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## Short Communication

# Effects of Gemcitabine on Renal Function in Patients with Non-small Cell Lung Cancer

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**Gemcitabine is a novel fluorine-substituted cytarabine (Ara-C) analogue with activity against a range of solid tumours. Besides dose-limiting haematological toxicity, renal side-effects were observed from phase I and II studies concerning elevations of serum creatinine, proteinuria and erythrocyturia. The aim of this study was to investigate the effect of gemcitabine on renal function in 11 untreated patients with non-small cell lung cancer (NSCLC). Gemcitabine was given as weekly infusions of 1250 mg/m$^2$ for 3 weeks, followed by 1 week rest. This comprised one cycle (maximum of six cycles). The glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured simultaneously with a constant infusion of $^{125}$I-iothalamate and $^{131}$I-hippuran, respectively. Tubular damage was monitored by excretion of tubular enzymes (lactic dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyltransferase (GT) and $\beta_2$-microglobulin); glomerular damage was monitored by excretion of albumin in the urine. In 9 patients, the effect of the first infusion was evaluated. After the first infusion of gemcitabine, no change was observed in renal function. After two, three, and six cycles of treatment, no significant changes in GFR and ERPF were noticed in 9 evaluable patients. However, in 3 patients, a decrease in GFR of > 10% was observed after multiple cycles. In one of them this was accompanied with albuminuria (360 mg/24 h) and erythrocyturia. There were no significant changes in urinary excretion of tubular enzymes or albumin. In conclusion, we did not observe acute renal toxicity with gemcitabine. No significant cumulative effects of gemcitabine on renal function could be detected, although 3 patients, treated with multiple cycles of gemcitabine, showed a moderate decrease in renal function. Glomerular damage might play a role in the development of renal function loss.** © **1998 Elsevier Science Ltd.**

**Key words: gemcitabine, renal function, non-small cell lung cancer**
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## INTRODUCTION

GEMCITABINE (2,2-difluorodeoxycytidine) is a novel fluorine-substituted cytarabine (Ara-C) analogue with activity against a range of solid tumours. In animal tumour models, gemcitabine has shown antitumour activity against colon, head and neck, breast, lung, pancreatic, ovarian, gastric and liver carcinomas [1, 2]. A range of phase I trials with gemcitabine have been conducted, and the toxicity has been shown to be schedule-dependent [3–5]. Most experience has been obtained in trials with the weekly schedule in which gemcitabine, administered by a 30 min infusion, is given once weekly for 3 weeks followed by a week's rest [5]. In this schedule the drug is well tolerated with major toxicity being myelosuppression, lethargy and mild flu-like symptoms. Furthermore, data from phase I and phase II studies have also revealed some signs of renal toxicity [6–8]. This concerned mainly mild (WHO grade 1 and 2) proteinuria, haematuria and temporary elevations of serum creatinine. Since renal elimination is the main route of excretion of gemcitabine, it is of interest to investigate more accurately whether the clearance of this drug is accompanied by a decrease in renal function. This becomes even more relevant when gemcitabine is combined with known nephrotoxic drugs such as cisplatin.

In this study, we determined the effects of gemcitabine on renal function by means of changes in glomerular filtration rate

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(GFR) and effective renal plasma flow (ERPF). The possible glomerular and tubular damage was monitored by measuring the urinary excretion of albumin and tubular enzymes, respectively.

## PATIENTS AND METHODS

*Patients and therapy*

11 patients, 2 females and 9 males (median age 60 years [range 43–70]) were studied. All patients had inoperable non-small cell lung cancer (NSCLC) and were not pretreated with chemotherapy. They had serum creatinine levels within the upper limit of our institution (<120 μmol/l), no proteinuria, normal blood pressure and did not use other potentially nephrotoxic medication.

All patients were treated with gemcitabine in a phase II study, of which details have been reported previously [9]. The study protocol was approved by the local ethical committee, all patients gave informed consent. In short, gemcitabine at 1250 mg/m$^2$ was administered intravenously over 30 min, once a week, for 3 weeks, followed by a week of rest. This comprised one cycle. Cycles were repeated every 4 weeks. Patients were planned to receive six cycles if they were responding or had stable disease. Patients who had progressive disease were taken off study. A total of 48 cycles were administered (median 5, range 1–6).

*Renal function studies*

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured, as previously described, simultaneously in the supine position with a constant infusion of $^{125}$I-iothalamate and $^{131}$I-hippuran, respectively [10]. After a standard primary radioisotope dose and sustaining infusion for 2 h, 1-h clearances were determined for acute effects and 2-h clearances for cumulative effects. For the latter, values are the mean of two 2-h clearances. The intrapatient day-to-day coefficient of variation of this method for GFR is < 2% and for ERPF < 5% [10]. Filtration fraction (FF) was calculated as the ratio of GFR and ERPF. These variables were studied before and 4 h after the first gemcitabine infusion in order to determine acute effects on renal function. Cumulative effects on renal function were also measured for 4 h in the rest week of cycles 2, 3 and 6. In addition, before the start of gemcitabine treatment and during the rest week of each cycle, serum and urine was collected for the determination of creatinine, lactic dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyltransferase (GT), $\beta_2$-microglobulin and albumin. Serum and urine creatinine, LDH, ALP and GT were determined with an automated multi-analyser (SMA-C, Technicon®). Urinary $\beta_2$-microglobulin concentration was determined by a radioimmunosorbent technique according to Evrin and associates [11]. Urinary albumin concentration was measured in 24 h urine collection with an ELISA and total protein with a pyrogallol red molybdate method [12]. The ratio of urinary LDH, ALP, GT, $\beta_2$-microglobulin and albumin concentrations divided by urinary creatinine concentrations were calculated. Additionally, urine samples were analysed with a dipstick (Merck, Darmstadt, Germany) for pH, red blood cells, urobilin, glucose, and in case of erythrocyturia with a microscopic examination.

*Statistics*

Statistical analysis was performed with Wilcoxon's test for paired observations (two-sided). A $P$ value < 0.05 was considered to indicate a significant difference.

## RESULTS

*Acute effects*

In Figure 1 the GFR and ERPF of the patients is shown just before and straight after the first infusion of gemcitabine. For 2 patients no renal measurements were available straight after the first infusion of gemcitabine because of technical problems. No significant change in GFR or ERPF was observed. Consequently, the FF did not change.

*Cumulative effects*

Absolute values of GFR and ERPF during gemcitabine treatment are shown in Table 1. 2 patients had tumour progression after one cycle, 1 had tumour progression after two cycles, and 5 patients had progressive disease after three cycles of gemcitabine. Only 3 patients received all six planned cycles of gemcitabine. Cumulative effects of gemcitabine on renal function could be studied in 8 patients who received 9–18 infusions of the drug. After two cycles of gemcitabine, there were no significant changes in GFR, ERPF or FF. In 3 of the 8 patients still on study after three cycles, their GFR decreased by more than 5%. However, the median values of GFR and ERPF did not change significantly after three and six cycles of gemcitabine.

During the observation period, no significant change in serum creatinine was found. The urinary excretion of tubular enzymes (LDH, ALP, gamma-GT and $\beta_2$-microglobulin) did not change significantly during treatment with gemcitabine (Table 2). Median levels of albumin in 24 h urine collections, expressed as albumin/creatinine ratio, did not change significantly after multiple cycles (Table 2). Patient 10, who experienced a decrease in GFR of 16%, developed significant albuminuria of 360 mg/24 h after the third cycle, which was accompanied by proteinuria (0.7 g/24 h) and erythrocyturia. These findings could also be explained by a culture-proven urinary tract infection. After treating this infection with ciprofloxacin, the albuminuria and erythrocyturia resolved and did not reappear during further gemcitabine administration. The serum creatinine of patient 10 rose from 100 μmol/l before the start of therapy to a maximum of 155 μmol/l after cycle 5. The serum creatinine decreased during cycle 6 to 133 μmol/l and during the months after the end of gemcitabine treatment to 112 μmol/l. Besides this patient, there were 3 other patients who developed transient erythrocyturia during gemcitabine treatment. This erythrocyturia lasted only for one or two treatment cycles. In one patient, it was attributed to urolithiasis, another patient suffered a urinary tract infection and in the third the cause could not be diagnosed. Of the 48 administered cycles of gemcitabine, 7 (15%) were accompanied by microscopic erthrocyturia.

## DISCUSSION

Gemcitabine is a new antimetabolite with definite activity against several solid tumours including NSCLC. Its toxicity profile is mild, with neutropenia and flu-like symptoms the most prominent features. Furthermore, proteinuria as a result of gemcitabine has been reported in up to 47% of cases [6–8]. No detailed studies have been reported concerning the possible influence of gemcitabine on renal function. In the current study, renal function was determined with an accurate radiochemical method. Results show that there was no acute detectable effect of gemcitabine on GFR, ERPF and FF. A cumulative effect of multiple cycles of gemcitabine on renal function could not be demonstrated. However, only 8

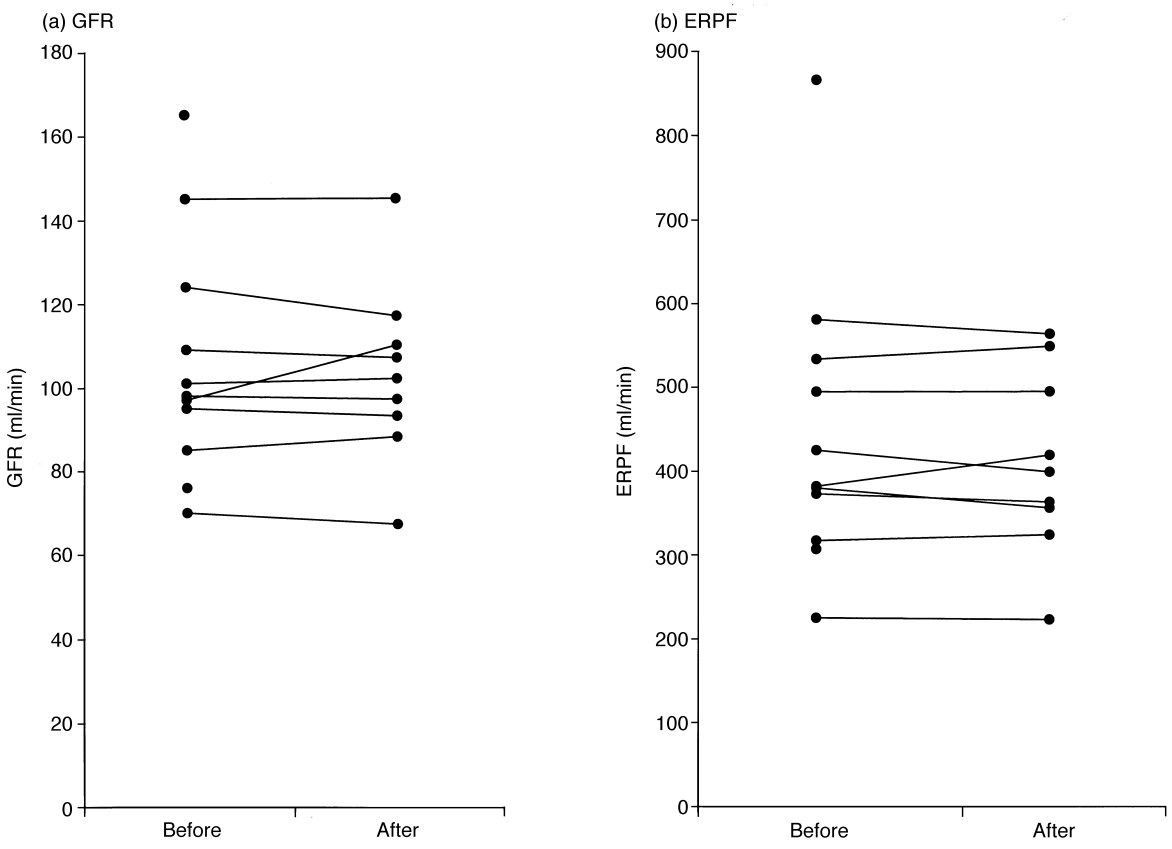


**Figure 1. GFR (a) and ERPF (b) before and straight after the first dose of gemcitabine (1250 mg/m$^2$).**

*Table* 1. *Changes in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) after multiple cycles of gemcitabine*

| | GFR (ml/min) | | | | ERPF (ml/min) | | | |
|---|---|---|---|---|---|---|---|---|
| Pt | Cycle 0 | Cycle 2 | Cycle 3 | Cycle 6 | 0 | Cycle 2 | Cycle 3 | Cycle 6 |
| 1 | 124 | — | — | — | 581 | — | — | — |
| 2 | 97 | — | — | — | 382 | — | — | — |
| 3 | 85 | 84 | 70 | 76 | 317 | 332 | 266 | 305 |
| 4 | 101 | 101 | 113 | — | 373 | 360 | 430 | — |
| 5 | 109 | 120 | 119 | — | 495 | 585 | 583 | — |
| 6 | 98 | 92 | 112 | 95 | 425 | 398 | 420 | 412 |
| 7 | 145 | 120 | 118 | — | 534 | 465 | 470 | — |
| 8 | 95 | 92 | 92 | — | 380 | 384 | 399 | — |
| 9 | 165 | 179 | 185 | — | 866 | 1121 | 972 | — |
| 10 | 70 | 78 | 64 | 59 | 225 | 261 | 254 | 228 |
| 11 | 76 | 107 | — | — | 307 | 470 | — | — |
| Median | 98 | 101 | 112.5 | 76 | 382 | 398 | 425 | 305 |
| Mean | 105.9 | 108.1 | 109.1 | 76.7 | 444.1 | 486.2 | 474.2 | 315.0 |
| S.D. | 26.6 | 21.0 | 25.3 | 12.2 | 144.3 | 163.3 | 151.6 | 64.7 |

*Table* 2. *Urinary excretion of tubular enzymes and glomerular protein. Expressed as ratio of ALP, LDH, gamma-GT, β2-microglobulin, albumin and creatinine, respectively, after multiple cycles of gemcitabine*

| | Cycle number | | | |
|---|---|---|---|---|
| Number of patients | 0 (before) ($n = 11$) | 2 ($n = 7$) | 3 ($n = 5$) | 6 ($n = 3$) |
| ALP/creatinine (U/mmol) | 1.4 (0.9–2)* | 1.2 (1–2.2) | 1.1 (0.7–2.7) | 1.4 (0.9–2.5)† |
| LDH/creatinine (U/mmol) | 2.2 (1.6–4.4) | 2.2 (1.7–2.5) | 2.5 (1.4–3.8) | 2.0 (1.5–3.4)† |
| Gamma-GT/creatine (U/mmol) | 5.4 (3.3–23) | 5.9 (2.8–9.0) | 4.8 (2.5–6.5) | 4.8 (2.5–8.0)† |
| β 2-microglobulin/creatinine (U/mmol) | 11.2 (3.2–41) | 4.6 (1.0–14) | 10 (3.8–22) | 15 (6.8–33)† |
| Albumin/creatinine (mg/mmol) | 0.87 (0.3–3.7) | 0.63 (0.3–2.4) | 0.51 (0.25–3.6) | 0.41 (0.4–33)† |

*Median (range). †Not significantly different from earlier cycles.

patients received three cycles and 3 patients all six planned cycles of gemcitabine. Of the 3 patients who received six cycles of gemcitabine, 2 suffered a GFR loss of more than 10%. Albuminuria occurred temporarily in only 1 patient. There were no signs of tubular damage during this study. We conclude from these data there is no acute renal toxicity with gemcitabine. No significant decrease of renal function could be found after multiple cycles of gemcitabine. However, because only few patients received all six cycles of gemcitabine (18 infusions), the effect of the drug on GFR could be underestimated, particularly since 2 of the 3 longest treated patients developed a decrease in GFR of more than 10%.

The mechanism of possible nephrotoxicity of gemcitabine is unclear. Anderson and associates [8] reported two cases of acute renal failure during gemcitabine treatment, both possibly due to microangiopathic haemolytic anaemia. Abratt and associates also reported a patient with renal function disturbance possibly accompanied by microangiopathic haemolytic anaemia [7]. The relationship with gemcitabine was uncertain. Elimination of gemcitabine from plasma is rapid and due mainly to deamination to its sole metabolite difluorodesoxyuridine (dFdU). Within 24 h, most of this metabolite is excreted in the urine. Abbruzzese and associates reported, in a phase I and pharmacokinetic study, that renal clearance of dFdU approximated creatinine clearance in most patients [5]. Therefore, glomerular filtration seems to be the most important route of excretion. The combination of erythrocyturia, albuminuria and GFR decrease found in some patients from the current study suggests glomerular damage as a possible cause for nephrotoxicity of gemcitabine. Additional studies are therefore warranted to investigate possible cumulative effects of gemcitabine on renal function, and its mechanism. During combination therapy of gemcitabine and, for instance, cisplatin, renal function should be monitored carefully in order to detect renal toxicity at an early stage.

In conclusion, we did not observe acute renal toxicity of gemcitabine. No significant cumulative effects of gemcitabine on renal function could be detected, but 3 of 8 patients, treated with multiple cycles of gemcitabine, showed a moderate decrease in renal function. Glomerular damage might play a role in the development of renal function loss.

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