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Activity of gemcitabine in non-small-cell lung cancer: results of the Japan gemcitabine group (A) phase II study

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Abstract *Purpose*: This phase II study was conducted to determine the response and toxicity of gemcitabine (2′,2′-difluorodeoxycytidine) in chemotherapy-naive patients with non-small-cell lung cancer (NSCLC). *Methods*: A group of 73 patients were entered into the study. The patients had received no previous chemotherapy and all had measurable disease. The initial starting dose of gemcitabine was 1000 mg/m^2 per week × 3 followed by a week of rest, and was escalated for the next cycle to 1250 mg/m^2, provided there were no signs of hematologic toxicity (WBC < 3000/μl and/or platelets < 70 000/μl) in the previous cycle. *Results*: Among 73 eligible patients, there were 19 partial responses (PRs), with an overall response rate of 26.0% (95% confidence interval 16.5–37.6%). The response rate for stage IIIa and IIIb disease was significantly higher than that for stage IV disease [41.4% (12/29) vs 15.9% (7/44); $P = 0.028$]. The median duration of response in patients showing a PR was 4.6 months (1.7–10.4 months). The median number of cycles given was two per patient (range one to seven). Grade 3 anemia, leukopenia and neutropenia occurred in 15 patients (20.5%), 7 patients (9.6%) and 20 patients (27.4%), respectively. Grade 3 thrombocytopenia occurred in one patient (1.4%) which was not associated with any bleeding. There was no evidence of cumulative toxicity in the later courses of gemcitabine treatment with regard to leukopenia and thrombocytopenia. Other toxicities, including hepatic toxicity, fatigue, nausea/vomiting and fever were mild (grade 2 or less) and transient. One patient was withdrawn from the trial because of a rash. Pulmonary toxicity was experienced in two patients and one patient died of respiratory insufficiency which was thought to be drug-related. *Conclusions*: Gemcitabine as a single agent has proven to be an active drug for NSCLC with a favorable, generally mild side-effect profile. Further trials in combination with other agents for this disease are currently underway.

Key words Gemcitabine · NSCLC · Phase II · Japan

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Introduction

Lung cancer is a leading cause of cancer-related death in Japan. Non-small-cell lung cancer (NSCLC) accounts for more than 80% of new cases of lung cancer.

The prognosis of advanced NSCLC remains poor [18]. Relatively few active agents have been identified which can produce reproducible response rates above 15% [8]. Consequently, new active drugs are eagerly sought to manage advanced NSCLC.

Gemcitabine is a new cytostatic agent classified as an antimetabolite with a close resemblance to cytosine-arabinoside (ara-C). However, the mechanism of intracellular action of gemcitabine has been found to be different from that of ara-C [3, 7, 9, 11]. Gemcitabine has demonstrated high activity against a wide range of human tumor xenografts, including lung tumors [4, 15].

Hertel et al. [10] have reported that gemcitabine exhibits a different schedule dependency, whereby intermittent rather than daily drug administration results in superior cytotoxicity. In addition, our phase I and early phase II studies [6, 20] suggested that the most favorable therapeutic index is achieved when gemcitabine is administered once a week for 3 weeks, followed by a week of rest. Based on these findings, we conducted this phase II trial.

Patients and methods

Patient selection

Patients with histologically or cytologically confirmed, inoperable NSCLC stage IIIa, IIIb and IV were entered into the study. None of the patients had received any prior chemotherapy. Prior irradiation and surgery were allowed, but only with postoperative recurrence, and those with concurrent lesions previously treated with radiotherapy were also included. The patients were required to have measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, and a life expectancy ≥ 2 months, and to be aged 18 to 80 years. Eligibility requirements also included: leukocyte count $\geq 4000/\mu l$, platelet count $\geq 100\,000/\mu l$, hemoglobin level ≥ 9 g/dl, serum bilirubin level < 1.5 mg/dl, AST/ALT not more than twice the upper normal limit, and serum creatinine level < 1.5 mg/ml. Exclusion criteria were severe concurrent medical conditions, pregnancy, symptomatic brain metastasis, hypercalcemia and active concomitant malignant disease. Informed consent was obtained from all patients.

Treatment schedule

Gemcitabine was administered intravenously over 30 min at an initial starting dose of 1000 mg/m^2, once per week for 3 weeks, followed by a 1-week rest, which constituted one cycle of chemotherapy. If a therapeutic effect (response or stable disease, SD) was observed and toxicities proved to be tolerable, treatment was continued. At scheduled retreatment, a new cycle was administered if the leukocyte count was ≥ 3000 /μl and the platelet count was $\geq$ 100 000 /μl. If the leukocyte and/or platelet counts were $< 3000/\mu l$ and $< 100\,000$ /μl, respectively, therapy was delayed by weekly intervals. If the leukocyte and/or platelet counts were $< 3000/\mu l$ and $< 70\,000/\mu l$, respectively, within a cycle, therapy was delayed until these counts improved. If after a delay of 4 weeks, the hematologic criteria were still not fulfilled, the patient was withdrawn from the study. Dosage escalation over and above two cycles of therapy was only allowed if nadir counts of leukocytes and platelets in the previous cycles did not fall to $< 3000/\mu l$ and $< 70\,000/\mu l$ (grade 2 or more), respectively. If the leukocyte and platelet counts had not fallen to below these levels, the dose was escalated to 1250 mg/m^2 for the next cycle of chemotherapy. If grade 3 (or above) hematologic toxicity (leukocyte count $< 2000/\mu l$ and/or platelet count $< 50\,000/\mu l$) and/or grade 3 (or above) non hematologic toxicity (excluding nausea and vomiting) occurred, the dose was reduced to 1000 mg/m^2 for patients on 1250 mg/m^2 and to 800 mg/m^2 for patients on 1000 mg/m^2.

Evaluation

A complete blood cell count, blood chemistry (including AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, creatinine, and BUN), urinalysis, and chest X-radiographs were performed once a week after the treatment began. In addition, ECG was evaluated before and after treatment. PS was documented weekly throughout therapy.

The eligibility, assessability, and response of each patient was evaluated by extramural review. Response evaluations were performed once per week after the start of treatment. Responses in patients who received at least one cycle of gemcitabine were assessed in accordance with World Health Organization (WHO) criteria [22]. To evaluate toxicity, the criteria of the Japan Society for Cancer Therapy [13], which reflect the WHO criteria [22], were used. The duration of response was measured from the start of treatment to disease progression. The survival time was calculated from the start of treatment to death, or to the last follow-up. The survival curves and time to progression curves were calculated by the method of Kaplan-Meier and subgroup survival was compared by log-rank statistics. Fisher's Exact test was used for comparison of response rates.

Calculation of the percentage of intended dose intensity

To investigate a possible correlation between dose intensity of gemcitabine monotherapy with treatment outcome, we calculated the percentage of intended dose intensity by the following method. If we estimated the planned dose of gemcitabine to be 1000 mg/m^2 weekly for 3 weeks every 4 weeks, the planned dose intensity of gemcitabine, calculated as a function of two consecutive 4-week cycles for a total 8-week treatment period, was $1000 \times 6 = 750$ mg/m^2 per week. The actual dose intensity of gemcitabine was calculated as total dose for the initial two cycles divided by the number of weeks required for two complete scheduled cycles. The percentage of intended dose intensity was defined as the actual dose intensity divided by the planned dose intensity.

Results

Between December 1992 and October 1993, 73 patients were entered into the study. All patients were eligible for entry. The characteristics of the patients are listed in Table 1.

Six patients were excluded from response analysis for the following reasons: early death (one patient), allergic skin rash (one), panperitonitis due to intestinal perforation not gemcitabine-related (one), lost to follow-up (two), progression of disease before any evaluation (one). The patient showing progression of disease before any evaluation was excluded from the response analysis because 2 days after the first dose (1000 mg/m^2), the patient developed cramp. A brain CT scan performed 3 days after this development indicated metastasis. During

Table 1 Patient characteristics

	No. of patients (%)
No. of patients eligible	73
Sex	
Male	54 (74.0)
Female	19 (26.0)
Age (years)	68
Mean range	32–79
Performance status (ECOG scale)	
0,1	58 (79.5)
2	15 (20.5)
Stage of disease	
IIIa	11 (15.1)
IIIb	18 (24.7)
IV	44 (60.3)
Histology	
Adenocarcinoma	47 (64.4)
Squamous cell carcinoma	16 (21.9)
Large cell carcinoma	10 (13.7)
Previous therapy	
None	68 (93.2)
Radiation	1 (1.4)
Surgery and radiation	1 (1.4)
Surgery	3 (4.1)

the short duration of gemcitabine therapy, the majority of investigators decided this patient was not evaluable and should therefore not be included in the response analysis. Therefore, 67 patients were considered evaluable for response and 73 patients for toxicity. The median follow-up time was 20.5 months (range 16.6 to 26.6 months).

Dose modification

The number of cycles given ranged from one to seven, with a median of two cycles per patient (median number of administrations six, range 1–20). Of the 73 patients, 45 were treated at 1000 mg/m^2 per week for 3 weeks during all 4-week cycles. Three patients were initially treated at 1000 mg/m^2 per week for 3 weeks, but experienced more than grade 3 hematologic toxicity during their first cycles of therapy. Consequently the administered doses of gemcitabine were reduced to 800 mg/m^2 in subsequent cycles. These 48 patients (45 + 3) were categorized as the lower dose group. For the 25 patients, initially treated at 1000 mg/m^2 per week for 3 weeks, but who did not experience more than grade 2 hematologic toxicity during their first cycle (22 patients) or after the second cycle (3 patients) of therapy, the administered dose of gemcitabine was escalated for the next cycles to 1250 mg/m^2. These patients were categorized as the higher dose group.

Response

Of the 73 eligible patients, 19 (26.0%) achieved a partial response (PR) (95% confidence interval 16.5–37.6%), 34 patients had stable disease (SD), and 14 experienced progressive disease (PD); there were no complete responses (CRs). The median number of cycles of gemcitabine for responders was four (range two to seven) and the median number of cycles to achieve a PR was one (range one to three). The responses according to patient characteristics are shown in Table 2.

Table 2 Response according to patient characteristic

	No. of eligible patients	No. of responses	%
Overall response	73	19	26.0
Histologic subtype			
Adenocarcinoma	47	15	31.9
Squamous	16	1	6.3
Large cell	10	3	30.0
Stage			
IIIa/IIIb	29	12	41.4
IV	44	7	15.9
Dose of gemcitabine			
Low dose (1000 mg/m^2)	48	10	20.8
High dose (1250 mg/m^2)	25	9	36.0

The response rate (41.4%) for patients with locoregional (stage IIIa and IIIb) disease was significantly higher ($P = 0.028$) than that for stage IV disease (15.9%). The response rates for adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma were 31.9%, 6.3%, and 30.0%, respectively. There was a significant difference ($P = 0.05$) between the response rates for squamous cell carcinoma and adenocarcinoma.

A 25% dose escalation to 1250 mg/m^2 resulted in a higher response rate (9 of 25, 36.0%) compared with the response rate at the 1000 mg/m^2 dose (10 of 48, 20.8%). The mean (±SD) of the percentage of intended dose intensity for the individual patients who were given at least two cycles of gemcitabine treatment was 101% (±11). The means of the percentage of the intended dose intensities were 101% (±11) in PR patients, 102% (±11) in SD patients, and 99% (±15) in PD patients.

Survival and time to progression

Overall survival time and time to progression are shown in Fig. 1. The median duration of survival for all patients was 10.3 months. In patients with a PR, the median time to progression was 4.6 months (range 1.7–10.4 months) and the median survival time was 15.6 months (range 5.1–19.9 months). For those with SD or PD, median survival was 8.0 months (range 0.3–21 months). The median survival time for stage IIIa/b was 11.0 months (range 0.3–21 months) and for stage IV was 10 months (range 0.5–20.2 months; $P = 0.604$).

Toxicity

The toxicities observed during treatment of all 73 patients are listed in Table 3. Grade 3 or above

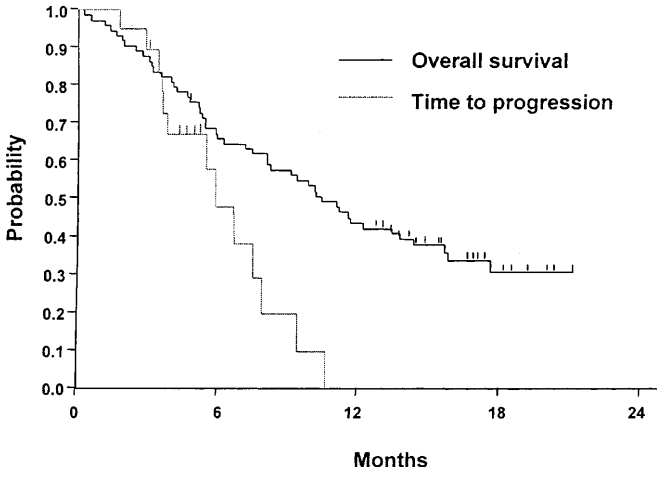

Fig. 1 Overall survival time ($n = 73$) and time to disease progression ($n = 19$) in patients treated with gemcitabine

neutropenia occurred in 24 patients (32.9%), only 4 of whom experienced grade 4 neutropenia. No episodes of febrile neutropenia were observed. Leukopenia occurred in 53 patients (72.6%). Seven patients (9.6%) experienced grade 3 leukopenia, but no patients experienced grade 4 leukopenia. The leukopenia was not associated with any infection. Grade 3 anemia was observed in 15 patients (20.5%), and grade 3 thrombocytopenia was observed in 1 patient (1.4%) which was not associated with any bleeding. Changes in leukocyte and platelet counts per cycle are shown in Fig. 2. There was no evidence of cumulative toxicity in the later cycles of gemcitabine treatment with regard to leukopenia and thrombocytopenia. In every cycle of gemcitabine treatment, leukopenia and thrombocytopenia occurred at around 2 weeks after the initiation of the first administration of each cycle, and recovered to pretreatment levels by 4 weeks (Fig. 2).

Nausea and/or vomiting occurred in 30 patients (41.1%), but these reactions were manageable with conventional antiemetic drugs. Mild (grade ≤2) and transient elevation of serum transaminase (AST and/or ALT) was observed in 38 patients (52.1%). Fever and skin rash were observed in 23 (31.5%), and 13 (17.8%), respectively.

Table 3 Toxicity ($n = 73$)

	Grade				Grade ≥3
	1	2	3	4	(%)
Anemia	21	19	15	0	20.5
Leukopenia	14	32	7	0	9.6
Neutropenia	8	21	20	4	32.9
Thrombocytopenia	18	4	1	0	1.4
Hepatic	21	17	0	0	0
Pulmonary	1	0	1	0	1.4
Fatigue	18	9	0	0	0
Nausea/vomiting	22	8	0	0	0
Fever	10	13	0	0	0
Rash	9	4	0	0	0

Two patients (2.7%) experienced possibly drug-related pulmonary toxicity (grade 1 and grade 3, respectively), one of whom experienced grade 3 toxicity and died of pulmonary fibrosis and the other, who had preexisting moderate pulmonary fibrosis, recovered completely without treatment. The patient who died was a 72-year-old male diagnosed with stage IV squamous cell carcinoma and no previous history of fibrosis. After completion of the first course of gemcitabine treatment (1000 mg/m^2 × 3) he developed respiratory insufficiency. The case was reviewed by third party specialists and was judged to be related to gemcitabine owing to diffuse radiographic shadow appearing after treatment, with concomitant occurrence of neutropenia, fever and decrease in PaO_2. The patient was removed from the study but died 27 days after the last dose of gemcitabine.

Neither hematologic nor nonhematologic toxicity increased significantly with dose escalation. None of the patients had flulike symptoms or peripheral edema.

There were no changes in PS in patients who achieved a PR or SD during the entire treatment cycles; however, PS in patients with PD declined according to the progression of the disease.

Discussion

In our trial, gemcitabine showed an overall response rate of 26.0% in patients with inoperable NSCLC who had received no previous chemotherapy, although no complete responses were observed. In a phase I trial of gemcitabine, which like the present study was conducted by institutions from the same group, the maximum tolerated dose identified in previously treated patients was 1000 mg/m^2 per week, when it was administered once a week × 3 followed by a week of rest [20]. Following this phase I trial, an early phase II trial in NSCLC was performed at an initial dose of 800 mg/m^2 [6]. During this study, it became apparent that there was little toxicity with gemcitabine and the starting dose was therefore increased from 800 mg/m^2 to 1000 mg/m^2. In the early phase II trial, 47 of the 64 patients entered were chemotherapy-naive, toxicities were modest and the response rate was 17.0%. Based on these results, a phase II trial of gemcitabine was initiated in chemotherapy-naive patients with NSCLC [21]. In trials conducted in other countries using the same schedule, but at doses of 800 to 1250 mg/m^2 per week, response rates were remarkably consistent, in the range 20% [1, 2] to 22% [16]. Taken together, the response rates with single-agent gemcitabine compare favorably with the 15% to 30% response rates achieved with the small number of other drugs that have shown single-agent activity against NSCLC (cisplatin, ifosfamide, mitomycin, vindesine, vinblastine, and etoposide) [12, 14].

The activity of gemcitabine and its unique mechanism of action has led to further studies with this drug in combination with other active agents in NSCLC; these

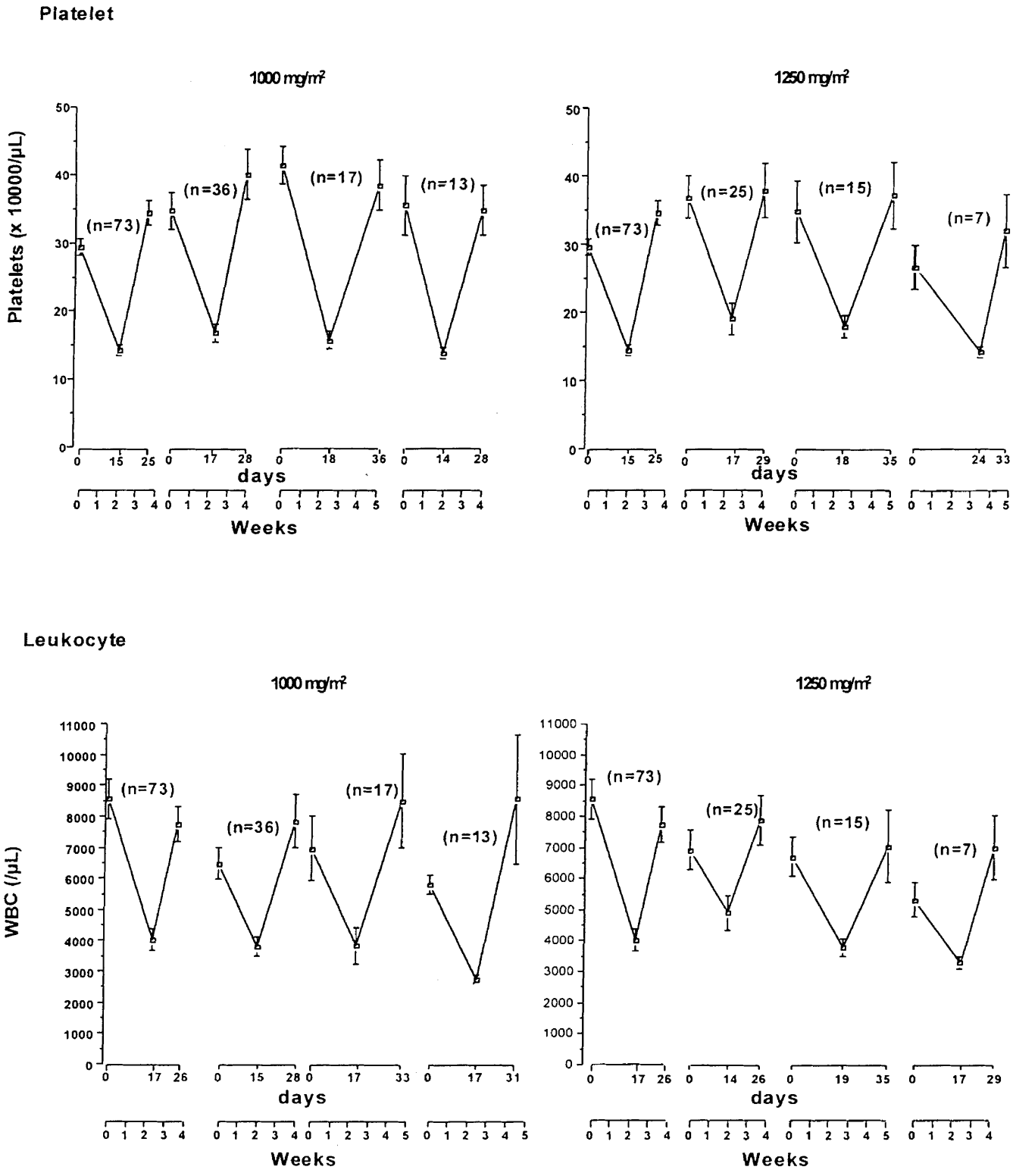

Fig. 2 Platelet and white blood cell counts during gemcitabine therapy. The mean times to nadir and recovery from first administration in each cycle are shown. Values are mean ± SE

studies are currently underway. Several preliminary reports suggest that gemcitabine may offer some advantages when administered with cisplatin [19], carboplatin [5] and ifosfamide [17].

In terms of toxicity, myelosuppression, mainly leukopenia, was the dose-limiting side effect, but grade 3 toxicity was observed in only about 10% of patients. There was no evidence of cumulative toxicity in the later

cycles of gemcitabine treatment with regard to leukopenia and thrombocytopenia, and good recovery from the nadir during each course (Fig. 2). The transient nature of the myelosuppressive effect of gemcitabine may reduce the need for hospitalization and colony-stimulating factors and is of particular importance to combination chemotherapy regimens, as gemcitabine can be incorporated without significantly compromising the doses of other agents.

Other toxicities included anemia, hepatic toxicity, fatigue, nausea/vomiting, fever, and rash, but they were mild to moderate and easily manageable with symptomatic treatment. Although no pulmonary toxicity was indicated in the previous reports, this was observed in two patients (2.7%) in our trial, and one died of respiratory insufficiency.

Neither hematologic nor nonhematologic severity increased significantly with gemcitabine dose escalation. A study by Abratt et al. [1], with doses commencing at 1000 mg/m^2 and increasing to 1250 mg/m^2, did include aggressive dose escalation within patients, on occasion reaching doses of 1850 mg/m^2. This dose level failed to produce any dose-limiting hematologic toxicity.

Overall, gemcitabine has a favorable side-effect profile when administered once a week for 3 weeks followed by a week of rest. It is unusual to see such a mild side-effect profile in such an active agent against NSCLC. Myelosuppression typically did not require any supportive care such as cytokines, blood transfusions and antibiotics. Nausea and vomiting were rare, and controlled by standard antiemetics. These characteristics suggest that gemcitabine is an active chemotherapeutic agent in NSCLC, with a relatively mild toxicity profile.

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