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Original Paper

Activity of Gemcitabine in Patients with Non-small Cell Lung Cancer: A Multicentre, Extended Phase II Study

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Gemcitabine is a novel nucleoside analogue with activity in solid tumours. This study assessed the objective response rate to gemcitabine given weekly intravenously at a dose of 1250 mg/m^2 for 3 weeks followed by 1 week of rest (one cycle) in chemonaive patients with inoperable non-small cell lung cancer (NSCLC). 161 patients with NSCLC were recruited from 10 sites in nine countries. Most patients had stage IIIb (31.3%) or IV (64.6%) disease, and 93.8% had a performance status of 0 or 1 according to the WHO scale. Of 151 evaluable patients, there were 3 complete responses and 30 partial responses lasting at least 4 weeks for an objective response rate of 21.8% (95% CI 15.5–29.3%). All responses were validated by an extramural Oncology Review Board. The mean duration of response was 8.8 months. The mean survival for all patients (16.1% of patients still alive 26 months after last patient started treatment) was 11.5 months. Improvements were also observed in secondary efficacy parameters such as performance status, weight, analgesic requirement, pain, and other disease-related symptoms including cough, dyspnoea, haemoptysis, anorexia, somnolence and hoarseness. Haematological and non-haematological toxicity was mild given the biological activity of gemcitabine. This study confirms gemcitabine as one of the most active agents in NSCLC with the added benefit of a modest toxicity profile and ease of administration on an out-patient basis. Gemcitabine is a suitable candidate for combination chemotherapy in patients with NSCLC.

Key words: chemotherapy, gemcitabine, non-small cell lung cancer
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INTRODUCTION

THE RESULTS of single agent and combination therapy against inoperable non-small cell lung cancer (NSCLC) do not modify substantially the clinical outcome in these patients. In 1985, only five agents, cisplatin, ifosfamide, mitomycin, vinblastine and vindesine, were reported to have response rates >15% [1]. Etoposide is often included in this list despite its low response rate (8%) [2] because it potentiates the activity of cisplatin. Currently, more than 10 agents are considered to have response rates >15%, including paclitaxel, docetaxel, vinorelbine, high-dose epirubicin, fotemustine and irinotecan (CPT-11). Outside clinical trials, combination chemotherapy is usually given and produces response rates from 25 to 50%, although median survival of treated patients still remains low in the range 5–12 months [3]. There is a clear need, therefore, for new agents which can achieve or surpass these response rates and survival times with a more acceptable toxicity profile, and which can also improve patient quality of life.

Gemcitabine is a novel nucleoside analogue with unique activity against a range of solid tumours. Gemcitabine is converted intracellularly into: (a) gemcitabine diphosphate

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which inhibits ribonucleotide reductase, the enzyme responsible for synthesising deoxynucleotide triphosphates for DNA synthesis [4]; (b) gemcitabine triphosphate which competes with dCTP for incorporation into DNA [4]. Gemcitabine allows more nucleotides to pair before DNA replication is terminated, in such a way that "proofreading" exonuclease enzymes are less able to detect, excise and repair the DNA lesion [4]. Gemcitabine promotes its own activation within the cell and reduces its clearance from the cell via at least three mechanisms of "self-potentiation" [5–7]. These self-potentiating mechanisms explain why, compared with the structurally similar ara-C, gemcitabine persists within tumour cells at higher levels and for longer periods, and why gemcitabine exhibits greater and broader activity against solid tumours.

In animal tumour models, gemcitabine has broad activity across a range of tumours including myeloma, mammary adenocarcinoma, ovarian carcinoma, lymphosarcoma, melanoma and leukaemia [8]. In human xenograft models, gemcitabine was active against colon, head and neck, mammary, NSCLC, small-cell lung, pancreatic, gastric and liver carcinomas [9–11].

Phase I studies examined a number of dose schedules in which gemcitabine was administered as a 30-min infusion. A daily schedule was not pursued because of severe flu-like symptoms and profound hypotension in some patients (which were dose limiting at approximately 7 mg/m^2) [12]. The twice-a-week schedule was abandoned due to flu-like symptoms and dose-limiting thrombocytopenia (MTD 65 mg/m^2) [13]. Dosing every other week was evaluated (MTD 4560 mg/m^2, myelosuppression) but efficacy was poor, and pharmacological studies suggested that less drug should be administered more frequently [14]. The weekly schedule (gemcitabine administered once a week for 3 weeks followed by a week of rest) provided a combination of activity and acceptable tolerability, with the dose-limiting toxicity being thrombocytopenia (MTD 790 mg/m^2 in previously-treated patients) [15]. Based on phase I investigations, the weekly schedule was carried forward for the initial phase II studies at planned starting doses of 800 mg/m^2. In the absence of significant toxicity, this starting dose was later increased up to 1200 mg/m^2 in a number of phase I–II studies with no evidence of increased toxicity. It was, therefore, felt that 1250 mg/m^2 was a safe starting dose for gemcitabine.

In phase II trials, activity has been seen in human solid tumours such as NSCLC [16, 17], previously-treated epithelial ovarian cancer [18], advanced breast cancer [19] and small-cell lung cancer [20], and in a cohort of a large phase I study, evidence of activity was also seen in bladder cancer [21].

This paper reports a large, multicentre, extended phase II study, designed to confirm the activity and toxicity profile of gemcitabine administered as a 30-min intravenous infusion, once a week for 3 weeks followed by a week of rest in patients with inoperable NSCLC.

PATIENTS AND METHODS

Criteria for inclusion

Patients were included in this multicentre, open-label, non-randomised, phase II trial if they were aged 18–75 years, had histologically or cytologically confirmed inoperable stage IIIa, IIIb or IV (according to the American Joint Committee on Cancer) [22] NSCLC (excluding large-cell variant), who were not eligible for curative radiotherapy or surgery. Patients should not have received prior radiotherapy or chemotherapy regimens, except local radiotherapy for pain control. They had to have performance status 0 to 2 according to the World Health Organisation (WHO) scale, bidimensionally measurable lesions as assessed by X-ray, computed tomography scan, physical examination or other diagnostic techniques as appropriate, life expectancy of at least 12 weeks, adequate bone marrow reserves defined as white blood cell count $\geq 4 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, haemoglobin ≥ 10 g/dl (6.7 mmol/l). Patients were excluded if they had current or previous CNS metastases, secondary malignancy (except *in situ* carcinoma of the cervix or adequately treated basal cell carcinoma of the skin), or life-threatening metastases.

High dose steroids were not allowed for at least 3 weeks before enrolment and also during the study. Male and female patients had to take medically approved contraceptive precautions, and females with childbearing potential had to have a negative pregnancy test on admission and were not to be breast feeding.

Patients were excluded if they had inadequate liver function defined as total bilirubin >2 times normal and/or aspartate transaminase (AST, SGOT) >3 times normal and/or alanine transaminase (ALT, SGPT) >3 times normal; AST and/or ALT could be elevated up to five times normal in patients with known liver metastases. Patients were also excluded if they had inadequate renal function defined as creatinine higher than the upper normal range; or if uric acid was outside $1.5 \times$ normal range. Other exclusion criteria were >10% weight loss in the previous 3 months; acute serious infection; abnormal prothrombin time (>1.5 times normal) and/or abnormal partial thromboplastin time (>1.5 times normal); active uncontrolled hypercalcaemia; serious concomitant systemic disorders deemed incompatible with the study at the discretion of the investigator; significant neurological (such as seizures) or psychiatric disorders.

The protocol was approved by the European Ethical Review Committee and by local ethics committees. Informed consent was obtained from all screened patients. The tumour histology and cytology of all patients was to be reviewed by an independent pathologist to ensure that it was adenocarcinoma, squamous cell or mixed adenosquamous carcinoma of the lung.

Treatment

Treatment was given on an outpatient basis. Gemcitabine was given at an initial dose of 1250 mg/m^2 and administered intravenously over 30 min, once a week, for 3 weeks, followed by a week of rest, this constituting a cycle. Treatment in responding patients or patients with stable disease was discontinued if disease progression or severe toxicity occurred. Patients who had completed one cycle of therapy at 1250 mg/m^2 could have their subsequent dose increased by up to 20% provided they had shown no significant change in haematological parameters required for inclusion, and non-haematological toxicity had not been greater than grade 1. If patients tolerated this escalation for the whole cycle, subsequent cycles could be given in dose escalations up to 20% and again for successive courses. Dose adjustments were made based on assessments of haematological and non-haematological toxicities. In particular, only 75% of doses were administered for granulocytes $0.5–0.9 \times 10^9$/l and/or platelets $50–99.9 \times 10^9$/l. If the cell counts fell below the lower level of either range, the injection was omitted. Patients with grade 3 non-haematolog-

ical toxicity could have a 50% dose reduction. Patients with life-threatening grade 4 non-haematological toxicity were removed from the study unless they were responding, in which case a 50% dose reduction could be instituted when toxicity resolved.

No other chemotherapy, hormonal therapy or experimental medications were permitted while the patients were in the study. Patients with disease progression discontinued gemcitabine treatment and were offered alternative specific antitumour therapy. However, if an existing lesion became more painful and was not accompanied by other objective changes indicating progression, palliative local irradiation could be applied without discontinuing treatment, as long as other measurable sites were being observed. The irradiated lesion was not then considered a targeted area of measurable disease.

Evaluation of response and toxicity

An extramural Oncology Review Board evaluated the response of each investigator-determined responder to gemcitabine therapy by review of the clinical history, signs, symptoms and appropriate radiological tests. The evaluations were conducted using standard WHO criteria for measurable disease [23]: complete response, partial response, stable disease and progressive disease.

A responder was defined as any patient who exhibited a complete or partial response lasting for at least 4 weeks, and validated by the Oncology Review Board. The same baseline assessment method was to be used consistently for efficacy evaluation throughout the study. All patients who completed at least one therapy course (three injections and a tumour reassessment after 1 week of rest) were analysed for efficacy. All enrolled patients were analysed for safety and for survival analysis. Patients who developed central nervous system metastases were regarded as having developed progressive disease and were discontinued from treatment. Patients were reviewed at every monthly visit in order to assess efficacy and toxicity. After discontinuation of treatment, patients were evaluated every 3 months in order to assess survival and disease-free status.

In assessing tumour response and survival, the following definitions were used: time to response (time from first injection to first objective response); time to progression (time from first injection to date of declaration of progression); duration of response (for partial responses, time from first injection to time of progression, for complete responses, time from declaration of complete response to time of disease progression); survival (time from first injection to death or last follow-up visit).

Efficacy data analysis methods included tumour response rate and calculation of the 95% confidence intervals, Kaplan–Meier analysis for survival and time to progression, including quartiles for each variable (Lifetest Procedure in Statistical Application Software), Kaplan–Meier curves and quartiles for duration of response.

Predefined scores for supportive response parameters such as performance status, weight gain (5% or more), analgesic consumption or pain level, and for other disease-related symptoms reflecting either patient benefit or clinical condition were also collected prospectively for all patients. To be considered an improvement, these changes from baseline had to be maintained for at least 4 weeks.

Not all patients had the potential to improve their secondary efficacy measures, therefore only "eligible" patients (i.e. those who had prestudy measures which could improve) are included in the analysis of secondary efficacy parameters.

RESULTS

Patient population

Between January and December 1992, 161 patients were recruited at 10 centres in eight European countries and Canada. All investigators recruited at least 5 evaluable patients. The baseline disease characteristics of the patient population are detailed in Table 1. Most patients were stage IV (64.6%) with performance status 1 (83.2%) and having adenocarcinoma (52.2%). The most frequent sites of distant metastases were the contralateral lung (19.6%), bone (18.3%), liver (15.7%) and adrenal glands (13.1%). 18 patients had previously had tumour resection.

Primary efficacy

Of 161 patients enrolled in the study, 151 (93.8%) patients fulfilled all evaluability criteria for response evaluation. 10 patients were not evaluable for efficacy analysis because of insufficient therapy (8 patients received less than one cycle of therapy and discontinued from the study for reasons other than toxicity, in 5 cases due to early progressive disease), concomitant radiotherapy of a target lesion (1 patient) and no tumour assessment (1 patient).

Of the 151 qualified patients, 3 patients achieved a complete response and 30 patients experienced a partial response for an overall response rate of 21.8% (95% confidence interval, CI

Table 1. *Summary of patient characteristics (all* 161 *patients enrolled)*

Males/females	124/37
Age (years)	
Mean ± S.D.	59.0 ± 8.3
Range	35–75
Current smokers/ex-smokers	54/91
Histology	
Squamous	70 (43.5%)
Adenocarcinoma	84 (52.2%)
Adenosquamous	6 (3.7%)
Unspecified NSCLC	1 (0.6%)
Grade of differentiation	
Moderate	32 (19.9%)
Poor	48 (29.8%)
Undifferentiated	6 (3.7%)
Unknown	52 (32.3%)
Well differentiated	23 (14.3%)
Stage	
Stage IIIa	7 (4.3%)
Stage IIIb	50 (31.1%)
Stage IV	104 (64.6%)
Performance status	
0	17 (10.6%)
1	134 (83.2%)
2	10 (6.2%)
Level of analgesia	
0	88 (54.7%)
1	31 (19.3%)
2	21 (13.0%)
3	21 (13.0%)

Table 2. Duration of response, survival, and time to disease progression in months (all 161 patients)

	All patients
Duration of response	
Median (range)	7.6 (2.6*–23.8*)
Mean	8.8
Survival	
Median (range)	9.4 (0.1–30.1*)
Mean	11.5
Time to progression	
Median (range)	4.6 (0.1*–30.1*)
Mean	6.3

* Censored observations.

15.5–29.3%); all responses were confirmed by an extramural Oncology Review Board. Responses were observed at nine of the 10 study centres, and the response rate ranged from 9.1% to 38.5% among these centres.

9 (27.3%) of the 33 responders were female, which is consistent with the sex ratio in the study population. There were no differences in response rate by disease stage, 21.9% for stage IV disease and 21.8% for stage IIIa and IIIb disease. Response by cell type was 15.4% for adenocarcinoma and 25.8% for squamous cell carcinoma. Response by grade of differentiation was 31.2% for moderately differentiated and 20.8% for poorly differentiated tumours.

Duration of response, survival and time to disease progression, analysed 26 months after the last patient started treatment, are given in Table 2. The mean time to response (partial or complete response) was 2.1 months with a mean duration of response of 8.8 months. By the second cycle (8 weeks after starting therapy), approximately 67% of the eventual responders had been declared as such. 9 patients achieved partial response status at cycle 3 and 2 patients at cycle 4. Mean time to disease progression in all patients was 6.3 months. Median and mean survival in the population was 9.4 and 11.5 months, respectively, with 16.1% of patients still alive at the cut-off date. The Kaplan–Meier curve for survival in all patients is shown in Figure 1. The median survival rates for patients with stage III and IV disease were 10.4 and 7.6 months, respectively. When comparing patients aged <65 and $\geqslant 65$ years, males and females, and patients with tumours of different cell type, survival rates were similar. Patients with PS 0 on entry had a median survival of 25 months compared with 8 and 6.3 months for those with PS 1 and 2, respectively.

Disease progression data during or after discontinuation from the study were available in 118 (73.3%) patients. Tumour progression was reported in 65 (55.1%) of these patients. The main sites of local or distant metastases where progression was observed during the study were lung (15.2% patients), liver (14.4% patients) and bone (11.1% patients). 71 patients (44.1%) received poststudy therapy after discontinuation of gemcitabine treatment: 4 patients underwent surgery while the other 64 patients received radiation therapy or chemotherapy.

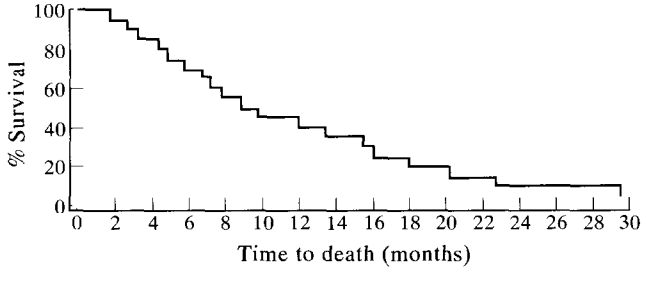

Figure 1. Kaplan–Meier curve for survival (all 161 patients).

Supportive response

No significant decrease in weight was experienced over the course of the study in 114 patients (70.8%) with 6 patients (4.0%) experiencing at least a 5% increase over prestudy body weight. Performance status improved in 12 (9%) of 134 eligible patients. However, these patients already had good performance status on entry. Of the 10 patients with PS 2 on entry, 3 improved to PS 1. 18 (27.7%) of the 65 eligible patients reduced their analgesic requirements. Of 83 eligible patients who experienced pain at study entry, these symptoms improved in 26 (31.3%) patients. Other disease-related symptom improvements included: cough (37 of 105 eligible patients, 35.2%); dyspnoea (18 of 81, 22.2%), haemoptysis (17 of 25, 68.0%).

Improvements in other disease-related symptoms were also observed for: anorexia (9/30 patients, 30.0%), fever (8/15, 53.3%), insomnia (9/15, 60.0%), pleural effusion (10/29, 34.5%), somnolence (12/28, 42.9%), sweating (10/13, 76.9%) and hoarseness (10/18, 55.6%).

The median durations of symptom improvement were: performance status, 18 weeks; analgesic level, 12 weeks; cough, 13 weeks; dyspnoea, 12 weeks; haemoptysis, 12 weeks; and pain, 11 weeks.

Supportive therapy

Of the 161 patients enrolled, 22 (13.7%) received one or more blood transfusions. The most common other supportive therapy was radiotherapy given to localised lesions requiring palliation in 7 patients (4.3%). The most frequently prescribed concomitant medications were acetaminophen (26.8% of patients) and metoclopramide (26.1%). Other antiemetics included prochlorperazine (19.0%) and ondansetron (17.0%) which were given either prophylactically (5.2%) or therapeutically (11.8%). Other frequently used analgesics included codeine/acetaminophen, morphine, diclofenac and aspirin. Anxiolytics, laxatives and bronchodilators were also often prescribed.

Summary of dose administrations

The mean number of cycles completed was 3.7 (range 0–14). Gemcitabine was generally well tolerated; only 6.3% of all injections were omitted and only 4.6% were reduced. There was no apparent trend toward dose reductions or escalations over consecutive cycles. In addition, 26.9% of injections were escalated above the protocol-defined starting dose of 1250 mg/m^2 and the maximum dose received was 2592 mg/m^2. The effective patient dose intensity (mg/m^2/injection) was calculated as total cumulative dose given to the patient divided by number of protocol-defined injections that should have occurred in ideal circumstances for the period during which the patient was on study. For gemcitabine, the mean effective dose was 1250 mg/m^2 which was the same as the protocol-planned initial dose.

Table 3. Maximum WHO grades for laboratory toxicity (% of patients, all 161 patients)

Toxicity parameter	0	1	2	3	4
Alkaline phosphatase	60.8	29.1	8.2	1.9	0.0
Alanine transaminase	29.7	31.6	25.9	10.8	1.9
Aspartate transaminase	26.6	41.8	22.8	6.3	2.5
Bilirubin	90.4	8.3	0.0	0.6	0.6
Blood urea nitrogen	84.8	14.6	0.6	0.0	0.0
Creatinine	94.9	5.1	0.0	0.0	0.0
Haemoglobin	32.3	41.1	21.5	4.4	0.6
White blood cells	41.8	27.2	24.1	7.0	0.0
Segmented neutrophils	32.9	17.7	24.1	19.6	5.7
Platelets	82.9	8.2	7.6	1.3	0.0
Proteinuria	61.5	30.1	8.3	0.0	0.0

WHO laboratory toxicity

WHO laboratory toxicities are reported in Table 3 as maximum toxicity experienced by patients. Only 2 patients with grade 3/4 leucopenia and/or neutropenia experienced WHO grade 1 infection with no septic complications. Leucopenia and thrombocytopenia were the two most common reasons for dose reductions or omissions; neither showed a cumulative tendency. There was no grade 3 or 4 renal toxicity for creatinine and blood urea nitrogen and there was no macroscopic haematuria.

WHO clinical toxicity

Clinical toxicity is summarised in Table 4. For the parameters reported, only 2 patients had WHO grade 4 toxicity, both these being nausea/vomiting. Grade 3 WHO toxicity was also infrequent for all parameters. 16 patients (10.0%) reported WHO grade 3 nausea and vomiting, defined as vomiting that required therapy, but only 3 of these patients were hospitalised due to nausea and vomiting. 6 of the patients who experienced grade 3 vomiting were already receiving prophylactic anti-emetic treatment. Alopecia was minimal. The majority of patients (90%) had no hair loss. There was no WHO grade 3 or 4 fever or infection. Oedema and peripheral oedema were reported by 21.1% and 7.5% of patients, respectively. This oedema was not associated with any evidence of cardiac, hepatic or renal failure. These events were frequently drug related, were mild or moderate and not clinically relevant. Only 3 patients reported serious oedema, although 2 discontinued gemcitabine treatment due to these events.

Table 4. WHO grade clinical toxicity (% of patients)

Toxicity parameter	0	1	2	3	4
Allergic	92.5	6.3	1.3	0.0	0.0
Constipation	94.4	3.8	1.3	0.6	0.0
Cutaneous	74.4	19.4	6.3	0.0	0.0
Diarrhoea	94.4	4.4	0.6	0.6	0.0
Fever	46.3	32.5	21.3	0.0	0.0
Cardiac function	98.8	1.3	0.0	0.0	0.0
Hair	90.0	5.6	4.4	0.0	0.0
Haemorrhage	97.5	1.3	1.3	0.0	0.0
Infection	91.3	6.3	2.5	0.0	0.0
Nausea and vomiting	35.0	33.8	20.0	10.0	1.3
Oral	95.6	2.5	1.3	0.6	0.0
Pain	81.9	7.5	8.8	1.9	0.0
Pericarditis	99.4	0.6	0.0	0.0	0.0
Peripheral neurotoxicity	95.0	4.4	0.6	0.0	0.0
Pulmonary	96.3	1.9	0.6	1.3	0.0
Cardiac rhythm	95.6	3.1	0.6	0.6	0.0
State of consciousness	94.4	3.8	1.9	0.0	0.0

DISCUSSION

The current treatment of advanced NSCLC is far from satisfactory, in terms of objective response rates, duration of survival and quality of life. It is important that these endpoints are evaluated objectively in new investigational drugs. This study was conducted to confirm the activity and toxicity profile of one such agent, gemcitabine, a novel pyrimidine antimetabolite. The majority of patients in this study had very advanced stage disease, 31.1% of patients were in stage IIIb and 64.6% in stage IV. There were 3 complete and 30 partial responses for an overall response rate of 21.8%. Responders were seen in poorly, moderately and well differentiated tumour categories and in squamous, adenocarcinoma, and mixed cell types and in both stage III and IV metastatic disease. Median time for response was 1.9 months. Of interest, the mean effective dose in this study was 1250 mg/m^2 which reflected the protocol commencing dose.

Mean survival seen in this study, with 16% of patients alive to date, was 11.5 months for all patients. These figures compare well with data from four randomised trials of best supportive care versus combination chemotherapy in stage III and IV NSCLC in which median survivals were 2.3–5.3 months for the best supportive care arms and 6.8–8.6 months for combination chemotherapy arms [3].

The 22% objective response rate seen in this study is similar to those observed with gemcitabine in NSCLC by Anderson and colleagues (22.5%) [17] and Abratt and colleagues (20%) [16]. All responses in the three gemcitabine NSCLC studies were independently validated by an extramural Oncology Review Board. Given these strict criteria, response rates of 20–22.5% are most encouraging for a single agent. Published phase II single-agent response rates above 15% (but not externally validated) in stage III and IV NSCLC for other investigational or recently introduced drugs, have been reported for vinorelbine (32.8%, 22%; 14% in a large multicentre, randomised study) [24–26], edatrexate (10-EDAM, 13.3%, 10%, 32% excluding "minor" responses) [27–29], paclitaxel (20.8%, 24%) [30, 31], irinotecan (CPT-11, 31.9%) [32], high-dose epirubicin (25%) [33].

Assessment of symptom improvement is not common in trials of NSCLC. However, confirmation of objective activity of gemcitabine was seen in this study, namely subjective improvements in secondary efficacy parameters such as performance status, weight, analgesic requirement and pain relief. Improvements were also seen in disease-related symptoms such as cough, dyspnoea, haemoptysis, anorexia, somnolence and hoarseness.

Gemcitabine was active, well tolerated and easy to administer on an outpatient basis. Given the biological activity of gemcitabine, haematological toxicity was particularly mild. Neutropenia was the most frequent dose-limiting toxicity but WHO grades 3 and 4 were only seen in 19.6% and 5.7% of patients, respectively. WHO grade 3 leucopenia occurred in 7.0% of patients, and there was no grade 4 toxicity. Only 2 patients with this myelosuppression had concurrent mild

infection. The incidence and severity of myelosuppression with gemcitabine is lower than that reported for traditional agents used in NSCLC. Myelosuppression did not result in hospitalisation or infection in most patients, and supportive therapy with colony stimulating factors was not necessary. Given the debilitating natural history of the disease, it is encouraging that 86% of patients did not require any transfusions during the study. The incidence of WHO grade 3 and 4 nausea and vomiting was 10% and 1.3%, respectively, again much lower than is seen with cisplatin-based chemotherapy for NSCLC. In this study, any episode of nausea and vomiting was controlled by standard anti-emetics, and rehydration and treatment with 5-HT_3-receptor antagonists were usually not necessary. The modest toxicity profile seen with gemcitabine suggests that this agent can be easily and routinely administered on an outpatient basis and that supportive inpatient hospitalisation for myelosuppression or rehydration will usually not be required.

In conclusion, the almost 22% response rate seen in this study and independently validated by an extramural Oncology Review Board confirms gemcitabine as an effective single agent in NSCLC. The activity of gemcitabine together with its mode of action and modest and non-overlapping toxicity support the investigation of gemcitabine in combination studies for the treatment of advanced NSCLC. Trials are currently underway investigating the combination of gemcitabine with cisplatin, carboplatin, vindesine and ifosfamide.

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