity continued with two additional cycles of monotherapy with low-dose gemcitabine in a prolonged infusion.

Evaluation of toxicity and treatment modification

The NCI Common Toxicity Criteria (CTC), version 2.0, were used for grading the toxicity. Gemcitabine was applied at a reduced dose of 180 mg/m^2 in the case of grade 1 neutropenia and/or thrombocytopenia and excluded in the case of grade 2 or greater myelotoxicity. Cisplatin was reduced to 60 mg/m^2 in the case of grade 1 nephrotoxicity. For patients with grade of at least 2 nephrotoxicity and for those who reported grade 3 nausea or vomiting despite antiemetics during a previous cycle, cisplatin was replaced by carboplatin at area under the curve 5.

Supportive treatment

Supportive treatment included standard hydration and antiemetic treatment with metoclopramide, corticoids, aprepitant, and granisetron. As our previous trials had indicated a possibly increased risk for thromboembolic events after low-dose gemcitabine in a long infusion [31,32], all patients received low-molecular-weight heparin for the duration of the active treatment. Virtually all treatment was given on an outpatient basis in a day hospital.

Evaluation for response, progression-free survival, overall survival, and quality of life

Response was assessed during the third and sixth cycles and every 2 months thereafter using CT examination with the modified RECIST criteria [35]. Upon completion of

the trial, a review of all CT scans was performed by an independent radiologist (A.M.). Tumor thickness was measured perpendicular to the chest wall in two sites at three levels. For each individual patient, the sum of the initial measurements was taken as 100% and compared with the corresponding measurements during and after the treatment. Confirmation of response after at least 6 weeks was required for the classification of response as partial or complete remission. However, the best response at any time was used for the construction of a waterfall plot.

Progression-free survival (PFS) (defined as progression according to the RECIST criteria or death of any cause) and overall survival (OS) were calculated from the first day of chemotherapy.

For a longitudinal assessment of quality of life, we used our own simplified scale, as validated in our prior clinical trials for lung cancer [31,32]. Before starting cycles 3 and 5, patients were asked to compare their general well-being with the pretreatment state:

How do you feel, in comparison with your feeling before treatment?

5	Much better
4	Better
3	About the same
2	Worse
1	Much worse

Treatment in remission and after progression

As per protocol, no additional specific anticancer treatment was planned for patients in remission. Nevertheless, patients in remission with good performance status were again discussed at the thoracic tumor board for eventual surgery.

Because of the heterogeneity of clinical situations, the protocol did not specify second-line systemic treatment. As a general rule, patients who previously responded to treatment with low-dose gemcitabine and cisplatin were considered for reinduction with the same or a similar chemotherapy schedule: gemcitabine at 130–250 mg/m^2 in a 6-h infusion and either cisplatin at 60–75 mg/m^2 or carboplatin at area under the curve 5. Other treatment options included pemetrexed, navelbine, or palliative irradiation.

Treatment was never prolonged at the expense of an unbearable quality of life.

Study planning, analysis, and ethical considerations

Simon's optimal two-stage design for phase II clinical trials was used to calculate the sample size [36]. P0 (clinically uninteresting true response rate) and P1 (sufficiently promising true response rate) were set at 20 and 35%, respectively, with 80% power and 5% type 1 error. In the first stage, 22 patients had to be included: if four or less responses were observed, accrual would stop; otherwise, 50 more patients had to be registered. Treatment was considered of interest if more than 19 responses were observed out of 72 evaluable patients.

The primary objective of the trial was OS; secondary objectives were response rate, PFS, treatment toxicity, and quality of life. PFS and OS were estimated using the Kaplan–Meier method. The close-out date for data collection was 1 March 2011. The results were analyzed using the SPSS statistical package (Release 19.0; SPSS Inc., Chicago, Illinois, USA) and Prism (Version 5, 1994–2011 GraphPad Software Inc., La Jolla, California, USA). Preplanned subgroup analysis with a log-rank test included age, sex, performance status, histological type of mesothelioma, and malignant tumors stage of disease.

The investigators strictly followed the recommendations of the Helsinki Declaration (1964, with later amendments) and of the European Council Convention on Protection of Human Rights in Bio-Medicine (Oviedo 1997). The protocol was approved by the Institutional Review Board (Institute of Oncology, Ljubljana) and by the National Committee for Medical Ethics, Ministry of Health, Republic of Slovenia. Trial registration: Clinical Trials.gov identifier NCT 01243632.

Results

Patient characteristics

Between December 2002 and May 2008, 78 patients (58 men; 20 women, age 33 to 82 years, median 58) were recruited into the trial. Thoracoscopy was performed in all except three patients, who had their tumor confirmed only by a US-guided needle biopsy. The histologic types were as follows: epitheloid 56 (71.8%); mixed 15 (19.2%); four sarcomatoid (5.1); and mesothelioma, three not otherwise specified (3.8%). Thirteen patients (16.6%) had performance status 2, and the majority (60 or 76.9%) had stage 3 or 4 disease. Patient characteristics are presented in Table 1.

In total, 60 patients (76.9%) had some degree of exposure to asbestos, classified as heavy/professional, light/occasional, and environmental in 47, six, and seven patients, respectively. The geographical distribution of their residence in Slovenia points to four distinct clusters (Fig. 1). Clusters 1 and 2 are Ljubljana and Maribor, the two major urban and industrial regions. Cluster 3 is the coast with a ship-building industry. Finally, cluster 4 is a small region around a large former asbestos factory in Anhovo. This region comprises only 2.9% of the national population but bears the burden of 35% of mesotheliomas.

Actual treatment and toxicity

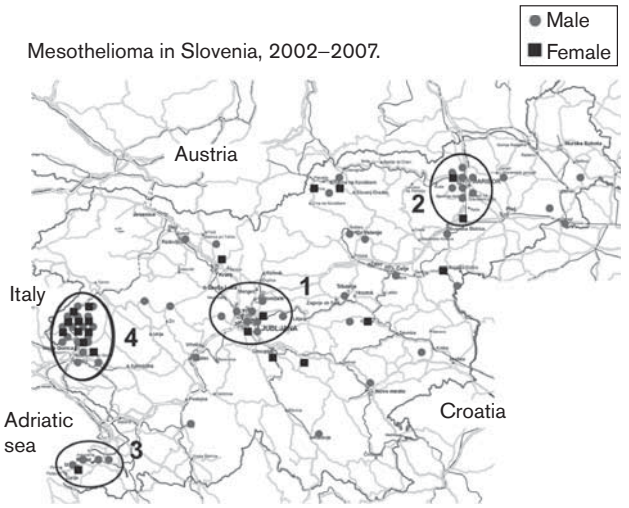
Data on the actual treatment and the dose intensity for gemcitabine and for cisplatin are shown in Table 2. Sixty-two patients (79.5%) completed all six cycles of chemotherapy. In a minority of patients, gemcitabine and/

Table 1 Patient characteristics

Characteristics	Patients, $n=78$ (%)
Age (years)	
Median	58
Range	33–82
Sex	
Male	58 (74.4)
Female	20 (25.6)
Asbestos exposure	
Heavy/professional	47 (60.2)
Light/occasional	6 (7.7)
Environmental[a]	7 (9.0)
No known exposure	18 (23.1)
Smoking	
Never smoker	37 (47.4)
Former, quit at more than 2 years	26 (33.3)
Smoked until current disease	10 (12.8)
Current smoker	5 (6.4)
Previous other cancer	1 (1.3)
ECOG Performance status	
PS 0	14 (17.9)
PS 1	51 (65.4)
PS 2	13 (16.6)
Histology	
Epitheloid	56 (71.8)
Mixed	15 (19.2)
Sarcomatoid	4 (5.1)
Mesothelioma, not otherwise specified	3 (3.8)
TNM stage	
I	3 (3.8)
II	15 (19.2)
III	38 (48.7)
IV	22 (28.2)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; TNM, malignant tumors.
[a]Patients living within 10 km from a large asbestos factory in Anhovo (production of asbestos abandoned in 1996).

Fig. 1



The geographical distribution of patients' residence points to four distinct clusters: urban and industrial areas of Ljubljana (1) and Maribor (2), the coast with a ship-building industry (3), and the area around a large former asbestos industry in Anhovo (4).

or cisplatin were excluded or applied at a reduced dose; nevertheless, the average dose intensity for all six cycles was above 80%.

Table 2 Chemotherapy dose intensity of 78 patients

Cycle of chemotherapy	Number of patients entering cycle	Average dose intensity (%)	
		Gemcitabine	Cisplatin
1	78	97.3	100
2	77	94.6	94.7
3	77	85.0	93.7
4	72	83.3	88.6
5	72	82.3	–
6	62	79.7	–

The treatment was tolerated very well. In general, toxicity was mild and manageable (Table 3). Grade 2 anemia was common (41 patients, 52.6%); grades 3 and 4 anemia were seen in one patient each. Grades 3 and 4 neutropenia were seen in 16 (20.5%) and two (2.6%) patients, respectively. No patient had febrile neutropenia and there were no treatment-related deaths. Although only a single patient had grade 2 thrombocytopenia, reversible thrombocytosis was common: 42 (53.8%) had platelets in the range $500–999 \times 10^9$/l and 10 (12.8%) above 1000×10^9/l. In the latter group, two developed grade 2 deep vein thrombosis, successfully treated with therapeutic doses of low-molecular-weight heparin. Grade 2 nausea/vomiting was common but manageable and only a single patient was switched from cisplatin to carboplatin. Other grade 2 toxicities included alopecia in 60 patients (76.9%), skin rash (seven patients), and neuropathy and edema (one patient each).

Response to treatment, survival, and quality of life

In the first stage, 11 out of 22 patients showed a complete or a partial response. According to the statistical design, we then proceeded to the second stage. In the entire series of 78 patients, a complete response was seen in four (5.1%) patients, all with epitheloid type of malignant pleural mesothelioma (Fig. 2). Partial response was documented in 35 (44.9%) patients, yielding a complete response + partial response rate of 39 (50%). Thirty-five (44.9%) additional patients showed minimal response with symptomatic improvement or stable disease. In four patients (5.1%), the disease progressed during treatment.

A waterfall plot – the ratio between the best response (measured according to the modified RECIST criteria) and the initial tumor extent – is presented in Fig. 3. The figure also illustrates the relation of response to histologic type.

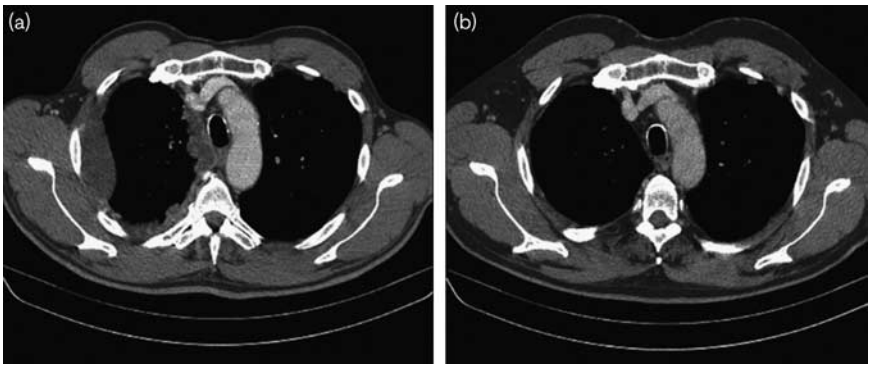
The median PFS was 8.0 months (confidence interval 6.9–9.0). The median OS was 17.0 months (confidence interval 14.7–19.2). One-year, two-year, and three-year survival rates were 67.3, 32.7, and 19.8%, respectively. (Table 4, Figs 4 and 5).

At cycle 3, 70 (89.7%) patients reported equal or better well-being (Table 4).

Table 3 Toxicity (Common Toxicity Criteria grading) in 78 malignant pleural mesothelioma patients receiving low-dose gemcitabine in a prolonged infusion and cisplatin

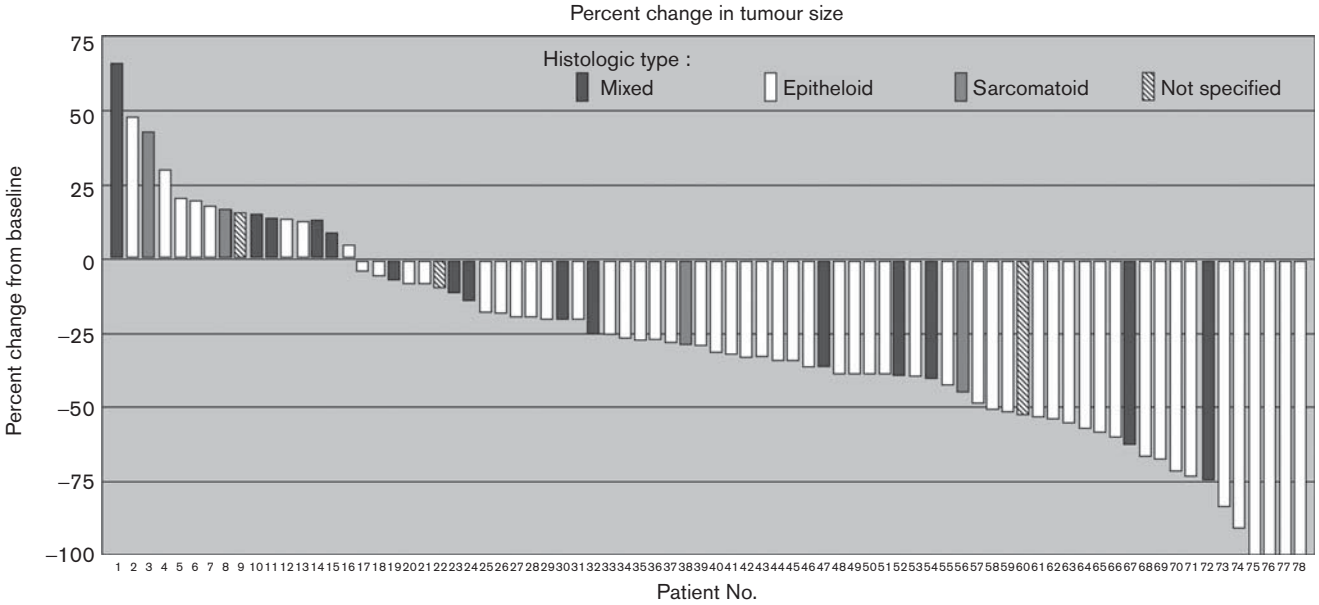
Adverse events	Grade 0, *n* (%)	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade3, *n* (%)	Grade 4, *n* (%)
Anemia	1 (1.3)	34 (43.6)	41 (52.6)	1 (1.3)	1 (1.3)
Neutropenia	27 (34.6)	11 (14.1)	22 (28.2)	16 (20.5)	2 (2.6)
Thrombocytopenia	69 (88.5)	8 (10.3)	1 (1.3)	–	–
Nephrotoxicity	48 (61.5)	29 (37.2)	1 (1.3)	–	–
Nausea/vomiting	15 (19.2)	38(48.7)	24 (30.8)	1 (1.3)	–
Alopecia	1 (1.3)	17 (21.8)	60 (76.9)	–	–

Fig. 2



Computed tomography scans of a 51-year-old man with epitheloid malignant pleural mesothelioma, stage T3N0M0, performance status Eastern Cooperative Oncology Group 1 before treatment (a) and 3 months after six cycles of chemotherapy (b).

Fig. 3



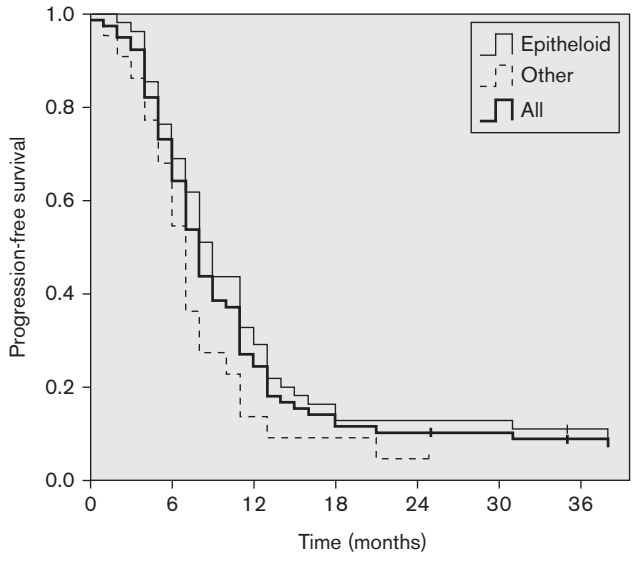
Waterfall plot with the best response of patients with different histologic types of malignant pleural mesothelioma. The bars indicate the percent change in tumor burden from baseline, as measured according to the modified RECIST criteria for mesothelioma.

Table 4 Response to treatment, progression-free survival, overall survival, and quality of life

Variables	Epitheloid *n*=56 (%)	Other histologies *n*=22 (%)	All histologic types *n*=78 (%)
Response to treatment			
CR	4 (7.1)	0 (0)	4 (5.1)
PR	28 (50.0)	7 (31.8)	35 (44.9)
MR + SD	23 (41.1)	12 (54.4)	35 (44.9)
Progression	1 (1.8)	3 (13.6)	4 (5.1)
Progression-free survival			
Median	9.0 months (CI 7.5–10.4)	7.0 (CI 5.7–8.2)	8.0 months (CI 6.9–9.0)
Overall survival			
Median	17.0 months (CI 12.8–21.1)	14.0 (CI 9.5–18.4)	17.0 months (CI 14.7–19.2)
QoL: patient's self-assessment at cycle 3			
5 (much better)	15 (26.8%)	1 (4.5)	16 (20.5%)
4 (better)	23 (41.1%)	14 (63.6)	37 (47.4%)
3 (equal)	12 (21.4%)	5 (22.7)	17 (21.8%)
2 (worse)	5 (8.9%)	0 (0)	5 (6.4%)
1 (much worse)	0 (0%)	1 (4.5)	1 (1.3%)
Nonevaluable	1 (1.8%)	1 (%)	2 (2.6%)

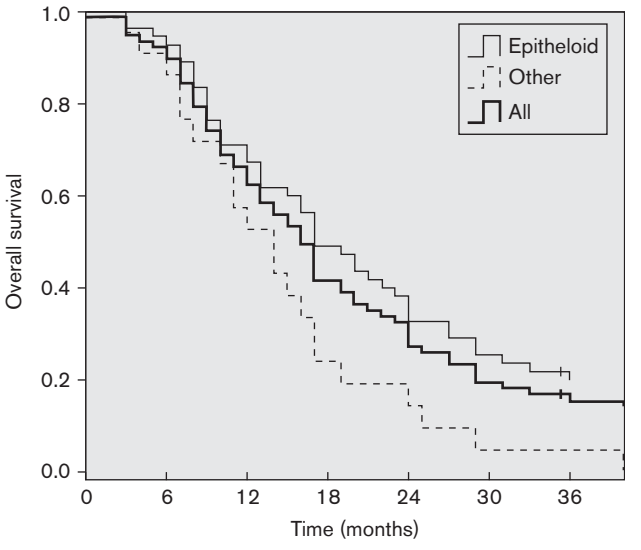
CI, confidence interval; CR, complete response; MR, minimal response; PR, partial response; SD; stable disease.

Fig. 4



Progression-free survival (median 8.0 months) for 78 mesothelioma patients.

Fig. 5



Overall survival (median 17.0 months) for 78 mesothelioma patients.

Poststudy treatment

After completing chemotherapy, surgical removal of the residual tumor was attempted in six patients who had a partial response to initial chemotherapy and had a good performance status. In five patients, extrapleural pneumonectomy was carried out; in the sixth patient, the tumor remained inoperable. One of these patients remains free of disease at 68 months after the initial treatment. For the rest, time to progression is between 8.5 and 48.5 months, and survival from 20.0 to 63.2 months.

A total of 33 patients (42.3%) received second-line chemotherapy. Patients who previously responded to the study combination were often treated with the same schedule. Among 27 patients who received reinduction treatment with low-dose gemcitabine in a long infusion and cisplatin or carboplatin, an objective response was confirmed in 22 patients (81.5%). Furthermore, the same combination was applied as the third-line chemotherapy in four patients (response rate 3/4), and twice as fourth-line (response rate 2/2) or as fifth-line chemotherapy (response rate 2/2).

Of the six patients who received second-line chemotherapy with other drugs including pemetrexed or navelbine, one achieved a partial response and two showed a minimal response.

Prognostic factors

Epitheloid histologic type was the only favorable prognostic factor for PFS and OS. Patients with epitheloid

Table 5 Univariate analyses of variables potentially affecting progression-free survival and overall survival

Variables	*N*	PFS (CI)	*P*	OS (CI)	*P*
Age					
≤ 55	24	8.0 (6.0–9.9)	0.37	24.0 (13.4–34.5)	0.15
>55	54	8.0 (6.2–9.7)		16.0 (13.4–18.5)	
Sex					
Males	58	8.0 (6.6–9.3)	0.89	16.0 (13.7–18.2)	0.46
Females	20	7.0 (4.2–9.8)		19.0 (11.9–26.0)	
ECOG performance status					
0	14	9.0 (7.4–10.5)	0.24	17.0 (12.3–21.6)	0.33
1–2	64	6.0 (4.3–7.6)		13 (8.0–17.9)	
Histology					
Epitheloid	56	9.0 (7.5–10.4)	0.049	17.0 (12.8–21.1)	0.01
Other	22	7.0 (5.7–8.2)		14.0 (9.5–18.4)	
Stage					
1, 2	18	7 (2.8–11.1)	0.45	17.0 (4.5–29.4)	0.46
3, 4	60	8.0 (7.0–8.9)		16.0 (13.7–18.2)	

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival; OS, overall survival.

histologic type had a median PFS of 9.0 months compared with 7.0 months for those with other histologic types ($P = 0.049$). Regarding OS, patients with epitheloid and other histologic types had a median survival of 17.0 and 14.0 months, respectively ($P = 0.010$). Differences in PFS and OS in age, sex, performance status, and stage of the disease were not significant (Table 5).

Discussion

Our phase II trial is the first to report treatment with low-dose gemcitabine in a long infusion in combination with cisplatin for patients with mesothelioma. The nonrandomized design is an obvious limitation to any conclusions that may be drawn from our experience. Nevertheless, due to the low incidence of mesothelioma, in the last decade, few prospective clinical trials including more than 80 patients have been published [37–45] and only four of these were phase III randomized studies [38–41]. Despite the limitations and biases, small nonrandomized phase II trials provide an important contribution to our knowledge about the treatment of this rare disease.

In Slovenia, with a population of 2 million, almost all patients with biopsy-proven mesothelioma and considered eligible for chemotherapy and/or radiotherapy are referred to the Institute of Oncology in Ljubljana. During the trial period, 139 patients with pleural mesothelioma were reported to the Cancer Registry of Slovenia [46]. After excluding those sent for surgery as the first choice of treatment and patients with a poor performance status or with significant comorbidity who were treated with best supportive care and/or palliative irradiation, a total of 89 patients received any form of systemic therapy. With 78 patients, our trial recruited 87.6% of patients with pleural mesothelioma treated with chemotherapy and may be considered as representative of the entire population of mesothelioma patients eligible for platin-based chemotherapy.

After a favorable experience with the treatment for a variety of other tumors [23–32], this trial confirms that low-dose gemcitabine in a long infusion in combination with cisplatin is also an effective treatment for mesothelioma. The high response rate, with 50.0% of the patients achieving complete or partial remission, the relatively long median time to progression (8.0 months), and the long median survival (17 months) are all considerably higher than the figures usually reported for mesothelioma. The favorable ratio between efficacy and toxicity of this regime is reflected in the high proportion of patients who had good symptomatic relief and improved quality of life during chemotherapy. In addition, our trial included an independent radiology review. While we recognize the difficulties of the assessment of response in mesothelioma [47], we believe that the high antitumor activity of our treatment is real and not attributable to observer bias.

Epitheloid histologic type predicted for longer PFS and survival, a finding reported in several previous trials and reviews [48–50]. The fact that the stage of the disease was of no prognostic significance may be partially attributable to the diagnostic process: during the trial period, PET-CT was not available and MRI was only rarely used, as its results would have no impact for treatment. Thus, it is likely that in a substantial proportion of patients declared as having early disease, the real stage was higher than defined during the initial diagnostics, as also seen in other studies [51]. Our experience may be compared with a recent report on good responses to chemotherapy even in advanced stages of mesothelioma [52].

Our protocol did not include guidelines for local treatment. Nevertheless, five patients in remission after chemotherapy had extrapleural pneumonectomy. Although their survival is indeed longer, the small number and a bias in selection for surgery preclude any comparison with other patients.

Second-line treatment was also not specified in the protocol. Although the variety of second-line treatments does not allow a clear conclusion, a notable finding is the high proportion of patients in progression after initial complete or partial remission who responded to reinduction of the same or similar treatment. Our favorable experience as well as a recent report on reinduction of pemetrexed-based second-line chemotherapy indicate that at least some patients do not develop resistance to the prior combination of chemotherapy [53].

After four cycles of the doublet of low-dose gemcitabine in a long infusion and cisplatin, we applied two additional courses of gemcitabine as monotherapy. It is clear that these two additional cycles should not be regarded as a true maintenance phase of the treatment and their contribution to the treatment outcome is uncertain. As almost all patients relapsed after a relatively short remission, proper maintenance (e.g. with pemetrexed) should be considered for future trials.

Because of the nonrandomized design and the relatively small size of our trial, comparison with other treatment schedules is only speculative. As already mentioned, gemcitabine at a standard dose in a brief infusion in combination with cisplatin or carboplatin was the most common treatment at the turn of the century, with a reported median survival of around 12 months. A similar survival of 12–14 months was achieved with pemetrexed in combination with cisplatin or carboplatin [38,44,54], which is nowadays considered as a standard systemic treatment [49,55]. Other recent reports on the treatment of mesothelioma include docetaxel–gemcitabine (25 patients, median survival 15 months) [56], vinorelbine–cisplatin (54 patients, median survival 16.8 months) [57], and a triplet of carboplatin, liposomized doxorubicin, and gemcitabine (173 patients, median survival 13 months) [42].

Platinum-based combination chemotherapy remains the gold standard for first-line chemotherapy of malignant pleural mesothelioma [58]. It is clear that we are still far from finding 'the best' systemic treatment for mesothelioma. It is also clear that additional treatment options are needed for patients in relapse who often have a good performance status and are in need of additional treatment.

In conclusion, our trial provides a new treatment within the spectrum of treatment options for mesothelioma. Gemcitabine at a low dose in a long infusion in combination with cisplatin may be considered for the primary treatment of mesothelioma, especially in economically deprived populations for whom the costs for pemetrexed are prohibitive. In addition, a substantial proportion of patients with relapse after a gemcitabine–cisplatin doublet remain sensitive to this combination and may benefit from reinduction of the same treatment. Because of the acceptable toxicity, remarkable activity, and reasonable cost, this treatment should be further explored.

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Conflicts of interest

The are no conflicts of interest.

References

1 Robinson BWS, Musk AW, Lake RA. Malignant mesothelioma. *Lancet* 2005; **366**:397–408.
2 Marinaccio A, Binazzi A, Cauzillo G, Cavone D, Zotti RD, Ferrante P, *et al.*; Italian Mesothelioma Register (ReNaM) Working Group. Analysis of latency time and its determinants in asbestos related malignant mesothelioma cases of the Italian register. *Eur J Cancer* 2007; **43**:2722–2728.
3 Rake C, Gilham C, Hatch J, Darnton A, Hodgson J, Peto J. Occupational, domestic and environmental mesothelioma risks in the British population: a case–control study. *Br J Cancer* 2009; **100**:1175–1183.
4 Krug LM, Pass HI, Rusch VW, Kindler HL, Sugarbaker DJ, Rosenzweig KE, *et al.* Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. *J Clin Oncol* 2009; **27**:3007–3013.
5 Milano MT, Zhang H. Malignant pleural mesothelioma. A population-based study of survival. *J Thorac Oncol* 2010; **5**:1841–1848.
6 Byrne MJ, Davidson JA, Musk AW, Dewar J, van Hazel G, Buck M, *et al.* Cisplatin and gemcitabine treatment for malignant mesothelioma: a phase II study. *J Clin Oncol* 1999; **17**:25–30.
7 Aversa SM, Favaretto AG. Carboplatin and gemcitabine chemotherapy for malignant pleural mesothelioma: a phase II study of the GSTPV. *Clin Lung Cancer* 1999; **1**:73–77.
8 Van Haarst JMW, Baas P, Manegold C, Schouwink JH, Burgers JA, de Bruin HG, *et al.* Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Br J Cancer* 2002; **86**:342–345.
9 Nowak AK, Byrne MJ, Williamson R, Ryan G, Segal A, Fielding D, *et al.* A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer* 2002; **87**:491–496.
10 Favaretto AG, Aversa SM, Paccagnella A, Manzini Vde P, Palmisano V, Oniga F, *et al.* Gemcitabine combined with carboplatin in patients with malignant pleural mesothelioma: a multicentric phase II study. *Cancer* 2003; **97**:2791–2797.
11 Castagneto B, Zai S, Dongiovanni D, Muzio A, Bretti S, Numico G, *et al.* Cisplatin and gemcitabine in malignant pleural mesothelioma: a phase II study. *Am J Clin Oncol* 2005; **28**:223–226.
12 Kalmadi SR, Rankin C, Kraut MJ, Jacobs AD, Petrylak DP, Adelstein DJ, *et al.* Gemcitabine and cisplatin in unresectable malignant mesothelioma of the pleura: a phase II study of the Southwest Oncology Group (SWOG 9810). *Lung Cancer* 2008; **60**:259–263.
13 Brand R, Capadano M, Tempero M. A phase I trial of weekly gemcitabine administered as prolonged infusion in patients with pancreatic cancer and other solid tumors. *Invest New Drugs* 1997; **15**:331–341.
14 Fossella FV, Lippman SM, Shin DM, Tarassoff P, Calayag-Jung M, Perez-Soler R, *et al.* Maximum-tolerated dose defined for single-agent gemcitabine: a phase I dose-escalation study in chemotherapy-naive patients with advanced non-small-cell lung cancer. *J Clin Oncol* 1997; **15**:310–316.
15 Touroutoglou N, Gravel D, Raber MN, Plunkett W, Abbruzzese JL. Clinical results of a pharmacodynamically-based strategy for higher dosing of gemcitabine in patients with solid tumors. *Ann Oncol* 1998; **9**: 1003–1008.
16 Anderson H, Thatcher N, Walling J, Hansen H. A phase I study of a 24 h infusion of gemcitabine in previously untreated patients with inoperable non-small-cell lung cancer. *Br J Cancer* 1996; **74**:460–462.
17 Pollera CF, Ceribelli A, Crecco M, Oliva C, Calabresi F. Prolonged infusion gemcitabine: a clinical phase I study at low- (300 mg/m^2) and high-dose (875 mg/m^2) levels. *Invest New Drugs* 1997; **15**:115–121.
18 Akrivakis K, Schmid P, Flath B, Schweigert M, Sezer O, Mergenthaler HG, *et al.* Prolonged infusion of gemcitabine in stage IV breast cancer: a phase I study. *Anticancer Drugs* 1999; **10**:525–531.
19 Maurel J, Zorrilla M, Puertolas T, Antón A, Herrero A, Artal A, *et al.* Phase I trial of weekly gemcitabine at 3-h infusion in refractory, heavily pretreated advanced solid tumors. *Anticancer Drugs* 2001; **12**:713–717.
20 Grunewald R, Abbruzzese JL, Tarassoff P, Plunkett W. Saturation of 2′,2′-difluorodeoxycytidine 5′-triphosphate accumulation by mononuclear cells during a phase I trial of gemcitabine. *Cancer Chemother Pharmacol* 1991; **27**:258–262.
21 Abbruzzese JL, Grunewald R, Weeks EA, Gravel D, Adams T, Nowak B, *et al.* A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. *J Clin Oncol* 1991; **9**:491–499.
22 Cattel L, Airoldi M, Delprino L, Passera R, Milla P, Pedani F. Pharmacokinetic evaluation of gemcitabine and 2′,2′-difluorodeoxycytidine-5′-triphosphate after prolonged infusion in patients affected by different solid tumors. *Ann Oncol* 2006; **17 (Suppl 5):**v142–v147.
23 Xiong JP, Feng M, Qiu F, Xu J, Tao QS, Zhang L, *et al.* Phase II trial of low-dose gemcitabine in prolonged infusion and cisplatin for advanced non-small cell lung cancer. *Lung Cancer* 2008; **60**:208–214.
24 Parikh PM, Narayanan P, Mistry RC, Agarwal JP, Pai VR, Nair R, *et al.* Treatment of advanced NSCLC (Stage IIIB and IV) with low dose gemcitabine and carboplatin [Abstract]. *J Clin Oncol* 2005; **23 (Suppl 1):**196 S.
25 Spath-Schwalbe E, Genvresse I, Koschuth A, Dietzmann A, Grunewald R, Possinger K. Phase II trial of gemcitabine in patients with pretreated advanced soft tissue sarcomas. *Anticancer Drugs* 2000; **11**:325–329.

26 Sezer O, Eucker J, Jakob C, Kaufmann O, Schmid P, Possinger K. Achievement of complete remission in refractory Hodgkin's disease with prolonged infusion of gemcitabine. *Invest New Drugs* 2001; **19**:101–104.
27 Schmid P, Heilmann V, Schulz CO, Dieing A, Lehenbauer-Dehm S, Jehn C, *et al*. Gemcitabine as prolonged infusion and vinorelbine in anthracycline and/or taxane pretreated metastatic breast cancer: a phase II study. *J Cancer Res Clin Oncol* 2005; **131**:568–574.
28 Eckel F, Schmelz R, Erdmann J, Mayr M, Lersch C. Phase II trial of a 24-h infusion of gemcitabine in previously untreated patients with advanced pancreatic adenocarcinoma. *Cancer Invest* 2003; **21**:690–694.
29 Khaled H, Emara ME, Gaafar RM, Mansour O, Abdel Warith A, Zaghloul MS, *et al*. Primary chemotherapy with low-dose prolonged infusion gemcitabine and cisplatin in patients with bladder cancer: a Phase II trial. *Urol Oncol* 2008; **26**:133–136.
30 Zwitter M, Kovac V, Smrdel U, Kocijancic I, Segedin B, Vrankar M. Phase I-II trial of low-dose gemcitabine in prolonged infusion and cisplatin for advanced non-small cell lung cancer. *Anticancer Drugs* 2005; **16**: 1129–1134.
31 Zwitter M, Kovac V, Smrdel U, Vrankar M, Zadnik V. Gemcitabine in brief versus prolonged low-dose infusion, both combined with cisplatin, for advanced non-small cell lung cancer: a randomized phase II clinical trial. *J Thorac Oncol* 2009; **4**:1148–1155.
32 Zwitter M, Kovac V, Rajer M, Vrankar M, Smrdel U. Two schedules of chemotherapy for patients with non-small cell lung cancer in poor performance status: a phase II randomized trial. *Anticancer Drugs* 2010; **21**:662–668.
33 Socinski MA. Clinical issues in the management of non-small-cell lung cancer and the role of platinum-based therapy. *Clin Lung Cancer* 2004; **5**:274–289.
34 Sobin LH, Gospodarowicz MK, Wittekind Ch. Pleural mesothelioma. In: UICC International Union Against Cancer, editor. *TNM classification of malignant tumours*. 7th ed. Chichester: Wiley-Blackwell. 2009; pp. 147–150.
35 Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Ann Oncol* 2004; **15**:257–260.
36 Simon R. Optimal designs for phase II clinical trials. *Control Clin Trials* 1989; **10**:1–10.
37 Mikulski SM, Costanzi JJ, Vogelzang NJ, McCachren S, Taub RN, Chun H, *et al*. Phase II trial of a single weekly intravenous dose of ranpirnase in patients with unresectable malignant mesothelioma. *J Clin Oncol* 2002; **20**:274–281.
38 Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, *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.
39 Van Meerbeeck JP, Gaafar R, Manegold C, Van Klaveren RJ, Van Marck EA, Vincent M, *et al*. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005; **23**:6881–6889.
40 Jassem J, Ramlau R, Santoro A, Schuette W, Chemaissani A, Hong S, *et al*. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol* 2008; **26**:1698–1704.
41 Muers MF, Stephens RJ, Fisher P, Darlison L, Higgs CM, Lowry E, *et al*. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet* 2008; **371**:1685–1694.
42 Hillerdal G, Sorensen JB, Sundström S, Riska H, Vikström A, Hjerpe A. Treatment of malignant pleural mesothelioma with carboplatin, liposomized doxorubicin, and gemcitabine: a phase II study. *J Thorac Oncol* 2008; **3**:1325–1331.
43 Santoro A, O'Brien ME, Stahel RA, Nackaerts K, Baas P, Karthaus M, *et al*. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program. *J Thorac Oncol* 2008; **3**:756–763.
44 Treasure T, Waller D, Tan C, Entwisle J, O'Brien M, O'Byrne K, *et al*. The mesothelioma and radical surgery randomized controlled trial: the Mars feasibility study. *J Thorac Oncol* 2009; **4**:1254–1258.
45 Ceresoli GL, Zucali PA, Favaretto AG, Grossi F, Bidoli P, Del Conte G, *et al*. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. *J Clin Oncol* 2006; **24**:1443–1448.
46 Cancer Registry of Republic of Slovenia. *Cancer incidence in Slovenia 2002–2008*. Ljubljana: Institute of Oncology Ljubljana; 2005–2011.
47 Tsao AS, Garland L, Redman M, Kernstine K, Gandara D, Marom EM. A practical guide of the Southwest Oncology Group to measure malignant pleural mesothelioma tumors by RECIST and modified RECIST criteria. *J Thorac Oncol* 2011; **6**:598–601.
48 Curran D, Sahmoud T, Therasse P, van Meerbeeck J, Postmus PE, Giaccone G. Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. *J Clin Oncol* 1998; **16**:145–152.
49 Kindler HL. Systemic treatments for mesothelioma: standard and novel. *Curr Treat Options Oncol* 2008; **9**:171–179.
50 Katirtzoglou N, Gkiozos I, Makrilia N, Tsaroucha E, Rapti A, Stratakos G, *et al*. Carboplatin plus pemetrexed as first-line treatment of patients with malignant pleural mesothelioma: a phase II study. *Clin Lung Cancer* 2010; **11**:30–35.
51 Wilcox BE, Subramaniam RM, Peller PJ, Aughenbaugh GL, Nichols Iii FC, Aubry MC, *et al*. Utility of integrated computed tomography-positron emission tomography for selection of operable malignant pleural mesothelioma. *Clin Lung Cancer* 2009; **10**:244–248.
52 Bech C, Sørensen JB. Chemotherapy induced pathologic complete response in malignant pleural mesothelioma: a review and case report. *J Thorac Oncol* 2010; **5**:735–740.
53 Ceresoli GL, Zucali PA, De Vincenzo F, Gianoncelli L, Simonelli M, Lorenzi E, *et al*. Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma. *Lung Cancer* 2011; **72**:73–77.
54 Castagneto B, Botta M, Aitini E, Spigno F, Degiovanni D, Alabiso O, *et al*. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). *Ann Oncol* 2008; **19**:370–373.
55 Scagliotti GV, Selvaggi G. Emerging drugs for mesothelioma. *Expert Opin Emerg Drugs* 2007; **12**:127–137.
56 Ralli M, Tourkantonis I, Makrilia N, Gkini E, Kotteas E, Gkiozos I, *et al*. Docetaxel plus gemcitabine as first-line treatment in malignant pleural mesothelioma: a single institution phase II study. *Anticancer Res* 2009; **29**:3441–3444.
57 Sørensen JB, Frank H, Palshof T. Cisplatin and vinorelbine first-line chemotherapy in non-resectable malignant pleural mesothelioma. *Br J Cancer* 2008; **99**:44–50.
58 Lee CW, Murray N, Anderson H, Rao SC, Bishop W. Outcomes with first-line platinum-based combination chemotherapy for malignant pleural mesothelioma: A review of practice in British Columbia. *Lung Cancer* 2009; **64**:308–313.