

Fatal Pulmonary Toxicity Resulting from Treatment with Gemcitabine

Nick Pavlakis, M.B.B.S.¹

David R. Bell, M.B.B.S.¹

Michael J. Millward, M.D.²

John A. Levi, M.D.¹

¹ Department of Clinical Oncology, Royal North Shore Hospital, St. Leonards, Australia.

² Department of Haematology & Medical Oncology, Peter MacCallum Cancer Institute, Melbourne, Australia.

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Address for reprints: David R. Bell, M.B.B.S., Department of Clinical Oncology, Royal North Shore Hospital, St. Leonards NSW 2065, Australia.

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BACKGROUND. Pulmonary toxicity reported with gemcitabine is usually mild and self-limiting. The authors report a series of three patients who had life-threatening pulmonary toxicity after receiving gemcitabine.

METHODS. The three patients presented to two major teaching hospitals with significant pulmonary dysfunction while receiving gemcitabine. Case data were obtained from patient records. A review of the literature was done to seek reports of pulmonary toxicity with gemcitabine and cytosine arabinoside (ara-C).

RESULTS. The common features of the respiratory illnesses of the three patients in this study were tachypnea, marked hypoxemia, and an interstitial infiltrate on chest radiograph consistent with pulmonary edema. There was no evidence of underlying heart disease in any patient. In addition, there was no evidence of infection, metabolic causes, or lymphangitic carcinomatosis to explain the clinical findings. Two patients died, and postmortem examination confirmed acute RDS (respiratory distress syndrome), whereas in the third patient a transbronchial biopsy showed interstitial pneumonitis. These findings were consistent with drug-induced pulmonary toxicity. Diuretics and corticosteroids were useful measures for treating the patients' symptoms, and one patient survived after gemcitabine was withdrawn.

CONCLUSIONS. These three cases of acute RDS may be the result of a capillary leak phenomenon due to treatment with gemcitabine, as observed in patients given intermediate dose and high dose ara-C, a drug similar in structure and metabolism to gemcitabine. The authors suggest caution in repeated administration of gemcitabine to patients who develop unexplained noncardiogenic pulmonary edema. Withdrawing gemcitabine and administering corticosteroids and diuretics may help to avert a fatal outcome. *Cancer* 1997;80:286–91.

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Gemcitabine (2'2'-difluorodeoxycytidine) is a new deoxycytidine analogue with structural similarities to cytosine arabinoside (ara-C) but with demonstrated single agent activity in nonsmall cell lung carcinoma^{1,2} and carcinoma of the pancreas,^{3–5} breast,⁶ and ovary.^{7,8} It differs structurally from ara-C by the substitution of two fluorine atoms at the 2' position of the carbohydrate moiety. Despite the structural similarities, the two drugs have different cellular pharmacology and schedule dependency.⁹

Like ara-C, gemcitabine requires intracellular conversion to its active forms, via phosphorylation in stepwise fashion by deoxycytidine kinase.^{10,11} Gemcitabine is transported more readily into the cell than ara-C and is more lipophilic. The intracellular concentration of the active triphosphate is 20 times that of ara-C, as has been shown

in Chinese hamster ovary cells.⁹ Gemcitabine self-potentiates its actions in at least three ways. Its metabolite, gemcitabine diphosphate, inhibits ribonucleotide reductase, an enzyme involved in producing deoxynucleotides for normal DNA synthesis and repair; this leads to lower levels of deoxynucleotide triphosphates, which oppose the feedback inhibition of deoxycytidine kinase, leading to increased production of the activated phosphorylated forms of gemcitabine. Gemcitabine also directly and indirectly inhibits the action of deoxycytidine monophosphate deaminase, its breakdown enzyme.¹⁰ Like ara-C, its cytotoxicity is mediated by incorporation into DNA, inhibiting DNA synthesis.^{10,11} However, by a process known as “masked chain termination,” one more deoxynucleotide is added to the DNA molecule before replication is terminated. This makes gemcitabine DNA binding more durable than ara-C by masking its incorporation into DNA and making it more resistant to removal by DNA repair enzymes.¹⁰

These differences in cellular pharmacology might explain the greater solid tumor activity of gemcitabine. Its lack of significant toxicity, coupled with its modest activity and symptomatic benefits, have seen it gain regulatory approval in the U.S., Europe, and Australia, as palliative therapy for advanced nonsmall cell lung carcinoma and/or pancreatic carcinoma. Myelosuppression is the major dose-limiting toxicity, yet the incidence of World Health Organization (WHO) Grade 3–4 toxicity is less than 29%, with less than 1% of patients requiring discontinuation of therapy.¹²

The most commonly reported toxicities are mild-to-moderate nausea and vomiting (65% of cases, WHO Grade 3 in 10%), influenza-like symptoms (20%), mild skin rash (26%; with pruritis, 10%), reversible elevation in serum transaminases (69%), fever (30–50%), and peripheral edema (9–40%).^{1,2,5,6,12,13}

Dyspnea after gemcitabine therapy is reported to occur in 8% of patients, with serious dyspnea occurring in 5%.¹³ In a review of dyspnea after treatment with gemcitabine, it was found that discontinuation of gemcitabine was necessary in only 0.6% of cases.¹³ The dyspnea is usually mild and self-limiting, occurs within hours of injection, and may be associated with bronchospasm in a minority of cases.^{1,2,6,12,13} Many of the patients reporting dyspnea after gemcitabine treatment had lung carcinoma or lung pathology from other malignancies, and it is possible that the dyspnea may have been disease-related.¹³ One case of dyspnea reported after gemcitabine treatment was associated with pulmonary infiltrates radiologically. Withdrawal of gemcitabine and administration of corticosteroids resulted in improvement.⁶

Ara-C, however, when used for relapsed or refrac-

tory acute myeloid leukemia, has clearly been associated with acute or subacute pulmonary syndrome manifesting as non cardiogenic pulmonary edema and often progressing to an acute RDS (respiratory distress syndrome). The incidence of this syndrome varies from 13% to 28% and has been documented in both intermediate dose and high dose ara-C.^{14–19}

The onset of acute RDS has been reported 2–38 days posttreatment (median, 6–8 days).^{14,15,18} A spectrum of radiologic abnormalities exists, including diffuse interstitial, mixed interstitial-alveolar, and alveolar pulmonary changes.¹⁷ The mortality rate varies from 9% to 69%.¹⁴ The mechanism of lung injury caused by ara-C is thought to be a direct cytotoxic effect causing capillary endothelial damage and subsequent fluid leakage and pulmonary edema.^{14,15}

We report a series of three cases of life-threatening pulmonary insufficiency with noncardiogenic pulmonary edema after treatment with gemcitabine, two of which were fatal.

CASE 1

A woman age 58 years was referred with Stage IV ovarian carcinoma 15 months after primary debulking surgery and 7 months after completion of 8 cycles of cisplatin 100 mg/m², doxorubicin 50 mg/m² (cumulative dose 337 mg), and cyclophosphamide 500 mg/m², administered intravenously every 4 weeks. She had palliative suboptimal debulking of her recurrent pelvic disease, and 7 weeks later she commenced treatment with gemcitabine at a dose of 1200 mg/m² given intravenously on Days 1, 8, and 15 every 4 weeks. She had no prior medical illnesses and in particular no prior cardiac history. The patient received seven cycles of gemcitabine with clinical improvement and partial radiologic response on follow-up.

The observed toxicities were WHO Grade 1 nausea; WHO Grade 1 thrombocytopenia, which necessitated dose reduction of Day 15 treatment by 25% and 1 omission in Cycle 6 on Day 15; and WHO Grade 2 anemia, which necessitated blood transfusion during Cycles 4 and 6. Exertional dyspnea was first reported after treatment on Day 15 in Cycle 4 and was associated with a dry cough. There was a gradual and progressive course over a 2-week period associated with facial and peripheral edema. The patient was admitted to the hospital with tachypnea (respiratory rate 33/minute), arterial hypoxemia (pO₂ 53 mmHg with pCO₂ 33 mmHg), anemia (hemoglobin 9.0 g/dL), and a bilateral interstitial pulmonary infiltrate on chest X-ray consistent with pulmonary edema. Clinical examination showed signs of raised venous pressure, peripheral edema, and bilateral basal crackles on auscultation of the chest. She responded well to diuretic ther-

apy and was placed on captopril 25 mg three times a day (t.i.d.) on the presumptive diagnosis of heart failure. She was discharged from hospital after 5 days, at which time an echocardiogram showed no evidence of left ventricular dysfunction. Apart from stable mild dyspnea on exertion, no increased dyspnea was reported during Cycle 5.

The patient was readmitted to the hospital with progressive dyspnea 13 days after Day 8 of Cycle 6, with hemoglobin 9.6 g/dL. Chest X-ray showed interstitial edema and small bilateral basal pleural effusions. There was a further good response to diuretic therapy (furosemide 80 mg daily) in addition to nitrates (isosorbide mononitrate 60 mg daily) and vasodilator therapy (hydralazine 50 mg t.i.d.). Serial chest X-rays showed clearing of the edema.

A repeat echocardiogram again showed no left ventricular systolic or diastolic dysfunction. A ventilation perfusion lung scan had no features to suggest pulmonary embolism. Lung function testing showed a ratio of 1-second forced expiratory volume to forced vital capacity of 1.57L/2.25L (64% and 77% of predicted, respectively) with a reduced diffusing capacity (ratio of carbon monoxide diffusing capacity of the lungs to alveolar ventilation 51% of predicted). She had a transient episode of atrial fibrillation during this admission but reverted to sinus rhythm after commencement of digoxin. Although there was no clear evidence of a cardiac cause for this pulmonary edema, the patient continued treatment with digoxin (125 g daily), nitrates, hydralazine, and diuretics, as occult coronary artery disease had not been ruled out.

Gemcitabine was continued and the Day 1 and Day 8 dose of Cycle 7 given. Day 15 was omitted due to a platelet count of $30 \times 10^9/L$. Her dyspnea gradually worsened after each injection and she was readmitted 11 days after her last dose of gemcitabine with dyspnea at rest.

The physical signs were similar to the previous admissions, and again there was absence of fever. She was markedly hypoxemic (pO_2 42 mmHg on air), with hemoglobin 6.3 g/L, platelet count $13 \times 10^9/L$, white blood cell count $11 \times 10^9/L$ with 83% neutrophils and no eosinophilia, urea 25.5 mmol/L, creatinine 0.17 mmol/L, and albumin 29g/L. Chest X-ray was again consistent with pulmonary edema. She was transfused with 4 units of packed red blood cells and 4 units of platelets and received intravenous diuretic therapy. A computed tomography (CT) scan of the chest showed interstitial edema, and she was commenced on 24 mg dexamethasone daily on the second day of this hospital admission.

After initial diuresis and some improvement in arterial oxygenation (pO_2 58 mmHg on air with oxygen

saturation 91%), her renal function began to deteriorate, so the diuretics were ceased on the fifth day. Twenty-four hours later, her condition rapidly deteriorated; and despite aggressive diuretic therapy and high dose steroids (48 mg of dexamethasone per day), she died.

A postmortem examination was performed. This showed minimal coronary atherosclerosis, no evidence of myocardial infarction, small bilateral serous pleural effusions with congested lungs, and ascites and tumor in the abdomen. Histologically the lungs showed patchy alveolar hemorrhage and edema with alveolar wall inflammation, edema, and focal hyaline membrane formation, but no evidence of malignancy. These features were consistent with early acute RDS.

CASE 2

A man age 48 years presented with large cell carcinoma of the lung. He had a history of asthma, which was treated with inhaled steroids and salbutamol. He was an ex-smoker, with a 20 pack year history, and a former marathon runner. He had a left pneumonectomy but relapsed 6 months later with mediastinal lymph node disease, for which he was treated with radiotherapy at a dose of 64 gray in 34 fractions with anterior/posterior fields to the mediastinum, with 2 cycles of concomitant carboplatin at a dose of 100 mg/m² for 3 consecutive days every 4 weeks. One week after completing radiotherapy, he presented with right adrenal and para-aortic lymph node metastases.

Consequently, he was commenced on gemcitabine 1250 mg/m² on Days 1, 8, and 15 every 4 weeks and had clinical improvement (reduced pain from adrenal metastases) but stable disease on CT scan. During his first course of gemcitabine, he was found to have cerebral metastases, and he received whole brain radiotherapy (34 gray in 17 fractions). He was placed on dexamethasone 4 mg twice daily during his cerebral radiotherapy. Transient dyspnea was observed (WHO Grade 1) after each injection during Cycle 1.

He was admitted to the hospital 12 days after Day 15 of Cycle 2 with a history of progressive dyspnea, occurring at rest and associated with productive cough and intermittent sweats. On physical examination, he had a temperature of 37.6 °C, tachypnea (35 breaths/minute), central cyanosis, bronchial breath sounds, and crackles in the right lung. His hemoglobin was 11.5 g/L, his white blood cell count was $8.7 \times 10^9/L$ with 95% neutrophils, and his platelet count was $290 \times 10^9/L$. Partial pressure of oxygen was 56 mmHg and of CO₂ was 36 mmHg with oxygen saturation of 93% on 6 L of oxygen via a Hudson mask. Chest X-ray showed widespread air space opacity in the right lung with

interstitial basal changes consistent with pulmonary edema.

He began receiving antibiotics (intravenous ceftriaxone and oral roxythromycin) in addition to diuretic therapy (furosemide 40 mg daily) and intravenous corticosteroids (hydrocortisone 400 mg per day). Despite this, he had rapid deterioration and died of acute respiratory failure 3 days after admission to the hospital.

A postmortem examination was performed. There was no evidence of significant heart disease. Within the lungs there was no evidence of infection, lymphangitis carcinomatosa, or radiation pneumonitis. However, there was extensive hyaline membrane formation with hyperplasia of type II pneumocytes as well as interstitial and intra-alveolar edema consistent with diffuse alveolar damage (acute RDS).

CASE 3

A woman age 55 years was referred with suboptimally debulked Stage IIIC epithelial ovarian carcinoma, which progressed during 2 cycles of carboplatin and cyclophosphamide. She had no radiologic evidence of pulmonary metastases and no history of respiratory disease, and she was a nonsmoker. She received 3 cycles of gemcitabine 1250 mg/m² on Days 1, 8, and 15 every 4 weeks with clinical improvement and partial response on CT scan. The observed toxicities were fever to 38.5 for 24–48 hours after each injection and Grade 2 skin rash.

One week after Day 15 of Cycle 3, she presented with rapidly progressive dyspnea. Prior to this she had had no respiratory symptoms. Physical examination showed fever (39 C), tachypnea (24/minute), and bilateral basal crackles. Her hemoglobin was 99 g/L, her white blood cell count was 9.0 10⁹/L, her neutrophils were 6.0 10⁹/L with toxic changes, and her platelet count was 190 10⁹/L. Broad spectrum intravenous antibiotics (ticarcillin with clavulanate, gentamicin, and erythromycin) were administered without improvement. Serial chest X-rays showed progressive bilateral pulmonary infiltrates. There was no clinical evidence of cardiac failure. A chest CT scan showed extensive infiltrates throughout both lungs with areas of peribronchial consolidation and collapse. Blood cultures were sterile. Serology for psittacosis, legionella, and mycoplasma were negative.

Over the 5 days that followed, her clinical condition deteriorated with persistent fever, worsening oxygen saturation (71% on air), and arterial hypoxemia (pO₂ 45 mmHg). She underwent bronchoscopy, bronchoalveolar lavage, and transbronchial biopsy of the right upper lobe. No pneumocystis organisms were observed and no fungi were observed or cultured. The

biopsy showed nonspecific interstitial pneumonitis consistent with drug-induced lung toxicity.

Dexamethasone 16 mg per day was commenced, and over the next 5 days there was progressive clinical and functional improvement. Her oxygen saturation increased to 98% on room air with no desaturation on exercise. Her chest X-ray cleared apart from a small area of basal atelectasis. After 1 week her steroids were changed to prednisolone 60 mg/day. A repeat chest CT scan after 2 weeks of steroid therapy showed that the air space infiltrate had resolved, but there were persistent abnormalities at the right lung base consistent with linear subsegmental atelectasis or a fibrotic process.

No further gemcitabine was given, and over the next 2 months the steroid therapy was progressively tapered and ultimately withdrawn with no recurrence of respiratory symptoms. The patient died of progressive ovarian carcinoma 6 months after the episode of lung toxicity. No postmortem was performed.

DISCUSSION

Severe dyspnea with gemcitabine has an incidence of 3–5%.^{12,13} We have treated over 170 patients with gemcitabine, and the 3 patients discussed herein were the only ones with significant pulmonary toxicity. These three cases illustrate the rare occurrence of non-cardiogenic pulmonary edema with the clinical manifestations of acute RDS after treatment with gemcitabine. The fatal outcome in Cases 1 and 2 may be attributable to repeated insult to the lungs with the ongoing administration of gemcitabine. Diuretic therapy did provide transient relief, especially in Case 1. Corticosteroids provided maximum benefit in Case 3 when it was commenced early during the acute illness coupled with the withdrawal of gemcitabine. In contrast, Case 2 was receiving corticosteroids prior to the onset of lung symptoms, and their use did not prevent rapid onset of acute RDS.

Case 2 had a much more rapid clinical course. The onset of respiratory failure was 6 weeks after commencement of gemcitabine and 7 weeks after completion of mediastinal radiotherapy. This close relationship to both modalities of treatment makes it more difficult to establish the dominant cause. Moreover, gemcitabine has been shown to have potent radiosensitization of tumor cells *in vitro*.^{20,21} It is possible that *in vivo*, it could exacerbate radiation effects on normal tissues. However, the radiologic and postmortem findings in Case 2 are in keeping with drug-induced and not radiation pneumonitis. The typical radiologic features of radiation pneumonitis are a diffuse infiltrate within the radiation field, although cases of bilateral radiation pneumonitis have been reported rarely

and usually in patients receiving higher doses of radiotherapy or with coexisting chest infection.²²⁻²⁴

Histologically, there is no pathognomonic feature of radiation pneumonitis, but typical features have been described.²² These include vasculitic changes affecting capillaries, arterioles, and small arteries with vessel wall edema; proliferation and presence of subintimal, lipid-laden macrophages; desquamation of cells into alveolar lumens; alveolar septal thickening; and widespread eosinophilic hyaline membrane formation.²²

Although present in the lung of Case 2, hyaline membrane formation is not specific for radiation pneumonitis,²² and there were no other typical features of radiation pneumonitis in the postmortem findings for this patient.

Clinical benefit has been reported for patients with noncardiogenic pulmonary edema and ara-C with the use of oxygen therapy and in some cases mechanical ventilation, high dose corticosteroids, and/or diuretics.^{15,18}

The acute respiratory illness seen in our three patients fulfills the diagnostic criteria for acute RDS set out by the European-American Consensus Conference on ARDS:²⁵ arterial hypoxemia (with ratio PaO_2 to FIO_2 < 200), bilateral pulmonary infiltrates on plain chest radiographs, and lack of clinical evidence of left heart failure. It was recently reported that early diuresis or fluid restriction may improve outcome, and it is recommended that corticosteroids be given later to patients who are not improving. Patients with eosinophilia, either on full blood count or on bronchoalveolar lavage, may benefit most from corticosteroids.²⁵

In our patients, as in reported series with ara-C, the diagnosis of a drug-induced acute RDS with noncardiogenic pulmonary edema relies on typical radiologic features (involving diffuse interstitial and/or alveolar infiltrates)¹⁷ and the exclusion of other potential causes (cardiorespiratory, infectious, metabolic, or lymphangitis carcinomatosa).¹⁴ In Cases 1 and 2, the diagnosis was evident on postmortem examination, whereas Case 3 had histologically confirmed interstitial pneumonitis with no other obvious cause and rapid improvement with corticosteroids.

In the syndrome of acute RDS observed with ara-C, postmortem findings of unexplained pulmonary edema suggest a drug-induced capillary leak phenomenon as a possible cause.^{14,15,16} Early Phase II studies of gemcitabine in nonsmall cell lung carcinoma reported edema, predominantly peripheral, in up to 53% of patients.^{1,2} This unexplained peripheral edema and the noncardiogenic pulmonary edema seen in our patients may also be explained by a capillary leak syndrome induced by gemcitabine. In view of the struc-

tural and metabolic similarities between ara-C and gemcitabine, perhaps the mechanism of lung injury is common to both these drugs.

Although gemcitabine is generally a well-tolerated chemotherapeutic agent, we recommend prompt discontinuation and lung biopsy to confirm drug-induced pneumonitis in patients with unexplained noncardiogenic pulmonary edema with an acute or subacute presentation. We also recommend caution in administering gemcitabine to patients who have had recent radiotherapy, due to gemcitabine's potent in vitro radiosensitization properties and because radiotherapy could not be excluded from having a causal role in the pulmonary toxicity observed in Case 2 of our study. In established cases, diuretic therapy and corticosteroids may be helpful, in addition to withdrawal of gemcitabine.

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