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# Safety profile of gemcitabine, a novel anticancer agent, in non-small cell lung cancer

**Hernan Cortes-Funes, Christophe Martin,[1] Raymond Abratt[2] and Birthe Lund[3]**
University Hospital, 12 De Octubre, Carretera Andalucia KM 5.5, 28041 Madrid, Spain. Tel (+34)1 390 8003; Fax: (+34)1 460 3310. [1]Lilly Research Centre, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU20 6PH, UK. [2]Groote Schuur Hospital, University of Cape Town, 7925 Cape Town, South Africa. [3]Rigshospitalet and Herlev Hospital, 2100 Kobenhavn, Denmark.

**Gemcitabine is a novel anticancer agent showing activity with relatively mild toxicity across a range of solid tumors including non-small cell lung cancer (NSCLC). In studies using similar doses and schedules, consistent response rates of around 20% were recorded in NSCLC. In an integrated safety study using data from 360 patients with NSCLC, gemcitabine exhibits a mild safety profile for such an active drug. Hematological toxicity is mild and short lasting, and the level of infection associated with this degree of myelosuppression was low. Mild transaminase elevations occurred frequently but were not progressive or dose limiting. There was no evidence of cumulative hepatic or renal toxicity. Nausea and vomiting were mild, rarely dose limiting and generally well controlled with standard antiemetics. Mild flu-like symptoms were experienced in a small proportion of patients and rarely resulted in discontinuation. Where edema or peripheral edema were experienced, there was no evidence of any association with cardiac, hepatic or renal failure. Hair loss was rare and there was no grade 4 alopecia. In conclusion, gemcitabine is a promising new agent in the treatment of NSCLC. Its mild toxicity which is non-overlapping with other cytotoxics has prompted investigation into its use in combination with other chemotherapy regimens.**

*Key words*: Chemotherapy, drug therapy, non-small cell lung carcinoma.

## Introduction

The incidence of lung cancer continues to rise and remains one of the main causes of death from malignant disease. Approximately 80% of cases are of the non-small cell sub-type.[1] Many of these patients with non-small cell lung cancer (NSCLC) have either locally advanced or metastatic disease at diagnosis and are therefore ineligible for curative surgery. The prognosis of patients with advanced NSCLC is poor, with a median survival duration not exceeding 8–9 months in large prospective studies. At present, surgery offers the only prospect of a cure to patients with NSCLC. However, surgery is inappropriate in the later stages of the disease and even in the earlier stages may not be able to control spread. Chemotherapy seems to represent the best chance for an improved outcome. Although the results of some individual studies with chemotherapy are equivocal, a meta-analysis indicated a beneficial effect of chemotherapy on survival when compared with best supportive care.[2]

Many cytotoxic agents have been used to treat NSCLC, but only a few drugs have been reported to yield reproducible objective response rates greater than 15%, including ifosfamide, vindesine, vinblastine, cisplatin and mitomycin.[1] Administering these drugs in combination may increase response rates. However, these drugs have toxic effects which may reduce the patients' quality of life and, therefore, it is necessary to assess new drugs which combine efficacy with modest toxicity.

Gemcitabine is a novel nucleoside analog anticancer agent which has demonstrated high activity against a range of human tumor xenografts including lung tumors[3–9] and is currently undergoing extensive clinical evaluation.

Activity has been observed in advanced breast cancer,[10] advanced pancreatic cancer,[11,12] previously treated epithelial ovarian cancer,[13] small cell lung cancer,[14] bladder cancer,[15] and head and neck cancer.[16] Four studies examined the efficacy of gemcitabine in patients with NSCLC.[17–20] All responses were validated by an independent Oncology Review Board and in three of these NSCLC studies, response rates of around 20% were observed (Table 1). Although the response rate in one small study of only 34 patients was 3%, it should be noted that the dose administered was significantly lower than in all the other studies. In addition, patients in this study had a higher median age and a higher incidence (almost 20%) of prior radiotherapy to the primary

Correspondence to H Cortes-Funes

**Table 1.** Protocol designs and objective tumor response rates in NSCLC studies (from references 17–20 and data on file, Eli Lilly and Company)

| Study | Protocol design | | | | | | Response rate | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of patients (enrolled/ qualified) | Starting dose ($mg/m^2$) | Previous chemotherapy | Age range (years) | Histologic cell type | Performance status (Zubrod Scale) | Complete responses | Partial responses | Overall response rate (%) (95% confidence interval) |
| US study[17] | 34/31 | 800 | no | 18–75 | any NSCLC | 0, 1 | 0 | 1 | 3.2<br>0.08–16.7% |
| Abratt *et al.*[18] | 84/76 | 1000 or 1250 | no | ⩾ 18 | any NSCLC | 0, 1 | 2 | 13 | 19.7<br>11.5–30.5 |
| Anderson *et al.*[19] | 82/71 | 800 or 1000 | no | 18–75 | squamous/ adenocarcinoma | 0, 1, 2 | 0 | 16 | 22.5<br>13.0–34.0 |
| Gatzemeier *et al.*[20] | 161/151 | 1250 | no | ⩾ 18 | any NSCLC except large cell | 0, 1, 2 | 3 | 30 | 21.9<br>15.3–28.4 |

thoracic tumor, and this may account for the lower response rate observed. The median durations of response in the three 'positive' studies varied from 7.6 to 12.7 months. The overall median, i.e. survival including responders and non-responders, was similar across the studies (range from 8.1 to 9.2 months).

Overall, the safety profile of gemcitabine is good, which is unusual for such an active agent. There was a particularly low incidence of those adverse effects normally associated with cytotoxic agents, i.e. myelosuppression, nausea and vomiting, and alopecia. In order to assess the safety profile of gemcitabine in patients with NSCLC, the safety data from the four clinical trials has been combined. Out of a total of 361 chemonaive patients who were enrolled into these studies in NSCLC, 360 patients received at least one dose of gemcitabine and were included in the integrated safety analysis.

Gemcitabine was administered as a 30 min infusion once a week for 3 weeks followed by a week of rest (1 cycle). Initially, based on the results of phase I studies, a starting dose of 800 $mg/m^2$/week was used. However, it was found that chemonaive patients could tolerate higher doses and in the later studies the dose was increased to 1000 and 1250 $mg/m^2$. The mean dose per patient was defined as the cumulative dose ($mg/m^2$) a patient received, divided by the theoretical number of injections the patient should have received as defined by the protocol. Therefore, the mean dose per patient reflects all the doses a patient received and also takes account of the fact that doses may have been delayed or administered in advance, thus providing a better estimate of the dose intensity. In these four studies, the mean of the mean dose per patient was 1119 $mg/m^2$ per injection and the median was 1167 $mg/m^2$. The mean number of cycles received per patient was 3.7.

The safety data was collated and assessed using the WHO toxicity grading scale, which is the established assessment of the toxicity of cytotoxic drugs. The WHO grades reported in these gemcitabine studies are the maximum reported at any time for the patient on the study and therefore represent a rigorous criterion for assessment.

## Laboratory toxicity

All 360 patients were assessed for laboratory toxicity. Table 2 summarizes the maximum WHO toxicity grade scores which were assigned irrespective of drug causality.

**Table 2.** Summary of maximum WHO toxicity grades for laboratory data (% of patients) ($n = 360$)

| Toxicity parameter | Maximum WHO grades | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Alkaline phosphatase | 52.4 | 32.4 | 13.2 | 2.0 | 0.0 |
| Alanine transaminase | 30.0 | 33.5 | 24.3 | 9.3 | 2.9 |
| Aspartate transaminase | 32.8 | 42.7 | 17.6 | 5.4 | 1.5 |
| Bilirubin | 91.5 | 7.1 | 0.8 | 0.3 | 0.3 |
| Blood urea nitrogen | 84.3 | 13.3 | 2.4 | 0.0 | 0.0 |
| Creatinine | 93.5 | 5.9 | 0.3 | 0.3 | 0.0 |
| Hemoglobin | 35.5 | 40.3 | 18.3 | 5.1 | 0.8 |
| White blood cells | 45.1 | 23.7 | 23.7 | 7.0 | 0.6 |
| Segmented neutrophils[a] | 38.9 | 16.4 | 19.9 | 19.9 | 4.9 |
| Platelets | 83.7 | 8.5 | 5.6 | 1.1 | 1.1 |

[a]Segmented neutrophils have been converted to WHO scores using granulocyte count criteria.

### Hematological effects

Anemia was generally considered moderate. Grade 3 and 4 toxicity was recorded in only 5.1 and 0.8% of patients, respectively. There was no evidence of cumulative toxicity in the later cycles of gemcitabine treatment. Overall, anemia was not considered to be a significant problem and was managed with the use of conventional transfusions.

The incidence of thrombocytopenia was low and mild (grade 3 and 4 toxicities were each recorded in 1.1% of patients), and of no clinical relevance.

Leukocyte grade 3 and 4 toxicity was recorded in 7.0 and 0.6% of the population. Counts of segmented neutrophils, a more sensitive indicator of toxicity than the total white cell count, were converted to WHO toxicity scores using criteria for granulocyte toxicity. Grades 3 and 4 toxicity were recorded in 19.9 and 4.9% of patients, respectively. The incidence of infection associated with this level of neutropenia was low; none of the patients had febrile neutropenia associated with grade 4 neutropenia. No grade 3 or 4 infection toxicity was recorded in patients from the studies where grades were assigned after assessment of causality. In studies where grades were assigned irrespective of causality, grades 3 and 4 toxicity were recorded in only 1.7 and 0% of patients, respectively. There was no evidence of cumulative toxicity.

### Hepatic effects

WHO grade 3 and 4 toxicity was as follows: ALT 9.3 and 2.9%; AST 5.4 and 1.5%; alkaline phosphatase 2.0 and 0%; bilirubin 0.3 and 0.3%. The toxicity was manifest as a transient, asymptomatic, rapidly reversible elevation of the enzymes which was rarely of clinical relevance. It should also be noted that these WHO grades were automatically derived by the computer from the actual laboratory values and therefore included patients who had abnormal liver function tests before study entry, as well as patients who developed liver metastatic disease while on study. When an analysis was performed on patients from all gemcitabine studies regardless of tumor type, it was found that although rises in transaminases occurred in patients with both normal and abnormal liver function at entry, they were less marked in the former group.[21]

### Renal effects

WHO grade 3 toxicity of blood urea nitrogen (BUN) and creatinine was very low, 0 and 0.3% respectively. No WHO grade 4 toxicity was recorded for these laboratory values. Mild proteinuria and hematuria were commonly reported but were rarely of clinical significance. (These two parameters are included in Table 3 as they were assessed for causality.) Renal toxicity as assessed by BUN and plasma creatinine was not classified as a significant problem although four cases of renal failure of uncertain etiology occurred during studies of gemcitabine in NSCLC.

## Symptomatic toxicity

Symptomatic adverse effects are reported here for two studies ($n = 243$ patients) (Table 3).[18,19] In these studies, the investigators assessed the causality

**Table 3.** Summary of maximum WHO symptomatic toxicity grades (% of patients) ($n = 243$)

| Toxicity parameter | Maximum WHO grades | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Allergic | 95.0 | 4.1 | 0.8 | 0.0 | 0.0 |
| Constipation | 92.6 | 5.8 | 1.2 | 0.4 | 0.0 |
| Cutaneous | 69.8 | 16.9 | 13.2 | 0.0 | 0.0 |
| Diarrhea | 93.8 | 4.1 | 1.7 | 0.4 | 0.0 |
| Fever | 54.1 | 27.7 | 17.8 | 0.4 | 0.0 |
| Cardiac function | 98.8 | 1.2 | 0.0 | 0.0 | 0.0 |
| Hair | 86.0 | 10.3 | 3.3 | 0.4 | 0.0 |
| Hematuria | 62.3 | 34.3 | 3.3 | 0.0 | 0.0 |
| Hemorrhage | 98.1 | 0.6 | 1.3 | 0.0 | 0.0 |
| Infection | 90.5 | 7.9 | 1.7 | 0.0 | 0.0 |
| Nausea/vomiting | 30.6 | 31.4 | 17.8 | 19.4 | 0.8 |
| Oral | 93.4 | 4.5 | 1.7 | 0.4 | 0.0 |
| Pain | 84.3 | 8.7 | 5.8 | 1.2 | 0.0 |
| Pericarditis | 99.6 | 0.4 | 0.0 | 0.0 | 0.0 |
| Peripheral neurotoxicity | 96.3 | 3.3 | 0.4 | 0.0 | 0.0 |
| Proteinuria | 61.1 | 37.2 | 1.3 | 0.4 | 0.0 |
| Pulmonary | 92.1 | 3.7 | 1.7 | 2.5 | 0.0 |
| Cardiac rhythm | 97.5 | 1.7 | 0.4 | 0.4 | 0.0 |
| State of consciousness | 94.2 | 2.9 | 2.9 | 0.0 | 0.0 |

of any adverse events. In contrast, in the other two studies[4,17] the investigators used the WHO toxicity rating scale for all events regardless of causality. Therefore the data on the 243 patients is more reflective of gemcitabine's toxicity.

## Gastrointestinal effects

Nausea and vomiting is a particularly troublesome toxicity of many cytotoxic regimens, causing psychological and physical distress. If severe, it warrants rehydration and may require hospitalization. Nausea and vomiting WHO grade 3 (vomiting requiring therapy) and grade 4 (intractable vomiting) was recorded in 19.4 and 0.8% of patients, respectively. Overall, treatment for nausea and vomiting was required in about 20% of patients, nevertheless it was rarely dose limiting and easily manageable with standard antiemetics; 5-$HT_3$ antiemetics were usually not required.

Diarrhea WHO grade 3 (intolerable, requiring therapy) and grade 4 (hemorrhagic dehydration) occurred in 0.4 and 0% of treated patients, respectively, and did not cause any discontinuation of treatment. WHO grade 3 and 4 constipation was reported in 0.4 and 0% of patients, respectively.

Oral toxicity WHO grade 3 (ulcers necessitating liquid diet only) and grade 4 (alimentation not possible) occurred in 0.4 and 0% of patients respectively.

## Pulmonary effects

Pulmonary toxicity was compared between the lung cancer data set ($n = 243$) and a dataset including five studies in various tumor types using the same schedule and the same dose range ($n = 196$). Irrespective of causality, the incidence of dyspnoea was higher in the lung cancer studies (35.4%) compared with the non-lung cancer studies (15.8%) which is not unexpected. Among these, the percentage of patients with reports of serious adverse events for dyspnoea is also higher in the lung cancer studies (8.2 versus 2.0%) in the non-lung cancer studies). When causality is assessed, the percentage of patients reporting dyspnoea that is possibly drug-related (WHO grade 1–4) is comparable between lung cancer studies (7.9%) and non-lung cancer studies (8.8%), although the severity of toxicity appeared to be slightly greater in the group of patients with lung cancer. This is thought to be because of pre-existing disease. Overall, dyspnoea possibly caused by gemcitabine was unusually mild. It was unusually reported by investigators as occurring within hours following gemcitabine infusion and usually lasted for a short time (3–12 h). These

events usually abated spontaneously without any specific therapy.

### Cutaneous effects

No WHO grade 3 and 4 cutaneous toxicity was reported. WHO grade 1 and 2 toxicity occurred in 16.9 and 13.2% of patients, respectively. A transient, mild erythematous pruritic rash was frequently reported. In many cases the rash was responsive to local treatment despite continuation of therapy. Desquamation was observed on at least one occasion. There were no reports of injection site necrosis.

### Alopecia

Hair toxicity WHO grade 3 (complete alopecia but reversible) and grade 4 (non-reversible alopecia) was reported in 0.4 and 0% of patients. Overall, there was little alopecia and 86.0% of patients had no hair loss at all. Alopecia remains one of the most distressing adverse effects of cytotoxic therapy and it is encouraging that gemcitabine produces little hair loss.

### Infection toxicity

No WHO grade 3 and 4 infections (major infection, major infection with hypotension) were reported. WHO grade 1 and 2 infection (minor infection, moderate infection) was reported in 7.9 and 1.7% of patients, respectively. Overall, drug-related infection was usually mild, rarely dose-limiting and was easily manageable.

### Fever

WHO grade 3 and 4 fever occurred in 0.4 and 0% of patients, respectively. It was frequently associated with other flu-like symptoms which will be discussed later. Fever was usually mild, of brief duration, easily manageable, rarely dose limiting and rarely related to infection.

### Cardiac effects

The incidence of WHO grade 3 and 4 cardiac toxicity was as follows: cardiac rhythm 0.4 and 0%; cardiac function 0 and 0%; pericarditis 0 and 0%. Overall, there is no significant evidence that gemcitabine causes cardiac toxicity.

### Peripheral neurotoxicity

There was no grade 3 or 4 peripheral neurotoxicity. WHO grade 1 and 2 peripheral neurotoxicity was reported in 3.3 and 0.4% of patients, respectively.

### Other adverse events

Some adverse events reported during treatment with gemcitabine are not covered by the WHO grading system. These are summarized for all patients on therapy. Adverse events were reported irrespective of causality.

### Flu-like symptoms

Flu-like symptoms (including headache, back pain, chills myalgia, asthenia and anorexia) have been reported during treatment with gemcitabine. A total of 84 out of the 360 patients (23.3%) reported these symptoms. They were usually mild, of short duration (sometimes just the day of treatment) and rarely dose limiting. Asthenia was commonly considered drug related even when reported as an isolated symptom. Cough, rhinitis, malaise, sweating and insomnia were also reported. Flu-like symptoms might also have accounted for some, but not all cases of fever. The mechanism of this effect is unknown but some investigators have reported that the symptoms are relieved by paracetamol or steroids.

### Edema

Edema and peripheral edema were frequently reported. Edema was reported in 15.8% of all patients and peripheral edema in 24.4% of all patients. This was usually mild to moderately severe. The mechanism is unknown, but the edema is not associated with any evidence of cardiac, hepatic or renal failure.

## Discussion and conclusions

Gemcitabine has demonstrated promising single-agent activity in studies in NSCLC. The analysis of

the safety database shows that gemcitabine was well tolerated with a low incidence of the toxicities usually associated with cytotoxic therapy. In particular, the toxicity profile of gemcitabine was generally non-hematological and any myelosupression typically did not require hospitalization or treatment with colony stimulating factors. Although nausea and vomiting were commonly reported they were generally mild and managed with conventional antiemetic agents. Therefore, as a single agent with activity and a good toxicity profile, gemcitabine may be considered as sole therapy in patients who choose not to have more toxic agents or who are less able to tolerate more toxic treatments because of co-existent medical disorders. The low incidence and severity of side effects with gemcitabine suggests that the costs associated with managing these adverse events are expected to be lower than with many other cytotoxic agents.

Combination regimens are designed to include active agents which have different mechanisms of action and different toxicities. The response rates obtained with gemcitabine and its safety profile which does not overlap with other cytotoxic drugs, suggest a potential use of gemcitabine in combination with other active chemotherapies in lung cancer. A number of combination regimens are already being studied, i.e. gemcitabine combined with either radiation, cisplatin, carboplatin, vindesine, doxorubicin or ifosfamide.

## References


1. Walling J. Chemotherapy of advanced non-small cell lung cancer. *Respir Med* 1994; **88**: 649–57.
2. Souhami RL, Stewart LA, Arriagada R, Parmar M, Le Chevalier T, Pignon JP. A data-based meta-analysis of randomised trials of chemotherapy versus best supportive care (BSC) in advanced non-small cell lung cancer (NSCLC). *Lung Cancer* 1994; **11**: 25 (abstr).
3. Bhalla K, Maclaughlin W, Cole J, Arlin Z, Birkhofer M, Graham G. Continuously administered 2′,2′-difluorodeoxycytidine (dFdC) and deoxycytidine (dCyd): a potentially selective cytotoxic regimen toward human leukemic myeloid progenitors in culture. *Proc Am Ass Cancer Res* 1988; **28**: 348 (abstr 1385).
4. Bouffard DY, Momparler LF, Momparler RL. Comparison of antineoplastic activity of cytosine arabinoside and 2′,2′-difluorodeoxycytidine on human myeloid, T-cell and B-cell leukemic cells. *Eur J Pharmacol* 1990; **183**: 161 (abstr 32).
5. Chubb S, Heinemann V, Novotny L, *et al.* Metabolism and action of difluorodeoxycytidine (dFdC) in human leukemia cell. *Proc Am Ass Cancer Res* 1987; **28**: 324 (abstr 1282).
6. Fujita F, Fujita M, Inaba H. Effects of a new anticancer agent LY188011 on human cancer xenografts in nude mice. *Forty-eighth Annual Meeting of the Japanese Cancer Association*, Nagoya, Japan. October 1989: 23–5 (abstr 1938).
7. Grindey GG, Boder, GB, Hertel LH, *et al.* Antitumor activity of 2′,2′-difluorodeoxycytidine (LY 188011). *Proc Am Ass Cancer Res* 1986; **27**: 296 (abstr 1775).
8. Plunkett W, Chubb S, Nowak B, Hertel L, Grindey GB. Increased cytotoxicity and therapeutic activity of 2′,2′-difluorodeoxycytidine over cytosine arabinoside (ara-C) in L1210 leukemia. *Proc Am Ass Cancer Res* 1988; **29**: 352 (abstr 1402).
9. Tanayanagi C, Takauji R, Ueda T. Action mechanism of difluorodeoxycytidine (dFdC), a new ara-C derivative. *Acta Hematol Jpn* 1990; **53**: 76 (abstr 132).
10. Carmichael J, Possinger K, Phillip P, *et al.* Advanced breast cancer: a phase II trial with gemcitabine. *J Clin Oncol* 1995; **13**: 2731–6.
11. Carmichael J, Fink U, Russell RCG, *et al.* Phase II study of gemcitabine in patients with advanced pancreatic cancer. *Eur J Cancer* 1993; **29A**: S101 (suppl 6, abstr 541).
12. Casper ES, Green MR, Kelsen DP, *et al.* Phase II trial of gemcitabine (2′,2′difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. *Invest New Drugs* 1994; **12**: 29–34.
13. Lund B, Hansen OP, Theilade K, Hansen M, Neijt JP. Phase II study of gemcitabine (2′,2′-difluorodeoxycitidine) in previously treated ovarian cancer. An update. *J Natl Cancer Inst* 1994; **86**: 1530–3.
14. Cormier Y, Eisenhauer E, Muldal A, *et al.* Gemcitabine is an active new agent in previously un-treated extensive small cell lung cancer. A study of the National Cancer Institute of Canada Clinical Treatment Group. *Ann Oncol* 1994; **5**: 283–5.
15. Pollera CF, Ceribelli A, Crecco M, Calabresi F. Weekly gemcitabine in advanced bladder cancer: a preliminary report from a phase I study. *Ann Oncol* 1994; **5**: 182–4.
16. Catimel G, Vermorken JB, Clavel M, De Mulder P, Judson I, Sessa C. A phase II study of gemcitabine (LY188011) in patients with advanced squamous cell carcinoma of the head and neck. *Ann Oncol* 1994; **5**: 543–7.
17. Abratt RP, Bezwoda WR, Folkson G, Goedhals L, Hacking D, Rugg TA. Efficacy and safety profile of gemcitabine in non-small cell lung cancer: a phase II study. *J Clin Oncol* 1994; **8**: 1535–40.
18. Anderson H, Lund B, Bach F, Thatcher N, Walling J, Hansen HH. Single-agent activity of weekly gemcitabine in advanced non-small cell lung cancer: a phase II study. *J Clin Oncol* 1994; **9**: 1821–6.
19. Gatzemeier U, Shepherd F, Le Chevalier T, *et al.* A multicenter phase II trial with gemcitabine in non-small cell lung cancer (NSCLC). *Lung Cancer* 1994; **II** (suppl 1): 121 (abstr 461).
20. Kaye SB. Gemcitabine: current status of phase I and II trials (editorial). *J Clin Oncol* 1994; **12**: 1527–31.
21. Hatty S. Elevations of LFTs with gemcitabine are mild, transient and rarely result in withdrawal or dose adjustment. *ECCO8* 1995 (abstr 939).


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