*Anti-Cancer Drugs 1997*, 8, pp. 574–581

# Activity of gemcitabine in the treatment of patients with non-small cell lung cancer: a multicenter phase II study

**Akira Yokoyama, Yushi Nakai,[1] Shuichi Yoneda,[2] Yuzo Kurita and Hisanobu Niitani[3]**
The Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan. Tel: (+81) 25 266 5111; Fax: (+81) 25 266 9385. [1]The Department of Internal Medicine, Sendai Kousei Hospital, Sendai, Japan. [2]The Department of Respiratory Medicine, Saitama Cancer Center, Saitama, Japan. [3]The Tokyo Cooperative Oncology Group, Tokyo, Japan.

**Gemcitabine is a novel nucleoside analog with unique activity against a wide range of solid tumors. We initiated a multicenter phase II study in patients with non-small cell lung cancer (NSCLC) to evaluate the efficacy and safety of gemcitabine. Eligible patients had stage III and IV, previously untreated with chemotherapy, age range from 18 to 80 years, and ECOG performance status 0–2. Gemcitabine was administered at 1000 mg/m$^2$ as a continuous i.v. infusion once a week for a consecutive 3 week period, followed by 1 week of rest. Of the 69 patients enrolled, 67 patients were eligible for efficacy evaluation. The overall response rate was 20.9% with a 95% confidence interval of 11.9–32.6%. The median survival time was 9.0 months and the 12 month survival rate was 31.3%. Grade 3 or 4 toxicities included neutropenia in 22.7%, anemia in 13.4%, leukopenia in 10.4%, anorexia in 10.4%, malaise in 7.5% and nausea/vomiting in 6.0%. Serious toxicities were septic shock and interstitial pneumonia (one patient each). Gemcitabine, administered weekly for three consecutive weeks followed by 1 week of rest, is an active agent for NSCLC. Gemcitabine is currently being evaluated in combination with cisplatin and other agents.**

*Key words*: Gemcitabine, multicenter, NSCLC, nucleoside analog, phase II study.

## Introduction

The vast majority of patients with non-small cell lung caner (NSCLC) present with advanced and unresectable disease. Although chemotherapy contributes to prolonging the survival of NSCLC patients, current regimens remain unsatisfactory. There is, therefore, an urgent need to develop new anticancer agents for NSCLC. Recently, several new drugs with promising activities for NSCLC have been identified including: paclitaxel, docetaxel, irinotecan (CPT-11), vinorelbine and gemcitabine. Among these compounds, gemcitabine, a novel nucleoside analog,[1] in which two fluorine atoms have been introduced into the side chain of the deoxyribose, has been developed as an anticancer agent by Eli Lilly and Company. The compound is a prodrug that is metabolized intracellularly into its active nucleotide forms, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP).[2] It has a unique mechanism of action termed 'masked chain termination' which allows base pairing of one or more nucleotides after insertion of dFdCTP into DNA, thus providing increased protection against incision repair.[3] Gemcitabine exhibited significant cytotoxic activity against established murine and human solid tumor lines and primary cultures of human tumors as well as human leukemias.[4–7] In animal tumor models, the antitumor activity of gemcitabine is schedule dependent.[6] Gemcitabine was effective not only in the treatment of mouse hematologic tumors but also in the treatment of mouse and human solid tumors, including human NSCLC, H-74 and CPH SCLC 54B, and human colon cancer, H-110, all of which are resistant to conventional anticancer drugs.[6,8,9]

In a phase I study, Taguchi *et al.*[10] reported that the maximum tolerated dose (MTD) was 1000 mg/m$^2$ and the dose-limiting toxicity (DLT) was myelosuppression (leukopenia, neutropenia and thrombocytopenia). Early phase II studies were conducted with a schedule in which gemcitabine was given on days 1, 8 and 15 of a 28 day cycle, at doses of 800 or 1000 mg/m$^2$ once weekly for three consecutive weeks, followed by 1 week of rest. The response rates were 25.0 and 14.3%, respectively. Most of the toxicities were mild and tolerable.[11] This multicenter phase II study of gemcitabine as a single agent was therefore conducted to clarify the efficacy and safety in patients with NSCLC.

Correspondence to A Yokoyama

## Patients and methods

### Patients

This study was conducted between January 1993 and February 1994 according to good clinical practice. Patients were enrolled in the study after giving informed consent. Eligibility criteria included histologically and cytologically confirmed NSCLC and inoperable (stage III or IV) measurable lesion(s) previously untreated with chemotherapy. Patients were required to have a performance status of 0–2, age 18–80 years and a life expectancy of at least 2 months. Patients were also required to have normal function of vital organs, i.e. hemoglobin greater than or equal to 9 g/dl, leukocyte greater than or equal to 4000/$\mu$l, platelet count greater than or equal to 100 000/$\mu$l, AST and ALT below twice the normal levels, and serum creatinine and total bilirubin, each less than or equal to 1.5 mg/dl. Patients with serious concurrent disease, pregnancy, lactation, childbearing potential, active concurrent malignancy, serious allergy, symptomatic brain metastasis and hypercalcemia were excluded from this study.

### Treatment and assessment

Gemcitabine was administered at a dose of 1000 mg/m$^2$ weekly for three consecutive weeks (days 1, 8 and 15) followed by 1 week of rest. Courses of treatment were repeated every 28 days. Response to therapy was assessed by WHO criteria after each course of gemcitabine treatment. All responses were independently validated by extramural review board. Laboratory tests (hematological and biochemical examinations) were performed at enrollment, once a week during the treatment period and for the follow-up of any abnormal finding. Disease-related subjective and objective symptoms were monitored during gemcitabine treatment. Toxicities were assessed using the Adverse Reaction Assessment List of the Japan Society for Cancer Therapy.[12]

### Dose modification

Dose escalation to 1250 mg/m$^2$ was permitted if the nadirs of leukocyte and platelet counts were above 3000 and 70 000/$\mu$l, respectively, in each of the previous courses of gemcitabine treatment. Doses were reduced from 1000 to 800 mg/m$^2$ in subsequent courses of gemcitabine treatment if grade 3 or higher toxicities were experienced in previous courses of gemcitabine treatment. Doses of gemcitabine in subsequent courses were delayed until recovery of the leukocyte and platelet counts to above 2000 or 70 000/$\mu$l. Patients were withdrawn from the study if they had still not recovered after a period of 4 weeks without treatment.

## Results

Sixty nine patients were enrolled in this study. Of the 69 patients, 67 patients were eligible. Two cases were excluded from evaluation of efficacy and safety due to protocol violations (one patient had a history of chemotherapy and one patient had stage I disease). Patient characteristics are listed in Table 1. The median age was 67.0 years. Stage III and IV NSCLC was seen in 47.7 and 52.2% of patients, respectively, and was histologically diagnosed as

**Table 1.** Patient characteristics

| No. of eligible patients | | 67 |
|---|---|---|
| Sex | male | 50 (74.6) |
| | female | 17 (25.4) |
| Age (years) | median | 67.0 |
| | range | (36–80) |
| Stage | IIIa | 11 (16.4) |
| | IIIb | 21 (31.3) |
| | IV | 35 (52.2) |
| Histology type | adenocarcinoma | 36 (53.7) |
| | squamous cell carcinoma | 28 (41.8) |
| | large cell carcinoma | 3 (4.5) |
| Performance status | 0 | 13 (19.4) |
| | 1 | 36 (53.7) |
| | 2 | 18 (26.9) |

adenocarcinoma in 53.7%, squamous cell in 41.8% and large cell in 4.5%. ECOG performance status was graded 0 or 1 in 73.1% and 2 in 26.9%.

## Dose modification

The median number of doses of gemcitabine received by all 67 eligible patients was six (range two to 20). Fourteen patients (20.9%) received doses escalating to 1250 mg/m$^2$ and two patients (3.0%) received doses reduced to 800 mg/m$^2$. Two patients (3.0%) had doses omitted. The reasons for dose reduction and omissions were leukopenia and thrombocytopenia. Dose modifications of gemcitabine are shown in Table 2.

## Response to gemcitabine

Response was evaluated after one course of chemotherapy and thereafter following every other course. Response rates are shown in Table 3. There were no complete responses. However, 14 patients (20.9%) of the 67 patients eligible demonstrated a partial response with a 95% confidence interval of 11.9–32.6%, by extramural review board. The response rates for adenocarcinoma and squamous cell carcinoma were 27.8 and 10.7%, respectively. The response rate for adenocarcinoma tended to be higher than those for other histological types. The median administration of gemcitabine required to achieve a partial response was four doses (range two to eight). The median duration of responses was 3.6 months (range 0.9–8.0 months) and the median of time to progression in partial response was 4.7 months (range 2.1–9.5 months).

## Survival

At a median follow up time of 18.4 months (range 13.3–24.0 months) overall median survival time (MST) for all 67 patients was 9.0 months. The Kaplan–Meier survival curve for 67 patients is shown in Figure 1. The 1 year survival rate was 31.3%.

The median survival times for responders and non-responders were 10.6 and 7.4 months, respectively ($p = 0.1073$).

## Toxicity

The toxicities observed during gemcitabine treatment are listed in Tables 4 and 5. Most of the toxicities were relatively mild and tolerable, and included anemia, myelosuppression (leukopenia, neutropenia, thrombocytopenia), AST/ALT elevation, anorexia, nausea/vomiting, fever and malaise.

**Table 2.** Delivered doses and dose modifications of gemcitabine

| | | |
|---|---|---|
| No. of doses | median | 6 |
| | range | 2–20 |
| Dose modification | increased (1250 mg/m$^2$) | 14 (20.9) |
| [no. of patients (%)] | unchanged (1000 mg/m$^2$) | 51 (76.1) |
| | reduced (800 mg/m$^2$) | 2 (3.0) |

**Table 3.** Tumor response

| Histology type | No. of eligible patients | No. of evaluable patients | CR | PR | MR | NC | PD | Not evaluable[a] | Response rate | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CR + PR eligible (%) | CR + PR evaluable (%) |
| Adenocarcinoma | 36 | 34 | 0 | 10 | 3 | 13 | 8 | 2 | 27.8 | 29.4 |
| Squamous cell carcinoma | 28 | 27 | 0 | 3 | 3 | 14 | 6 | 2 | 10.7 | 11.1 |
| Large cell Carcinoma | 3 | 3 | 0 | 1 | 1 | 1 | 1 | 0 | 33.3 | 33.3 |
| Total | 67 | 64 | 0 | 14 | 6 | 28 | 15 | 4 | 20.9 (11.9–32.6) | 21.9 (12.5–34.0) |

95% confidence interval in parentheses.
[a]This includes three patients who did not complete one treatment course and one patient who completed one treatment course but whose study lesion became unmeasurable after treatment with gemcitabine.
CR, complete response; PR, partial response; MR, minor response; NC, no change; PD, progressive disease.

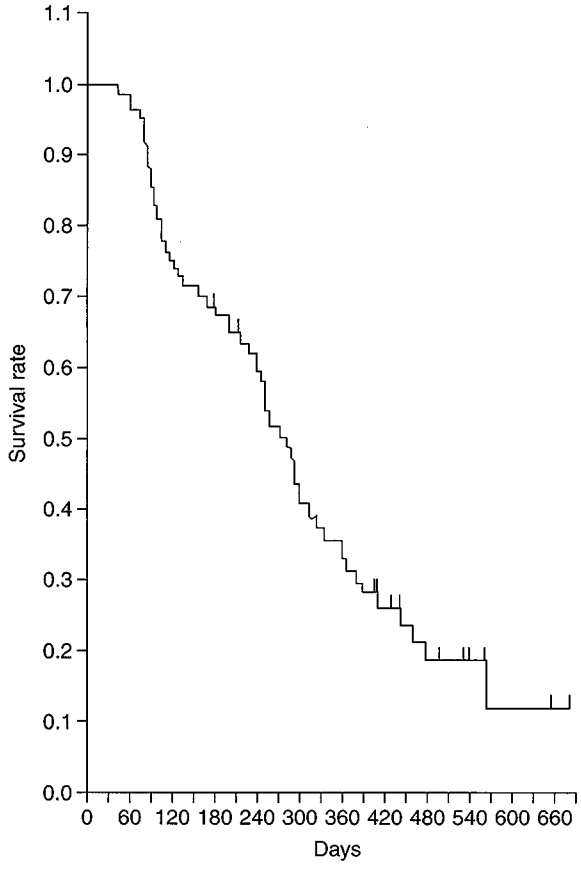


**Figure 1.** Overall survival time for 67 patients.

## Hematological toxicity

Grade 4 toxicities were rarely seen, with neutropenia in two of 66 (3%), leukopenia in one of 67 (1.5%) and thrombocytopenia in one of 67 (1.5%) patients, respectively. Grade 3 or higher toxicities were frequent: anemia occurred in nine of 67 (13.4%), leukopenia in seven of 67 (10.4%) and thrombocytopenia in three of 67 (4.5%) patients, respectively. Of these, one patient experienced grade 4 leukopenia, neutropenia and thrombocytopenia simultaneously after receiving three doses of gemcitabine and died of septic shock. The patient who developed septic shock experienced fever, grade 4 myelosuppression (leukopenia, neutropenia, thrombocytopenia) and infection after one cycle of gemcitabine treatment, and despite treatment with antibiotics and granulocyte colony-stimulating factor (G-CSF), died of septic shock 12 days after the third administration of gemcitabine.

## Non-hematological toxicity

Sixty-seven eligible patients were assessable for symptomatic toxicities. The most common toxicities were anorexia, nausea/vomiting, fever and malaise. Patients experiencing grade 3 or higher toxicities were less frequent: anorexia occurred in seven (10.4%), nausea/vomiting in four (6.0%), malaise in five (7.5%), interstitial pneumonia in one (1.5%) and septic shock in one (1.5%), respectively. Of these, grade 4 toxicities were seen with malaise in two (3%), septic shock in one (1.5%) and interstitial pneumonia in one (1.5%). The patient who developed interstitial pneumonia had a mild fibrosis complication prior to gemcitabine treatment. This patient experienced fever and severe dyspnea after one cycle of gemcitabine treatment. Although this patient was treated with 1000 mg methylprednisolone, sodium succinate and oxygen inhalation treatment, he had repeated recurrences of interstitial pneumonia and died of dyspnea approximately 7 months after gemcitabine treatment. One patient developed a bronchomediastial fistula. This patient died of a complication secondary to disease progression 44 days after completion of two cycles of gemcitabine treatment. The causal relationship between this death and gemcitabine treatment is unknown.

Grade 3 toxicities were also seen, with lactate dehydrogenase increased in one of 66 (1.5%), hypoalbuminemia in one of 59 (1.7%) and alkaline phosphatase increased in one of 67 (1.5%) patients, respectively. Twenty-four of 67 patients (35.8%) had

**Table 4.** Hematological toxicity

| Findings | No. of patients with data | No. of patients with toxicities | Incidence (%) | Grade (no. of patients) | | | | Incidence of grade 3 and 4 toxicities (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 | |
| Anemia | 67 | 49 | 73.1 | 14 | 26 | 9 | – | 13.4 |
| Neutropenia | 66 | 39 | 59.1 | 10 | 14 | 13 | 2 | 22.7 |
| Leukopenia | 67 | 34 | 50.7 | 9 | 18 | 6 | 1 | 10.4 |
| Thrombocytopenia | 67 | 14 | 20.9 | 7 | 4 | 2 | 1 | 4.5 |

**Table 5.** Non-hematological toxicity

| Findings | No. of patients evaluated | No. of patients with reactions | Incidence (%) | Grade (no. of patients) | | | | Incidence of grade 3 and 4 reactions (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 | |
| Anorexia | 67 | 34 | 50.7 | 17 | 10 | 7 | | 10.4 |
| Nausea/vomiting | 67 | 31 | 46.3 | 16 | 11 | 4 | | 6.0 |
| Fever | 67 | 25 | 37.3 | 11 | 14 | | | |
| Malaise | 67 | 20 | 29.9 | 8 | 7 | 3 | 2 | 7.5 |
| Interstitial pneumonia | 67 | 2 | 3.0 | | 1 | | 1 | 1.5 |
| Alopecia | 67 | 2 | 3.0 | 2 | | | | |
| Septic shock | 67 | 1 | 1.5 | | | | 1 | 1.5 |
| AST/ALT increased | 67 | 24 | 35.8 | 17 | 7 | | | |
| Lactate dehydrogenase increased | 66 | 9 | 13.6 | 6 | 2 | 1 | | 1.5 |
| Hypoalbuminemia | | | | | | | | |
| Alkaline phosphatase increased | 59 | 7 | 11.9 | 6 | | 1 | | 1.5 |
| BUN increased | 67 | 5 | 7.5 | 3 | 1 | 1 | | 1.5 |
| bilirubinemia | | | | | | | | |
| Abnormal ECG | 67 | 3 | 4.5 | 2 | 1 | | | |
| | 66 | 1 | 1.5 | 1 | | | | |
| | 15 | 1 | 6.7 | | | 1 | | 6.7 |

grade 1 or 2 transient elevation of AST/ALT. Increase in serum creatinine level was not observed.

Median values of nadir on leukopenia in each of the four cycles were 1110, 1333, 1266 and 1692/$\mu$l, respectively. Median values of nadir on neutropenia in each of the four cycles were 2600, 3100, 2800 and 3260/$\mu$l, respectively. Median values of nadir on thrombocytopenia in each of the three cycles were 6.95, 8.6 and 7.7/$\mu$l, respectively. Therefore, hematological toxicities (leukopenia, neutropenia, thrombocytopenia) could not be intensified by continuous gemcitabine treatment.

## Discussion

Four dosing schedules were evaluated in phase I studies in the US. These phase I studies have shown gemcitabine to be schedule dependent for toxicity. Three of the four dosing schedules were discontinued. In two schedules, non-hematological toxicity was a problem. Fever, flu-like symptoms and severe hypotension occurred during the 5 day continuous dosing study,[13] and fatigue, fever, flu-like symptoms and rash occurred in the twice weekly dosing study (Vermorken *et al.*, submitted). Gemcitabine was well tolerated in a once every 2 weeks dosing study.[14] In the initial foreign dose-finding study in previously treated patients with solid tumor, using the once weekly dosing schedule for 3 weeks followed by a week of rest,[15] non-hematological toxicity was minimal and MTD was 790 mg/m$^2$. Taguchi *et al.*[10] reported that MTD in patients with tumor was 1000 mg/m$^2$ in a phase I study using a once weekly dosing schedule for 3 weeks followed by 1 week of rest. Fukuoka *et al.*[11] reported that the response rate with a dose of 800 mg/m$^2$ of gemcitabine, for weekly administration over 28 days, followed by 1 week of rest, was 25% (95% confidence interval 5.5–57.2%). The study was conducted in chemonaive patients with NSCLC and toxicity was tolerable. Therefore, doses of gemcitabine were increased from 800 to 1000 mg/m$^2$ during the study. The response rate was 14.3% (95% confidence interval 4.8–30.3%), with a dose of 1000 mg/m$^2$ in chemonaive patients and almost all toxicities were tolerable.

The current phase II study was conducted based on the results by Fukuoka *et al.*[11] Gemcitabine was proven to be active as a single agent for chemonaive NSCLC patients, with a validated response rate of 20.9% (95% confidence interval 11.9–32.6%) by extramural review. The response rate was favorable, especially the response rate for adenocarcinoma (27.8%) which tended to be higher than those for other histologic types. It is important to note the response rates were validated by extramural review, as this demonstrates the data has undergone a more rigorous evaluation than drugs that did not use a similar review process.

The response rates in our study were very similar to the results of the study by Anderson *et al.*[16] and Abratt *et al.*[17] Anderson *et al.* reported that 16 (20%) of the 79 patients evaluable for response had a partial response in the study (95% confidence interval 12–31%). Fifty-four of these patients received 800 mg/m$^2$ and 28 received 1000 mg/m$^2$ at a dosing schedule of once a week for 3 weeks, followed by a week of rest. Abratt *et al.*[17] reported two complete responses and 13 partial responses (20%; 95% confidence interval 11.6–30.8%) observed in the study, in which 53 patients received 1000 mg/m$^2$ and 31 patients received 1250 mg/m$^2$ at a dosing schedule of once per week for 3 weeks followed by 1 week of rest.

Overall MST of gemcitabine as single agent (responders and non-responders combined) was 9 months in our study. These results are similar to those of the study by Anderson *et al.*[16] and Abratt *et al.*[17] (7 and 9.2 months, respectively), which further supports gemcitabine's suitability as a single agent in NSCLC.

In addition, Lund *et al.*[18] reported a response rate of 19% using a schedule of 90 mg/m$^2$ twice weekly, but the schedule showed poor tolerance, with a higher frequency of non-hematologic toxicity, including fever and severe flu-like symptoms. Our schedule of gemcitabine administration, once weekly for 3 weeks followed by 1 week of rest, was acceptable for the patients. Almost all patients received gemcitabine administration according to protocol. Therefore, we concluded that this would be an optimal dose schedule.

Hematological toxicities included myelosuppression including leukopenia, neutropenia and thrombocytopenia. The incidence of grade 3 or higher toxicities of gemcitabine included neutropenia (22.7%), leukopenia (10.4%) and thrombocytopenia (4.5%) which were considered to be easy to control. Obvious intensification of hematological toxicities (leukopenia, neutropenia and thrombocytopenia) by administration of this compound were not observed.

Non-hematologic toxicities included anorexia, nausea/vomiting, fever and malaise, and the incidence of grade 3 or higher toxicities included nausea/vomiting (6.0%), malaise (7.0%) and anorexia (10.4%). Almost all were corrected with supportive care or without treatment. However, we did experience two interstitial pneumonias and one septic shock due to myelosuppression. Consequently, to prevent the occurrence of interstitial pneumonia, we recommended that the patient who had fibrosis as a complication should not be treated with gemcitabine. With regard to the patient who, in spite of treatment with antibiotics, died of septic shock due to myelosuppression, the leukocyte value of this patient was 12 000/$\mu$l prior to gemcitabine treatment. There was, therefore, a possibility the patient already had an infectious disease. To prevent the occurrence of severe myelosuppression, it is desirable that hematological examination should be carried out before gemcitabine administration, and gemcitabine treatment should not be administered to patients with infection and severe complications.

Recently, further gemcitabine combination studies have been undertaken with cisplatin, carboplatin and ifosfamide.[19–25] In these studies response rates of combination therapy on gemcitabine were superior to those of gemcitabine as a single agent. Many of the reports show the results of combination with cisplatin.[19–23] The dosing schedule of cisplatin or gemcitabine and cisplatin combination was investigated on day 1, day 2 and day 15, respectively. Abratt *et al.*[19] reported that gemcitabine was given at a dose of 1000 mg/m$^2$ weekly for 3 weeks and cisplatin was given at a dose of 100 mg/m$^2$ on day 15 with gemcitabine. The response rate was 52% (95% confidence interval 37–66%) and toxicities were relatively modest. Crinò *et al.*[20] reported that gemcitabine was administered at a dose of 1000 mg/m$^2$ weekly for 3 weeks and cisplatin was administered at a dose of 100 mg/m$^2$ on day 2 with gemcitabine. The response rate was 54% (95% confidence interval 40–68%) and toxicities were modest. Sandler *et al.*[21] reported that gemcitabine was administered at a dose of 1000 mg/m$^2$ weekly for 3 weeks and cisplatin was given at a dose of 100 mg/m$^2$ on day 1 with gemcitabine. The response rate was 42% and toxicities were mainly hematologic.

## Conclusion

In conclusion, gemcitabine is an active single agent with a 20% or higher response rate in chemonaive NSCLC patients. The toxicities of gemcitabine were tolerable and non-hematological toxicity was relatively mild. Therefore, gemcitabine is a suitable agent for combination chemotherapy for NSCLC cancer. Further investigation into the suitability of combination chemotherapy with gemcitabine is currently underway.

## Acknowledgments

The authors would like to thank the following investigators for their participation in this study: Eiichi Sakai, Internal Medicine, National Dohoku

Hospital, 7 Hanasaki-cho, Asahikawa-city Hokkaido 070. Mitsuo Asakawa, Internal Medicine III, Sapporo Medical College Hospital, 16-291 Nishi, Minamiichijo, Chuo-ku, Sapporo-city, Hokkaido 060. Akihisa Fujita, Respiratory Medicine, Hokkaido Keiaikai Minamiichijo Hospital, 13 Nishi, Minamiichijo, Chuo-ku, Sapporo-city, Hokkaido 060. Takehito Nakabayashi, Respiratory Medicine, National Sapporo Hospital, 2-3-54, Shijo, Kikusui, Shiraishi-ku, Sapporo-city, Hokkaido 003. Hiroshi Miyamoto, Internal Medicine, Ebetsu General Hospital, 6-1, Wakakusa-cho, Ebetsu-city, Hokkaido 067. Haruo Kikkawa, Internal Medicine, Akita Red-Cross Hospital, 1-4-36, Nakadori, Akita-city, Akita 010. Kyoshi Konno, Internal Medicine, Tohoku Central Hospital, 3-2-5, Wago-cho, Yamagata-city, Yamagata 990. Sadahiro Koinumaru, Respiratory Medicine, Miyagi Prefectural Cancer Center, 47-1, Nodayama, Merishimashioto, Natori-city, Miyagi 981-12. Yoshiyuki Anzai, Respiratory Medicine, Takeda General Hospital, 3-27, Yamago-cho, Aizuwakamatsu-city, Fukushima 965. Kohichi Hasegawa, Internal Medicine, Jizankai Medical Institute Tsuboi Hospital, 1-10-13, Nagakubo, Asaka-cho, Koriyama-city, Fukushima 963-01. Toshiaki Tsuchiya, Internal Medicine, National Nishiniigata Hospital, 1-14-1, Masago, Niigata-city, Niigata 950-21. Takayuki Kuriyama, Respiratory Medicine, Institute for Lung Cancer, School of Medicine, University of Chiba, 1-8-1, Inohana, Chuo-ku, Chiba-city, Chiba 260. Harubumi Kato, Surgery I, Tokyo Medical College Hospital, 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo 160. Kazuo Yoneyama, Respiratory Medicine, Tokyo Medical College Kasumigaura Hospital, 3-20-1, Chuo, Amicho, Inashiki-gun, Ibarigi 300-03. Hajime Goto, Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo 113. Nobuyuki Hara, Respiratory Medicine, Chest Disease Research Institute, Faculty of Medicine, Kyushu University, 3-1-1, Maedashi, Higashi-ku, Fukuoka-city, Fukuoka 812. Yukihito Ichinose, Respiratory Medicine, Kyushu Cancer Center, 3-1-1, Notame, Minami-ku, Fukuoka-city, Fukuoka 815. Hidehiko Yamamoto, Respiratory Medicine, Aso Cement Iizuka Hospital, 3-83, Yoshio-cho, Iizuka-city, Fukuoka 820. Masamoto Nakano, Internal Medicine, Nagasaki City Hospital, 6-39, Shinchi-cho, Nagasaki-city, Nagasaki 850. Jun Araki, Internal Medicine, Sasebo City Hospital, 9-3, Hirase-cho, Sasebo-city, Nagasaki 857.

## References

1. Hertel LW, Kroin JS, Misner JW, *et al.* Synthesis of 2-deoxy-2,2-difluoro-D-ribose and 2-deoxy-2,2-difluoro-D-ribofuranosyl nucleotides. *J Org Chem* 1988; **53**: 2406–9.
2. Heinemann V, Hertel LW, Grindey GB, Plunkett W. Comparison of the cellular pharmacokinetics and toxicity of 2′,2′-difluorodeoxycytidine and 1-β-D-arabinofuranosy cytosine. *Cancer Res* 1988; **48**: 4024–31.
3. Huang P, Chubb S, Hertel LW, Grindey GB, Plunkett W. Action of 2′,2′-difluorodeoxycytidine on DNA synthesis. *Cancer Res* 1991; **51**: 6110–7.
4. Hanauske AR, Degen D, Marshall MH, Hilsenbeck SG, Grindey GB, Von Hoff DD. Activity of 2′,2′-difluorodeoxycytidine (Gemcitabine) against human tumor colony forming units. *Anti-Cancer Drugs* 1992; **3**: 143–6.
5. Bhalla K, Holladay C, Lutzky J, *et al.* Deoxycytidine protests normal bone marrow progenitors against ara-C and gemcitabine cytotoxicity without compromising their activity against cisplatin-resistant human ovarian cancer cells. *Gynecol Oncol* 1992; **45**: 32–9.
6. Hertel LW, Boder GB, Kroin JS, *et al.* Evaluation of the antitumor activity of Gemcitabine (2′,2′-difluoro-2′-deoxycytidine). *Cancer Res* 1990; **50**: 4417–22.
7. Gandhi V, Plunkett W. Modulatory activity of 2′,2′-difluorodeoxycytidine on phosphorylation and cytotoxicity of arabinosyl nucleosides. *Cancer Res* 1990; **50**: 3675–80.
8. Kristjansen PEG, Quistorff B, Spang-Thomsen M, Hansen HH. Intratumoral pharmacokinetic analysis by $^{19}$F-magnetic resonance spectroscopy and cytostatic *in vivo* activity of gemcitabine(dFdC) in two small cell lung cancer xenografts. *Ann Oncol* 1993; **4**: 157–60.
9. Fujita M, Fujita F, Inaba H, Taguchi T. Antitumor activity of LY188011, a new deoxycytidine analog against human cancers xenografted into nude mice. *Jpn J Cancer Chemother* 1994; **21**: 517–23.
10. Taguchi T, Furuse K, Fukuoka M, *et al.* LY188011 phase I study. *Jpn J Cancer Chemother* 1996; **23**: 1011–8.
11. Fukuoka M, Noda K, K Hasegawa, *et al.* An early phase II study of Gemcitabine hydrochloride. *Jpn J Cancer Chemother* 1996; **23**: 1813–24.
12. The Criteria of the Adverse Reaction Assessment List of Japan Society for Cancer Therapy. *J Jpn Soc Cancer Ther* 1986; **21**: 943–53.
13. O'Rourke TJ, Brown TD, Harvin K, *et al.* Phase I clinical trial of gemcitabine given as an intravenous bolus on five consecutive days. *Eur J Cancer* 1994; **30**: 417–8.
14. Poplin E, Corbett T, Flaherty L, *et al.* Difluorodeoxycytidine (dFdC)–gemcitabine: a phase I study. *Invest New Drugs* 1992; **10**: 165–70.
15. Abbruzzese JL, Grunewald R, Weeks EA, *et al.* A phase I clinical plasma, and cellular pharmacology study of gemcitabine. *J Clin Oncol* 1991; **9**: 491–8.
16. Anderson H. Single-agent activity of weekly gemcitabine in advanced non-small-cell lung cancer: a phase II study. *J Clin Oncol* 1994; **12**: 1821–6.
17. Abratt RP, Bezwoda WR, Falkson G, Hacking D, Rugg TA. Efficacy and Safety Profile of Gemcitabine in non-small-cell lung cancer: a phase II study. *J Clin Oncol* 1994; **12**: 1535–40.
18. Lund B, Ryberg M, Meidahl-Petersen P, Anderson LH. Thatcher N, Dombernowsky P. Phase II study of

gemcitabine (2′,2′-difluorodeoxycytidine) given as a twice weekly schedule to previously untreated patients with non-small cell lung cancer. *Ann Oncol* 1994; **5**: 852–3.
19. Abratt RP, Bezwoda WR, Goedhals L, Hacking DJ. Weekly gemcitabine (days 1, 8, 15) with monthly cisplatin (day 15): active combination chemotherapy for advanced non-small cell lung cancer. *J Clin Oncol* 1997; **15**: 744–9.
20. Crinò L, Scagliotti G, Marangolo M, *et al.* Cisplatin-gemcitabine combination in advanced non-small cell lung cancer (NSCLC). A phase II study. *J Clin Oncol* 1997; **15**: 297–303.
21. Sandler A, Crin L, Steward WP, Abratt RP. Extended survival in stage III and IV non-small cell lung cancer (NSCLC) patients treated with gemcitabine plus monthly cisplatin. *Ann Oncol* 1996; **7** (suppl 5, abstr 435P).
22. Shepherd FA. Phase I dose-escalation trial of gemcitabine and cisplatin for advanced non-small cell lung cancer: usefulness of mathematic modelling to determine maximum tolerated dose. *J Clin Oncol* 1996; **14**: 1656–62.
23. Steward WP, Dunlop DJ, Dabouis G, Lacroix H, Talbot D. Phase I/II study of gemcitabine and cisplatin in the treatment of advanced non-small cell lung cancer—preliminary results. *Semin Oncol* 1996; **23** (suppl 10): 43–7.
24. Carmichael J, Allerheiligen S, Walling J. A phase I study of gemcitabine and carboplatin in non-small cell lung cancer (NSCLC). *Semin Oncol* 1996; **23** (suppl 10): 55–9.
25. Manegold CH, Eberhard W, Wilke H, *et al.* Phase II study of gemcitabine (GEM) and ifosfamide (IFO) in advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1996; **15**: 380 (abstr 1137).

*(Received 24 April 1997; accepted 12 May 1997)*