

A Phase II Study of Gemcitabine in Patients with Malignant Pleural Mesothelioma

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BACKGROUND. Gemcitabine has shown activity in patients with less chemosensitive solid tumors. Phase II screening of novel drugs is an accepted method with which to investigate new therapies in malignant mesothelioma. The European Organization for Research and Treatment of Cancer-Lung Cancer Cooperative Group has performed several sequential Phase II trials of new agents for the treatment of mesothelioma over the last 10 years.

METHODS. Twenty-seven chemotherapy-naïve patients with histologically proven malignant mesothelioma were treated with gemcitabine as a 30-minute intravenous administration of 1250 mg/m² on Days 1, 8, and 15 of a 28-day cycle. Therapy continued for up to ten cycles unless disease progression or excessive toxicity mandated discontinuation.

RESULTS. With a median relative dose intensity of 96%, toxicity was mild and neutropenia of \geq Grade 3 (according to National Cancer Institute criteria) occurred in 30% of patients, without episodes of febrile neutropenia. One case of hemolytic-uremic syndrome, most likely related to gemcitabine use, was observed. Overall, 2 objective responses were observed (response rate of 7%; 95% confidence interval, 1-24%). The median survival was 8 months.

CONCLUSIONS. At the prescribed dosage and schedule, single agent gemcitabine appears to have limited activity in chemotherapy-naïve patients with malignant pleural mesothelioma. *Cancer* 1999;85:2577–82.

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KEYWORDS: malignant mesothelioma, chemotherapy, Phase II study, gemcitabine, pleura, hemolytic-uremic syndrome.

Malignant mesothelioma (MM) is an invariably lethal tumor whose appearance often is strongly linked with prior asbestos exposure. In some countries, its rate of incidence is expected to increase further in the coming years. The natural history of MM is characterized by a median survival of 9–14 months, with $< 5\%$ of patients surviving for 5 years. Disease extent at diagnosis and histologic subtype are the main prognostic factors impacting on survival.^{1,2}

Chemotherapy results in a response rate of $< 20\%$ and does not appear to be associated with prolonged survival. Doxorubicin, mitomycin, cisplatin, and high dose methotrexate are among the agents that have shown some activity. Combination chemotherapy does not appear to provide better results than single agents, although response rates have been higher in some studies and combinations.^{3,4} There clearly is a need for new drugs in the treatment of this disease, with testing in Phase II trials in chemotherapy-naïve patients. These studies should be multiinstitutional and have a rigorous design, state of the art evaluation of response, external review of tissue diagnosis, and appropriate information regarding prognostic factors. Because of the

TABLE 1
Distribution of Histologic Subtypes and Pathology Review of 27 Eligible Patients

Subtyping according to local pathologist	Subtyping according to pathology review					Total
	Epithelial	Sarcomatous	Mixed	Insufficient material	Report review only	
Epithelial	10	1	1	1	5	18
Sarcomatous	—	2	—	—	1	3
Mixed	—	—	4	1	1	6
Total	10	3	5	2	7	27

rarity of MM, multicenter studies usually are more effective when conducting such trials. For the past 10 years, the European Organization for Research and Treatment of Cancer-Lung Cancer Cooperative Group (EORTC-LCCG) has been conducting sequential Phase II studies in MM patients according to a master protocol. To our knowledge, none of the agents tested thus far had significant activity in pleural MM.⁵⁻⁸

Gemcitabine (2',2'-difluorodesoxycytidine) is a novel pyrimidine analogue with unique activity against a wide range of solid tumors, including pancreatic carcinoma and nonsmall cell lung carcinoma.⁹ Its mechanism of action, toxicity, and clinical pharmacology have been reviewed extensively.^{10,11} In the current study we report the results of a multicenter EORTC-LCCG Phase II study with gemcitabine in the treatment of chemotherapy-naïve patients with MM.

METHODS

Patients

Patients with histologically confirmed MM of the pleural cavity who had received no prior chemotherapy were accrued into this study. Pathology was reviewed centrally. Tumor extension was classified according to the International Union Against Cancer and had to be measurable bidimensionally in at least one target lesion.^{12,13} Pleural effusion alone was not accepted as evaluable disease. Previous intracavitary treatment was allowed, provided no cytotoxic agents were applied. Patients were required to be age > 18 years and age < 75 years, with a World Health Organization (WHO) performance status of 0-2, and have adequate hematologic (hemoglobin > 100 g/L, granulocyte count $\geq 2 \times 10^9/L$, and a platelet count $\geq 100 \times 10^9/L$), hepatic (bilirubin $\leq 25 \mu\text{mol/L}$), and renal (creatinine clearance $\geq 60 \text{ mL/minute}$) function. Prior surgery was permitted provided that measurable disease was present. Prior and concomitant radiotherapy was permitted to painful lesions, needle tracks, or surgical scars, provided that the indicator lesions were outside the irradiated field. Patients with symptoms or signs of metastases in the central nervous system and

those with a recent history of body weight loss of > 10% were excluded. Written informed consent was obtained from each patient prior to patient entry onto the study.

Therapy

Gemcitabine at a dose of 1250 mg/m² was diluted in normal saline and administered intravenously over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Blood cell counts were assessed weekly after administration and liver/renal function controlled before each cycle. Treatment cycles were repeated every 28 days, provided toxic effects were not prohibitive and there was no clinical evidence of tumor progression. Dose escalation of gemcitabine was not permitted. The dose of gemcitabine for subsequent cycles was adjusted according to the patient's actual weight at retreatment and reduced by 50% of the starting dose of the previous cycle in the event of febrile neutropenia, Grade 4 thrombocytopenia, or thrombocytopenia-related bleeding. This reduction was applied for all three injections of that cycle. Subsequent dose escalation to the original dose was allowed provided the patient tolerated the doses given at the 50% level. The dose of gemcitabine within a cycle was reduced to 50% in the event of Grade 3 leukopenia, neutropenia, or thrombocytopenia and withheld in the case of a Grade 4 hematologic toxicity. Gemcitabine was to be discontinued in the case of > Grade 2 nonhematologic toxicities, with the exception of Grade 3 nausea/emesis and alopecia. Administration continued up to ten cycles unless tumor progression, death, patient refusal, or unacceptable toxicity developed or the investigator believed that further treatment was no longer beneficial.

Response Criteria

Tumor response was assessed with target lesions at baseline, every second cycle, and at the end of treatment according to WHO criteria.¹³ Target lesions were required to be at least 2.5 cm in their largest dimension. Nodular thickening of the pleura was accepted as

TABLE 2
Patient and Tumor Characteristics in 27 Eligible Patients

Characteristic	No. of patients	Percentage
Gender		
Male	22	81
Female	5	19
Median age (yrs) (range)	62 (43–74)	
Performance status (WHO)		
0	6	22
1	18	67
2	3	11
TNM stage (UICC) ¹²		
I–II	11	41
III–IV	16	59
Asbestos exposure		
Yes	15	56
No	10	37
Unknown	2	7
Prior treatment		
Pleurodesis	14	52
Prior radiotherapy	3	11
Surgery	2	8
Baseline leukocyte count (× 10 ⁹ /L)		
Normal	11	41
Elevated ^a	16	59
Baseline platelet count (× 10 ⁹ /L)		
Normal	14	52
Elevated ^a	13	48
Baseline LDH		
Normal	26	96
Abnormal ^a	1	4

WHO: World Health Organization; UICC: International Union Against Cancer; LDH: lactate dehydrogenase.

^a Greater than 1.25 times the upper limit of the normal value of the population studied.

a target lesion if the thickening was at least 2 cm in its largest perpendicular dimension and associated with a bidimensional lesion. The use of computed tomography scans was mandatory for evaluation. Objective responses had to be confirmed by 2 measurements, at least 4 weeks apart, during which time no new lesions could appear and no existing lesion could enlarge. Toxicity was scored according to the common toxicity criteria of the National Cancer Institute completed by the NCIC.¹³

Pathology and Radiology Review

Patient suitability for enrollment was determined by the pathologic report at the treating institution. Central pathology review of available diagnostic tissue was performed by the LCCG reference pathologist (E.A.vM.). Routine histochemical stains (hematoxylin and eosin stains, periodic acid–Schiff stain after diastase digestion, and alcian blue with hyaluronidase

digestion stains) were performed. In addition, immunohistochemical staining with antibodies directed against pan-cytokeratin, vimentin, epithelial membrane antigen, carcinoembryonic antigen, and LeuM1 were performed at the discretion of the reference pathologist.¹⁵ Only patients with a definite or probable histologic diagnosis of pleural MM were considered eligible. Radiologic responses were reviewed by an independent radiologist.

Quality Assurance

As part of the quality assurance of this trial, a member of the EORTC Data Center (C.D.) made at least one on-site visit to all institutions during the study period. Compliance with protocol requirements was verified in the medical records of all patients, including eligibility, treatment, tumor response, toxicity, and follow-up.

Statistical Methods

This study was planned according to the Simon one sample, two stage testing procedure, having Type I and Type II error rates of < 10% each to differentiate between a response rate of 10% and one of 30%.¹⁶ Initial analysis was planned after 14 patients had been treated, and there was further accrual to a total of 25 patients if ≥ 1 objective responses were observed in the first 14 patients. The regimen would be considered for further evaluation if > 4 objective responses were observed, suggesting a true response rate of at least 30%. To compensate for ineligibility, some extra patients were included. The Kaplan–Meier method was used to estimate overall survival of all eligible patients.¹⁷

RESULTS

Patient Characteristics

Between June and December 1995, 32 patients were registered into the study from 8 institutes in Europe after written informed consent was obtained. The interval between diagnosis and inclusion in the study was 2 months (range, 0–18 months). Pathology review was completed for 20 of the 32 patients (63%) (Table 1). Of these, 19 patients (95%) were classified as having definite or probable MM and 1 patient was classified as having metastatic adenocarcinoma. The latter patient was considered ineligible, together with four other patients (one had received prior chemotherapy, two lacked measurable lesions, and in one patient chemotherapy was initiated before registration). In the remaining patients a review of the local pathologist's report confirmed the diagnosis. Some major characteristics of prognostic significance in the 27 eligible patients and their tumors are listed in Table 2.

TABLE 3
Toxicities (According to CTC) and their Study Drug Relation in 27 Eligible Patients^a

Toxicity (grade)	0	1	2	3	4	Drug relation ^b
Leukocytes	12	6	9	–	–	–
Granulocytes	11	5	3	6	2	–
Platelets	22	3	1	–	1	–
Hemoglobin	–	18	9	–	–	–
Infection	21	2	3	1	–	3
Allergy	25	2	–	–	–	–
Alopecia	21	6	–	–	–	–
Fever w/o infection	19	–	6	2	–	2
Dysrhythmias	25	2	–	–	–	–
Heart failure	22	2	–	3	–	–
Hypertension	24	–	–	3	–	2
Venous thrombosis	26	–	–	1	–	1
Edema	17	4	5	1	–	1
Anorexia	14	8	5	–	–	–
Nausea	7	13	6	1	–	–
Emesis	12	6	7	–	2	2
Diarrhea	23	2	1	–	1	2
Stomatitis	24	3	–	–	–	–
Other GI	21	2	3	1	–	3
Dyspnea	16	2	3	5	1	5
Cough	15	7	5	–	–	12
Arthralgia	24	1	1	1	–	2
Myalgia	21	4	1	1	–	–
Rigors/chills	20	6	1	–	–	–
Lethargy	11	9	5	2	–	1
Sweating	22	2	3	–	–	–
Flu-like syndrome	19	6	2	–	–	–
Renal failure	25	–	–	1	1	1

CTC: Common Toxicity Criteria; w/o: without; GI: gastrointestinal.

^a The highest Common Toxicity Criteria grade for each patient is reported.^b The number of patients whose toxicity (of any grade) was believed by the investigator to be unrelated or unlikely to be related to the administration of the study drug.

In total, gemcitabine was administered 386 times in 133 cycles; 13 administrations were not given, 5 of which were toxicity-related. Eight were due to obvious progression of the tumor at the time of scheduled administration of gemcitabine. The median number of cycles per patient was 5 (range, 1–12 cycles), with 12 patients receiving at least 6 cycles. A median relative dose intensity of 96% (range, 64–107%) was reached.

Toxicity

Details regarding toxicity are described in Table 3. The median neutrophil nadir count was $1.67 \times 10^9/\text{L}$ and the median platelet nadir count was $159 \times 10^9/\text{L}$. The following serious toxicities (\geq Grade 3) were believed to be related to drug administration: neutropenia, thrombocytopenia, nausea and emesis, fever, lethargy and flu-like syndrome, nonneutropenic infection, edema, and hypertension. In five instances hemato-

logic toxicity was the reason for omitting the gemcitabine dose on Day 15 within a cycle. Three patients went off study due to toxicity, including one after a drug-related, biopsy proven hemolytic-uremic syndrome developed, requiring hemodialysis for acute renal failure after the eleventh cycle. This persisted until the patient's death from tumor progression. Three patients experienced Grade 3 cardiac failure after the fourth and fifth cycles, respectively. It is unclear whether the latter episodes and the case of dyspnea reflect true drug toxicity or disease progression (e.g., by accumulation of pleural fluid). One additional patient died of intestinal obstruction and prerenal failure after the third cycle, but this was not believed to be drug related.

Response

Two patients (7%) refused further treatment after the first cycle and were considered treatment failures. The other eligible patients all were assessable for response. There were 2 partial responses (response rate of 7%; 95% confidence interval [95% CI], 1–24%), both of which were observed after 2 cycles at the site of the primary tumor and intrathoracic lymph nodes and confirmed after 4 cycles (Fig. 1). Both responses occurred in pathology-reviewed patients. The duration of response was 17 and 5 months, respectively. Two additional patients with partial responses were not confirmed and so were considered as achieving stable disease together with 13 other patients (56%), whereas 8 patients (30%) were found to have disease progression during chemotherapy.

Survival

The median survival after diagnosis was 10 months and was 8 months after the initiation of treatment (95% CI, 5–12 months), with 33% of patients still alive at 1 year (Fig. 2). At last follow-up, one patient still was alive.

DISCUSSION

Experts in the field of mesothelioma treatment agree that the results of available clinical studies justify the current policy of continuing to investigate new single agents in patients with this refractory tumor type.³ The rationale for selecting gemcitabine as an agent for Phase II testing in patients with MM was the observed activity in other chemoresistant solid tumors such as pancreatic carcinoma.⁹

In this study, only limited therapeutic activity of single agent gemcitabine against MM was observed at a dosage and schedule that commonly are employed in untreated patients. The patient characteristics and median survival time were similar to those of previous

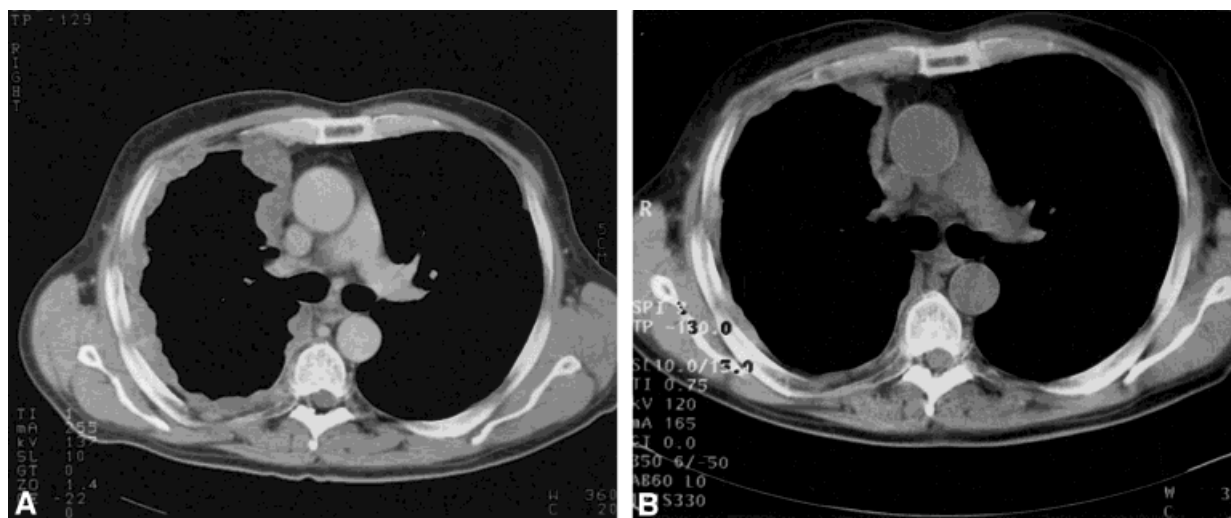


FIGURE 1. Computed tomography scan of the thorax in a patient with malignant pleural mesothelioma obtained (A) before and (B) after two cycles of gemcitabine shows a partial remission of the target lesions within the thorax. These findings were confirmed 4 weeks later.

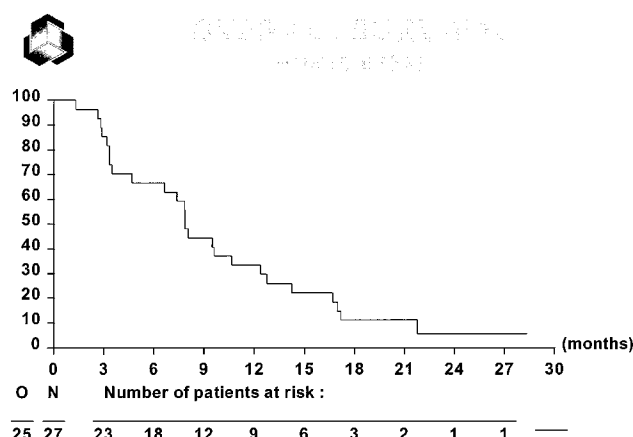


FIGURE 2. The overall survival (Kaplan-Meier plot) after the 27 eligible patients were registered on this study. EORTC: European Organization for Research and Treatment of Cancer.

EORTC studies. Two other trials examining gemcitabine treatment in patients with MM have been reported in abstract form.^{18,19} The Cancer and Leukemia Group B claims no significant activity among 13 evaluated patients treated with a three-times-weekly schedule of gemcitabine at 1500 mg/m².¹⁸ Conversely, Bischoff et al. reported a 30% response rate using the same schedule as in the current study.¹⁹ An additional 40% of their 16 patients experienced a clear symptomatic improvement. The reasons for these diverging results are unclear and await full publication of the manuscripts. Differences in methodology most likely account for the observed differences in response rate. In this study, as in others with single agent gemcitabine, hematologic toxicity was mild resulting in few dose re-

ductions and hence a high median dose intensity. Nonhematologic toxicity was equally well tolerated and its relation with the drug was not always easily discernable from disease progression. As reported previously, the occurrence of hemolytic-uremic syndrome requiring hemodialysis in 1 patient after 11 cycles of gemcitabine most likely was drug related.¹⁴

Several investigators have observed important clinical benefits and symptom improvement with chemotherapy, most notably in the areas of pain and analgesic consumption.^{19,20} Symptomatic improvement does not necessarily correlate with objective tumor response and can be considered evidence of the effectiveness of settings in which no standard life-prolonging or curative therapy exist.²¹ Based on these findings, the EORTC-LCCG will include thorough symptom assessment in its next Phase II trials in patients with MM.

The question arises whether testing gemcitabine as combination therapy (e.g., with cisplatin) is warranted. Both additive and synergistic effects of this combination have been described.^{22,23} However, to our knowledge combination chemotherapy in MM seldom has resulted in improved response rates or survival compared with single agents.²⁴ Furthermore, initial promising data are not always present in the final publication.²⁰ Thus, the recently reported response rate of 48% observed with cisplatin and gemcitabine in patients with MM is surprising and requires confirmation by a multiinstitutional trial.²⁵ Testing the latter combination is the aim of the next Phase II trial of the EORTC-LCCG.

In the current study gemcitabine was well toler-

ated at this dose and schedule in patients with pleural MM that was untreated by chemotherapy. The limited activity observed does not warrant further testing of the drug as a single agent in this disease.

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