

A phase II trial of weekly chemotherapy with paclitaxel plus gemcitabine as a first-line treatment in advanced non-small-cell lung cancer

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Abstract

Purpose The efficacy and toxicity of combined paclitaxel (PTX) and gemcitabine (GEM) was evaluated as a protocol for first-line chemotherapy in 40 patients with advanced non-small-cell lung cancer (NSCLC).

Methods Paclitaxel, 100 mg/m², was administered intravenously (IV) as a 1-h infusion, followed by GEM, 1,000 mg/m², IV over 30 min on days 1 and 8 of a 21-day cycle. The median age of patients was 66 years with a range of 33–75 years. Nearly all patients (39/40) had an ECOG performance status of 0 or 1. Thirteen patients (32%) had initial stage IIIB disease and 27 patients (68%) had stage IV disease. Histological subtypes were adenocarcinoma (73%) and squamous cell carcinoma (25%).

Results Twenty-two patients (55%) achieved a partial response and none achieved a complete response, giving an overall response rate of 55% (95% confidence interval: 38.2–71.8%). Disease stability was achieved in 14 patients (35%), and 4 patients (10%) had progressive disease. The median survival time was 11.9 months (95%

CI: 10.3–14 months), with a 1-year survival rate of 47.5%. Grade 3 or 4 hematological toxicities observed included neutropenia in 37.5%, anemia in 2.5%, and thrombocytopenia in 5.0% of these patients. Non-hematologic toxicities were mild, with the exception of grade 3 and 4 pneumonitis. There were no deaths due to toxicity.

Conclusion Weekly chemotherapy with PTX plus GEM is effective and is acceptable for the first line treatment of advanced NSCLC.

Keywords Non-small-cell lung cancer · First-line chemotherapy · Weekly chemotherapy · Gemcitabine · Paclitaxel

Introduction

Lung cancer ranks among the most commonly occurring malignancies and currently is the leading cause of cancer-related deaths worldwide [21]. In Japan lung cancer is responsible for approximately 55,000 cancer-related deaths per year [5]. Even though the clinical usefulness of first-line chemotherapy has been established for the cases of advanced non-small-cell lung cancer (NSCLC), the prognosis is still extremely poor.

A number of new agents have become available recently for the treatment of unresectable and metastatic NSCLC in Japan, including the taxanes, gemcitabine (GEM), and vinorelbine. In randomized phase III trials, these agents in combination with a platinum compound have been associated with improved survival of patients having advanced NSCLC [8, 17, 23, 24]. However, a platinum compound is associated with a greater toxicity than other drugs used to treat NSCLC. In addition to nausea and vomiting, it causes neuropathy, profound fatigue, and renal toxicity. Some

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patients are unable to tolerate the drug toxicity and terminate treatment early. Based on these observations, non-platinum regimens have been proposed as an alternative to the platinum-based combinations for treatment of advanced NSCLC [13].

Paclitaxel (PTX) and GEM are new anti-cancer agents having significant single-agent activity against advanced NSCLC. A recent clinical phase II study of 122 patients with previously untreated, unresectable stage III or IV NSCLC receiving a 3-h infusion of PTX at a dose of 210 mg/m^2 showed a good response rate of 35% [25]. Although PTX is usually given once every 3 weeks, Chan et al. [10] demonstrated that weekly administration of PTX at a dose of $80\text{--}90 \text{ mg/m}^2$ provides similar tolerability and a possible increase in efficacy.

Gemcitabine, a novel deoxycytidine analog, had a response rate of 20% with a single weekly administration in previously untreated advanced NSCLC [4]. As a first-line treatment, single-agent GEM has been shown to have anti-tumor activity equal to that of cisplatin/etoposide, resulting in less toxicity and a slightly better quality of life [27].

These agents have different mechanisms of action, and their toxicities are partially non-overlapping. Although the usual administration of PTX is once every 3 weeks, a weekly administration can increase efficacy with good tolerability [1, 2]. We demonstrated that weekly administration with PTX and GEM is a tolerable and active regimen for patients with advanced NSCLC previously treated with platinum-containing chemotherapy regimens [20]. Based on these findings, we designed a phase II trial to examine the efficacy and tolerance of the non-platinum-based combination of PTX and GEM administered weekly for patients with untreated advanced NSCLC.

Patients and methods

Patient selection

All patients with histologically or cytologically confirmed advanced NSCLC were eligible for this phase II trial. The subjects of this study were patients with clinical stage IV NSCLC or stage III with unresectable disease or for whom radiotherapy with curative intent is not possible. Patients with unresectable disease or radiotherapy with curative intent is not possible include those with pleural effusion and dissemination, those with intrapulmonary metastasis within the ipsilateral lobe, those with an irradiation field exceeding one-half of one lung, those with metastasis to the contralateral hilar lymph nodes, and those with reduced lung function. Other eligibility criteria included: age older than 20 years and younger than 76 years; Eastern Cooperative

Oncology Group (ECOG) performance status (PS) of 0–2; measurable lesions; life expectancy ≥ 12 weeks; adequate bone marrow reserve with a WBC count $\geq 4,000$ per mm^3 ; platelet count $\geq 10 \times 10^4$ per mm^3 ; and hemoglobin level $\geq 9.0 \text{ g/dL}$; liver function with a AST and ALT $\leq 2.5 \times$ upper normal limit, unless as a result of liver metastases; and adequate renal function with a serum creatinine level $\leq 1.5 \text{ mg/dL}$. No prior radiotherapy treatment was allowed if the irradiated area was not the site of measurable lesion and the therapy was completed at least 2 weeks before enrollment into the study.

Patients were excluded for the following indications: ≥ 76 years of age (vinorelbine as single agent treatment), severe cardiovascular or cerebrovascular disease, uncontrolled diabetes or hypertension, active infection, pulmonary fibrosis, massive pleural effusion or ascites, active peptic ulcer, and severe neurological disorders. Patients were also excluded in case of previous malignancy and any evidence or history of hypersensitivity or other contraindications for the drugs used in this trial. Written informed consent was obtained from all patients.

Treatment

Paclitaxel, 100 mg/m^2 , was administered IV during a 1-h infusion, followed by GEM, $1,000 \text{ mg/m}^2$, IV over 30 min on days 1 and 8 of 21-day cycle. Premedication for PTX consisted of dexamethasone 20 mg, diphenhydramine 50 mg, and ranitidine 50 mg IV for 30 min before PTX infusion. After the premedication for PTX was completed, a serotonin receptor antagonist was given as a 30-min infusion for prophylactic antiemetic therapy. Treatment was repeated every 3 weeks until maximum response plus two cycles or unacceptable toxicity. In stable disease, patients received a maximum of six cycles. At the investigator's discretion, patients were treated with up to eight cycles of the drug combination.

Dose modifications were planned according to hematologic and severe non-hematologic toxic effects. Once the doses were reduced, they were not increased. Patients who experienced grade 4 neutropenia, grade 4 thrombocytopenia, reversible grade 2 neurotoxicity, or liver dysfunction received reduced doses of both PTX, 75 mg/m^2 , and GEM, 800 mg/m^2 , for the next cycle. The next course of chemotherapy was started after 3 weeks when the leukocyte count was 3,000 per mm^3 or greater, the neutrophil count was 1,500 per mm^3 or greater, the platelet count was 75,000 per mm^3 or greater, serum creatinine was less than 1.5 mg/dL , GOT and GPT were less than twice the upper limit of the normal range, and the neurotoxicity was grade 1 or less. If hematologic recovery was not achieved by day 35 of treatment, the patient was withdrawn from the study.

Evaluation of responses and toxicity

Responses and toxicity were evaluated on the basis of tumor images obtained by computerized tomography (CT), laboratory results, subjective/objective symptoms, signs before, during, and after administration of the study drugs and during the period from completion of treatment to the final analysis. Measurable disease parameters were determined every 4 weeks by various means such as CT. Evaluation was performed in compliance with the response evaluation criteria in solid tumors (RECIST) guidelines for anti-tumor activity. Adverse events were assessed using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0). Patients were withdrawn from the study if evidence of tumor progression was observed. The institutional ethical review committee gave approval to the study.

Statistical analysis

The primary end point of the study was the response rate. Simon's two-stage design was used to determine sample size and decision criteria. It was assumed that a response rate of 40% in eligible patients would indicate potential usefulness, while a rate of 20% would be the lower limit of interest; $\alpha = 0.05$ and $\beta = 0.10$. Using these design parameters, the first stage of the study was to enroll 24 patients, and the regimen was rejected if fewer than five patients had an objective response. If six or more patients responded, the accrual was continued until 45 patients were enrolled (45 patients were required because of anticipated percentage of dropout cases). Combination therapy was considered effective if ≥ 14 of the 45 patients showed a response in the final analysis. Secondary end points were toxicity and overall survival. Response and survival rates were both calculated on an intent-to-treat basis. Overall survival and time to progression were measured from the start of this treatment until time of death or the date of the last follow-up clinical assessment. Survival curves were constructed using the Kaplan–Meier method (Fig. 1).

Results

Patient characteristics

A total of 40 patients were enrolled in the study between September 2001 and July 2004. The majority of patients were treated as outpatients. The clinical characteristics of the patients are listed in Table 1. The median age was 66 years with a range of 33–75 years. Nearly two-thirds of the patients were men. Twenty-four patients had an PS

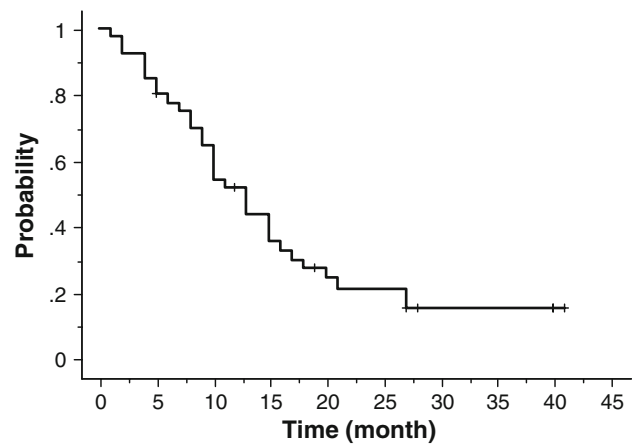


Fig. 1 Kaplan–Meier estimated overall survival curves. Median survival time, 11.9 months; 1-year survival rate, 47.5%

Table 1 Patient characteristics

Eligible patients	40
Gender	
Male	26
Female	14
Age (years)	
Median	66
Range	33–75
Performance status	
0	24
1	15
2	1
Histology	
Adenocarcinoma	29
Squamous cell	10
Large cell	1
Stage	
III	13
IV	27
Number of metastatic sites	
Median	2
Range	0–3
Location of metastases	
Bone	12
Lung nodules	10
Liver	9
Lymph nodes	8
Adrenals	6
Brain	3
Subcutaneous	1

of 0, and 15 had PS of 1. Histological subtypes were 73% (29/40) adenocarcinoma and 25% (10/40) squamous cell carcinoma.

Toxicities

The toxicities observed during this study are provided in Table 2. Hematological toxicities were the most common, but grade 3–4 toxicities, including neutropenia (37.5%), thrombocytopenia (5.0%), and anemia (2.5%) were relatively modest. There were only two cases of febrile neutropenia (5.0%). Grade 1 nausea, fatigue, alopecia, neuropathy, and angialgia occurred with a greater frequency than the non-hematologic toxicities. Grade 3–4 non-hematologic toxicities were not seen except in cases of pulmonary toxicity. Two patients (5.0%) developed interstitial pneumonitis (grade 3; one patient, grade 4; one patient), and were responsive to steroid therapy.

Efficacy of treatment

The median number of cycles administered per patient was 4, and the number of cycles ranged from 1 to 8. Twenty-two patients exhibited a partial response. The overall response rate was 55% (22/40) [95% confidence interval (CI): 38.2–71.8%]. Stable disease was achieved in 14 patients (35%), and 4 patients (10%) had progressive disease. All 40 patients were included in the survival analysis. The overall median survival time was 11.9 months (95% CI: 10.3–14 months). The 1-year survival rate was 47.5% (19/40). The median time to disease progression was 6.4 months. Thirty patients (75%) received chemotherapy, and 4 patients (10%) received thoracic irradiation as second-line treatment.

Discussion

Although a standard regimen of first-line chemotherapy for advanced NSCLC is being established, it is important to develop a more active and well-tolerated regimen. Several published randomized studies reported that non-platinum-

based chemotherapy in advanced NSCLC was as effective and less toxic than platinum-based regimens [13, 15, 18, 29]. Georgoulis et al. [13] compared the combination of a cisplatin and docetaxel regimen with the GEM and docetaxel regimen. Objective response rates were similar in the two groups, with 32.4% in the former and 30.2% in the latter. The two groups did not differ in the overall survival or 1- or 2-year survival rates. They concluded that both drug combinations had comparable activity and the non-platinum-based regimen had the more favorable profile.

Generally, non-cisplatin-containing treatment does not require supplemental hydration as does standard cisplatin-based chemotherapy. This may be advantageous for elderly patients, patients with poor PS, and patients with renal or cardiac impairment. Recchia et al. [22] conducted a trial of PTX plus GEM in advanced NSCLC patients with a low PS. The chemotherapy regimen consisted of 200 mg/m² PTX on day 1 plus 1,000 mg/m² GEM on days 1 and 8, repeated every 3 weeks, for a maximum of eight cycles. They achieved a reasonable response rate of 41.3%. Median overall survival time was 13.6 months; the authors concluded that a satisfactory clinical benefit could be obtained with GEM plus PTX regimen in NSCLC patients with a poor PS.

Thus, non-platinum-based chemotherapy may be used as alternative to platinum-based regimens. We conducted a phase II trial was designed to examine the efficacy and tolerance of the non-platinum-based combination of weekly PTX and GEM for patients with untreated advanced NSCLC. Results including an overall response rate of 55%, a median survival time of 11.9 months, and a 1-year survival probability rate of 47.5% suggested that this regimen might have anti-tumor activity equal to that of platinum-based regimens.

Weekly chemotherapy for lung cancer has recently been carried out at several facilities, and favorable results were reported [9, 16, 26, 30]. Compared to standard chemotherapy with administration of drugs at intervals of 3–4 weeks, weekly chemotherapy appears acceptable for the reduction of a single dose level of anti-cancer drugs with fewer side effects. In addition, weekly dose level is more easily adjusted according to the general clinical condition of individual patients or if hematologic toxicity develops. Belani et al. [6] conducted a randomized phase II trial of a 3-week schedule of GEM plus PTX (ArmA) versus a weekly schedule of GEM plus PTX (ArmB) in the treatment of NSCLC. It was concluded that a weekly schedule resulted in improved survival and lower hematologic toxicity than the 3-week schedule.

The clinical outcomes of weekly PTX and GEM therapy found in the literature [3, 6, 7, 11, 12, 14, 19, 28] and in our results are summarized in Table 3. The response rate ranges were from 23.1 to 55%; overall median survival time was 4.9–11.9 months; and 1-year survival rates were 26–53%. Most adverse reactions were hematologic (such as leukope-

Table 2 Maximum toxicity over 40 patients

	CTCAE v 3.0 grade (no. of patients)		Grade 3 or 4 (%)
	Grade 3	Grade 4	
Leukopenia	11	1	12 (30)
Neutropenia	11	4	15 (37.5)
Febrile neutropenia	2	0	2 (5.0)
Anemia	1	0	1 (2.5)
Thrombocytopenia	2	0	2 (5.0)
Pneumonitis	1	1	2 (5.0)

CTCAE v 3.0: Common Terminology Criteria for Adverse Events version 3.0

Table 3 PG regimens used as first-line treatment of advanced NSCLC

First author (ref.)	No. of patients	Regimen and schedule	Response rate (%)	Survival median	One-year (%)
Belani et al. [6]	50	Arm A P 200 mg/m ² day 1 q3w G 1 g/m ² days 1, 8 q3w	28.2	7.5	34
	50	Arm B P 100 mg/m ² days 1, 8 q 3w G 1 g/m ² days 1, 8 q3w	26.8	9.6	42
Bhatia et al. [7]	39	P 110 mg/m ² days 1, 8, 15 q 4w G 1 g/m ² days 1, 8, 15 q4w	38.2	4.9	26
De Pas et al. [12]	54	P 100 mg/m ² days 1, 8, 15, 22 q 4w G 1 g/m ² days 1, 8, 15, 22 q4w	46	9.6	53
Akerley et al. [3]	39	P 85 mg/m ² days 1, 8, 15, 22, 29, 36 q 8w G 1 g/m ² days 1, 8, 15, 22, 29, 36 q8w	23.1	7.5	32
Gillenwater et al. [14]	39	P 100 mg/m ² days 1, 8, 15, 21 q 4w G 1 g/m ² days 1, 8, 15, 21 q4w	35	4.9	35
Kosmidis et al. [19]	225	P 200 mg/m ² day 1 q 3w G 1 g/m ² days 1, 8, q3w	31	9.3	42
Treat et al. [28]	312	P 200 mg/m ² day 1 q 3w G 1 g/m ² days 1, 8, q3w	43.6	8.4	33
Our study	40	P 100 mg/m ² days 1, 8, q 3w G 1 g/m ² days 1, 8 q3w	55	11.9	47.5

NSCLC non-small-cell lung cancer, P paclitaxel, G demcitabine

nia and neutropenia of grade 3 or greater occurrence) in 28–53%. Variable toxicities may be due to population-related pharmacogenomics [11]. Overall, the non-hematologic toxicity was mild, and there were few adverse reactions of grade 3 or greater. A few patients had pneumonitis which was not responsive to steroid therapy. The treatment in our current study was reasonably tolerated, especially in the area of non-hematologic toxicity. Nausea, vomiting, and fatigue, which are often seen in cisplatin-containing regimens, were relatively mild; no patients developed renal toxicity.

In conclusion, weekly chemotherapy with PTX and GEM is a well-tolerated and effective regimen for previously untreated patients with advanced NSCLC. Further studies are expected for the application of this regimen to the elderly, and patients with a poor PS or suspected vulnerability to platinum compound toxicity.

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Conflict of interest statement None.

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