

# Clinical Experience with Single-Agent Gemcitabine Chemotherapy in Patients with Non-Small-Cell Lung Cancer in Whom Previous Chemotherapy Has Failed

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**Background:** In a phase II study, responses and toxicity to single-agent gemcitabine chemotherapy were evaluated in patients with non-small-cell lung cancer (NSCLC) who had failed previous cisplatin-based chemotherapy.

**Methods:** Twenty patients were enrolled from December 2001 to December 2003: 17 of them had received first-line cisplatin-based regimens and second-line docetaxel treatment; and 3 had previously received cisplatin plus paclitaxel. Study treatment comprised an intravenous infusion of gemcitabine 1200 mg/m<sup>2</sup> on days 1, 8, and 15 of each 4-week cycle.

**Results:** Fifty-seven cycles of treatment were given (mean, 2.9 cycles per patient). All patients were evaluable for toxicity profile, and 16 were evaluable for response rate. The principal toxicity was myelosuppression: grade 3 neutropenia occurred in 2 patients (10%), thrombocytopenia in 3 (15%), and anemia in 1 (5%). Other toxicities were few and mild in severity. After 2 cycles of treatment, 2 of 16 patients (12.5%) had a partial response. The median time to disease progression was 2.1 months, and median survival time was 7.5 months. The 1-year survival rate was 36%.

**Conclusion:** Salvage, single-agent chemotherapy with gemcitabine has modest activity, is well tolerated, and yields good survival in NSCLC patients who have failed previous chemotherapy. Such single-agent therapy may therefore be suggested for use in patients with good performance status who ask for further chemotherapy, when disease progresses after cisplatin-based therapy, but especially after second-line docetaxel therapy. [*J Chin Med Assoc* 2005;68(4):163–166]

**Key Words:** gemcitabine, non-small-cell lung cancer, salvage therapy

## Introduction

Since first-line chemotherapy with new, platinum-based agents for non-small-cell lung cancer (NSCLC) has been documented as being superior to conventional chemotherapy, the use of salvage therapy for cancer patients who fail primary chemotherapy is under active investigation. Docetaxel, a novel anticancer agent, prolonged patient survival in phase III, randomized studies versus vinorelbine, ifosfamide, or best supportive care, in NSCLC patients in whom previous chemotherapy had failed,<sup>1,2</sup> and has therefore been recommended as a second-line treatment for NSCLC.<sup>3</sup>

Gemcitabine, a nucleoside analog with confirmed activity against chemotherapy-naïve NSCLC,<sup>4</sup> generally has few, and only mild, toxicities. Significant adverse effects of gemcitabine that have an impact on patient quality of life, or that require treatment withdrawal, are reported to be less than with any other single new agent or combination of agents.<sup>5</sup> In addition, gemcitabine is safe and easy to administer in an outpatient setting.

Gemcitabine probably also has activity in the second-line treatment of NSCLC, with a response rate to single-agent therapy ranging from 6.0–20.6% in phase II studies,<sup>6–10</sup> and documented superior survival and

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response rates in phase III trials of gemcitabine plus cisplatin versus cisplatin alone (or versus other cisplatin-based conventional regimens).<sup>5</sup> However, the potential roles of gemcitabine as second- and third-line chemotherapy have not been well defined. Because of the relatively favorable safety profile of gemcitabine, and marked activity of the compound as first-line chemotherapy for NSCLC, we conducted a phase II study to determine the efficacy and toxicity profiles of single-agent gemcitabine in NSCLC patients in whom previous first-line, cisplatin-based, new-agent chemotherapy had failed; several patients had also received second-line docetaxel therapy.

## Methods

### *Study population*

Patients with NSCLC who had failed previous cisplatin-based chemotherapy, and who were aged  $\geq 18$  years, were enrolled in the study after giving informed consent. Eligibility criteria comprised the following: histologic or cytologic diagnosis of stage IV NSCLC; performance status of 0–2 on the Zubrod scale; clinically measurable disease defined as bi-dimensionally measurable lesions, with clearly defined margins on a chest computed tomography (CT) scan; no previous radiotherapy for measurable lesion(s); adequate bone marrow reserve, with a white blood cell count  $\geq 4000/\text{mm}^3$ , platelets  $\geq 100,000/\text{mm}^3$ , and hemoglobin  $\geq 10$  g/dL; and no previous history of gemcitabine treatment. Exclusion criteria comprised the following: active infection; inadequate liver function (bilirubin  $> 1.5$  times the normal range, alanine aminotransferase and aspartate aminotransferase levels  $> 3$  times the upper limit of normal); and inadequate renal function (serum creatinine  $> 2.0$  mg/dL).

### *Study treatment*

All patients received a 30-minute, intravenous infusion of gemcitabine  $1200 \text{ mg}/\text{m}^2$  on days 1, 8, and 15 of each 4-week cycle. A complete blood cell count was done in the 24 hours before chemotherapy. Serum biochemistry studies were performed before every course of chemotherapy, and during each course, if clinically indicated. Drug-related adverse events and toxicities were recorded, according to established Eastern Cooperative Oncology Group (ECOG) criteria.<sup>11</sup>

Within each cycle, the dose of gemcitabine was reduced by 50% if absolute neutrophil count (ANC) ranged from  $1.0\text{--}1.5 \times 10^9/\text{L}$ , and/or platelet count ranged from  $75\text{--}99 \times 10^9/\text{L}$ , on the day of scheduled

chemotherapy; the dose was omitted if ANC was  $< 1.0 \times 10^9/\text{L}$ , or platelet count was  $< 75 \times 10^9/\text{L}$ . During each cycle, and in subsequent cycles, and for toxicities other than nausea, vomiting and alopecia, the dose of gemcitabine was reduced by 50% if grade 3, non-hematologic toxicities were noted; the dose was omitted in case of grade 4 toxicities.

### *Study measurements*

Baseline evaluations included documentation of patient history, a physical examination, and an assessment of performance score. A complete blood cell count, urinalysis, serum biochemistry profile, electrocardiogram, chest X-ray, whole-body bone scan, brain CT scan, and chest (including liver and adrenal glands) CT scan, were also performed.

Response was evaluated after the first 2 cycles of chemotherapy, and after every 2 cycles thereafter. The types of response were also assessed, according to established ECOG criteria.<sup>11</sup> Patients who responded, and those with stable disease, continued treatment until disease progression or the completion of 6 cycles of treatment. Overall survival and time to disease progression were analyzed using the Kaplan-Meier estimation method. Survival was measured from the time the first dose of gemcitabine was administered until the time of death or last follow-up.

## Results

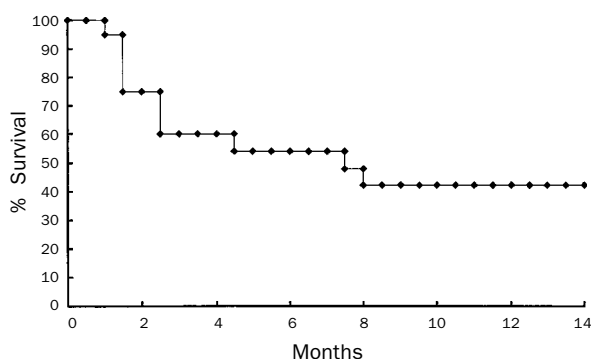
### *Demographic data*

Between December 2001 and December 2003, 20 patients (9 males; 11 females) were enrolled in the study. Patient age ranged from 45–75 years (mean, 61.4 years), and performance status was 1 ( $n = 5$ ) or 2 ( $n = 15$ ). Regarding histologic sub-type, 7 patients had adenocarcinoma, 5 had squamous cell carcinoma, and 8 had other NSCLC. All patients had stage IV disease, and all had undergone previous cisplatin-based combination chemotherapy and taxane treatment (paclitaxel as first-line, and/or docetaxel as second-line treatment). Thus, gemcitabine was second-line chemotherapy in 3 patients, and third-line therapy in 17 patients. All patients were evaluable for toxicity profile, but 4 patients were unevaluable for response (all were using gemcitabine as third-line therapy) because they refused further treatment after the first gemcitabine cycle.

### *Clinical findings*

A total of 57 treatment cycles were administered (mean, 2.9 cycles per patient; median, 2 cycles per patient).

After 2 cycles of treatment, 2 of 16 patients (12.5%; 95% confidence interval [CI], 0, 28.7) had a partial response, stable disease was noted in 6 patients (37.5%), and progressive disease was documented in the remaining 8 (50%). The 2 patients with a partial response had responded to third-line therapy. The overall median time to disease progression was 2.1 months (95% CI, 1.4, 2.9), and overall median survival was 7.5 months (95% CI, 1, 14) (Figure 1). The 1-year survival rate was 36%. For the 17 patients who received gemcitabine as third-line therapy, the median survival time was 4.5 months.



**Figure 1.** Kaplan-Meier survival curve for 20 patients with non-small-cell lung cancer treated with gemcitabine. The overall median survival was 7.5 months and the 1-year survival rate was 36%.

### Toxicity data

The principal toxicities were hematologic and were mild in severity. There was no grade 4 hematologic toxicity; however, grade 3 neutropenia occurred in 2 patients (10%), grade 3 thrombocytopenia occurred in 3 (15%), and grade 3 anemia occurred in 1 (5%). No febrile neutropenia occurred. Non-hematologic toxicities were few and mild ( $\leq$  grade 2).

### Discussion

As the response rate to chemotherapy for patients in whom previous chemotherapy has failed is usually low ( $\leq$  25%),<sup>12</sup> the options available to patients with advanced NSCLC resistant or refractory to first-line chemotherapy are very limited. However, as new anticancer drugs and their combinations with cisplatin have recently shown better response rates and survival than conventional regimens, increased survival has become the main motivation when considering second-line chemotherapy for NSCLC. Since 2003, after several clinical trials of new anticancer agents as sal-

vage chemotherapy, docetaxel has been suggested as standard, second-line chemotherapy, whereas gefitinib has been suggested for patients in whom both platinum-based and docetaxel chemotherapies have failed.<sup>3</sup>

When considering salvage chemotherapy with second-line or subsequent regimens, symptomatic relief and low rates of treatment-related toxicity are relatively more important than the pursuit of high response rates. In phase II trials, the response rate to single-agent gemcitabine as second-line therapy for NSCLC has ranged from 6.0–20.6%; median survival has ranged from 4–7.9 months.<sup>6–10</sup> The present study revealed a response rate of 12.5% and a median survival of 7.5 months; these values are within the aforementioned ranges. The toxicity of single-agent gemcitabine therapy has been minimal and mild in severity, both in the present and previous studies.<sup>6–10</sup> The present trial also identified a median survival time of 4.5 months, together with very mild toxicity, in the 17 patients receiving gemcitabine as third-line therapy. This finding warrants further clinical study, even though median survival was shorter than that reported for daily, oral gefitinib therapy in the Iressa<sup>®</sup> Dose Evaluation in Advanced Lung Cancer (IDEAL)-2 study, in which previous platinum-based combination chemotherapy and docetaxel regimens had also failed.<sup>13</sup>

Other commonly used and investigated, non-platinum-based, salvage chemotherapies are gemcitabine plus taxanes or vinorelbine.<sup>14–18</sup> These regimens have been evaluated in phase II studies, but patient survival was not significantly better than that in previous studies of single-agent docetaxel therapy,<sup>1,2</sup> even though response rates may be greater with the combination schedules. Importantly, gemcitabine (plus taxanes or vinorelbine) is well tolerated and relatively safe, and is an active salvage regimen in patients with NSCLC in whom previous platinum-based chemotherapy has failed. From the results of our study, gemcitabine alone is also a well-tolerated agent with modest activity, even in patients who have undergone previous first-line, platinum-based, combination chemotherapy and second-line docetaxel therapy.

In summary, gemcitabine is an effective salvage regimen for NSCLC patients in whom previous chemotherapy has failed. This agent may be suggested for patients who ask for further chemotherapy, when they experience disease progression after cisplatin-based chemotherapy, but especially after second-line docetaxel therapy. Further studies of single-agent gemcitabine therapy, such as a comparison with gefitinib, now warrant consideration, particularly in patients for whom both cisplatin-based chemotherapy and second-line docetaxel therapy have failed.

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