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ORIGINAL ARTICLE

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Paclitaxel and gemcitabine combination in a biweekly schedule in patients with advanced non small-cell lung cancer: a phase i study

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Abstract *Purpose*: This phase I study was designed to determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) of the paclitaxel–gemcitabine combination in a biweekly schedule in chemotherapy-naive patients with advanced non small-cell lung cancer (NSCLC). *Patients and methods*: Treatment was administered on an outpatient basis every 2 weeks: paclitaxel over a 1-h IV infusion and gemcitabine as a 30-min IV infusion immediately following paclitaxel. *Results*: Twenty-nine patients were treated at six different dose levels, ranging from paclitaxel 135–175 mg/m^2 and gemcitabine 1,500–3,000 mg/m^2. A total of 198 cycles were administered (median 7, range 1–13). DLTs in the first two cycles were grade 4 neutropenia and myocardial ischemia at the dose level paclitaxel/gemcitabine 150/2,000 mg/m^2, febrile neutropenia and grade 4 neutropenia at the dose level paclitaxel/gemcitabine 175/2,500 mg/m^2, fatal pneumonitis, sudden death and grade 3 neutropenia at the dose level paclitaxel/gemcitabine 175/3,000 mg/m^2. The MTD was paclitaxel 175 mg/m^2 and gemcitabine 2,500 mg/m^2. The average dose intensity at this dose level was 98%. The overall intent-to-treat response rate was 35.7% (95% confidence interval [CI] 17.97% - 53.47%). Overall median survival was 36 weeks (95% CI, 24-48). *Conclusion*: Paclitaxel and gemcitabine can be safely administered at a high dose intensity on an every-other-week schedule. The recommended phase II dose is paclitaxel 175 mg/m^2 and gemcitabine 2,500 mg/m^2.

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Introduction

Cisplatin-based chemotherapy is a standard for the treatment of advanced non small-cell lung cancer (NSCLC) rendering a modest improvement of 1.5 months median survival and a 1-year survival benefit of 10%, in comparison with best supportive care [1]. Several new chemotherapeutic agents (paclitaxel, gemcitabine, vinorelbine, docetaxel and irinotecan) have shown good single-agent activity, and they are also active in combination with a platinum compound [2]. Cisplatin combinations with the newer generation compounds have become the current practice for treating patients with advanced NSCLC and a good performance status, but no combination has yet emerged as the gold standard [3, 4].

Cisplatin has been associated with substantial side effects such as nausea, vomiting, neuropathy, renal toxicity, ototoxicity, fatigue and myelotoxicity, all of which limit its use, despite intensive antiemetic and hydration regimens. In order to overcome cisplatin-induced toxicities, one modality involves replacing cisplatin with its analogue, carboplatin, or another antineoplastic drug.

Paclitaxel and gemcitabine have different mechanisms of action and nonoverlapping toxicities and they are active as monotherapy in advanced NSCLC [5–9]. On the basis of paclitaxel and gemcitabine single-agent activities, these two drugs have been introduced into clinical practice as a combination, and have shown substantial activity as first-line chemotherapy in advanced NSCLC patients: the response rate has been 24–36% and the toxicity profile is acceptable [10–13].

In clinical practice, paclitaxel is administered most often on an every-3-week schedule, while gemcitabine is given on a weekly basis three out of 4 weeks. The paclitaxel/gemcitabine combination has been studied in

several phase I and II studies, in different administration schedules. In a phase I study, Giaccone et al. escalated the dose of paclitaxel on day 1 with a fixed dose of gemcitabine 1,000 mg/m^2 on days 1 and 8, every 3 weeks. The paclitaxel dose of 200 mg/m^2 was well-tolerated and the overall response rate was 24% [10].

In a phase I dose-finding study in patients with advanced solid tumors, Rothenberg et al. administered paclitaxel and gemcitabine on an every-2-week basis, addressing the logistical problem that the difference in the frequency of drug administration and treatment cycle length, pose in daily practice. The recommended phase II dose in this study was paclitaxel 150 mg/m^2 and gemcitabine 3,000 mg/m^2 [14].

To optimize the efficacy of chemotherapy with available drugs, a possible relationship between the delivery of cancer chemotherapy and the outcome could be considered. Variables related to anticancer drug delivery are: cumulative dose, dose intensity and drug schedule. By intensifying the chemotherapy schedule we can probably deliver the same or higher dose and cumulative dose, achieving higher dose intensity. [15]. The optimal administration schedule of the paclitaxel/gemcitabine combination warrants further study.

In the present study, our aim was to evaluate the every-other-week administration of the paclitaxel and gemcitabine combination as initial treatment in patients with advanced NSCLC. Our main objectives were to investigate the feasibility of this schedule and to define the maximum tolerated dose (MTD) of both drugs in chemotherapy-naive patients with inoperable locally advanced or metastatic NSCLC. The secondary objectives were to evaluate the toxicity and antitumor activity of paclitaxel and gemcitabine given on a biweekly schedule.

Patients and methods

Eligibility criteria

Chemotherapy-naive patients with histologically or cytologically confirmed, inoperable, locally advanced or metastatic NSCLC, performance status ≤ 2 (ECOG scale) and life expectancy of at least 12 weeks, were eligible for the study. Patients were also required to have adequate bone marrow function (absolute neutrophil count $\geq 1.5\times10^9$/l, platelet count $\geq 100\times10^9$/l and hemoglobin $\geq$100 gr/l), adequate liver function (total bilirubin ≤ 1.5 time the upper normal limit, AST and/or ALT $\leq$ 3 times the upper normal limit) and a creatinine clearance rate of $\geq$60 ml/min. Patients with asymptomatic brain metastases were eligible. Patients with cardiac arrhythmias, heart failure, AV block or acute myocardial infarction within 4 months before study entry, as well as those with concurrent or previous malignancies, (except adequately treated squamous-cell carcinoma of the skin), were excluded. No prior irradiation was allowed within the 4 weeks preceding treatment.

All patients gave their written informed consent and the protocol was approved by the Hospital and local Ethics regulatory bodies.

Pretreatment evaluation included the following investigations: full medical history and physical examination, complete blood cell count and differential, full chemistry profile, ECG, chest X-ray, computed tomography (CT) of the brain, chest and upper abdomen, and radionuclide bone scans.

Physical examination and routine laboratory tests were performed at the time of each chemotherapy course and all of the diagnostic procedures required to evaluate response to treatment, according to WHO guidelines, were performed every 4 courses. Toxicity was scored according to the National Cancer Institute common toxicity criteria (NCI-CTC) scale.

Study design

The dose finding study was aimed to determine the MTD of paclitaxel and gemcitabine, both administered on day 1, every 2 weeks. The doses of the drugs were escalated alternatively. For each dose level the dose of one drug was escalated while the other was held constant.

Treatment consisted of sequentially escalated doses of paclitaxel and gemcitabine, starting from 135 mg/m^2 and 1,500 mg/m^2, respectively. Both drugs were given on day 1 and cycles were repeated every 2 weeks. Paclitaxel was administered in 500 ml of sodium chloride 0.9% over 1 h. Gemcitabine was infused over 30 min diluted in 500 ml sodium chloride 0.9% soon after the administration of paclitaxel. All patients received premedication to prevent hypersensitivity reactions. Dexamethasone 20 mg was administered intramuscularly 12 h and intravenously 30 min before the paclitaxel treatment. Ranitidine 50 mg and dimethidene maleate 4 mg were also administered intravenously 30-min before paclitaxel infusion.

Full doses of chemotherapy were given if the neutrophil and platelet counts on the day of treatment were $\geq 1.5\times10^9$/l and $\geq 100\times10^9$/l, respectively; otherwise chemotherapy administration was delayed for 1 week.

Granulocyte colony stimulating factor (G-CSF) administration was not permitted, except in case of hospitalization due to febrile neutropenia.

Because the aim of the study was to explore the feasibility of the dose intensity, on an every-2-week schedule, dose-limiting toxicity (DLT) was defined as WHO grade 3–4 neutropenia, any grade of thrombocytopenia on day 15, febrile neutropenia and $\geq$grade 3 nonhematologic toxicity (excluding alopecia, nausea, vomiting and fever), observed in the first two cycles.

At least three patients were enrolled at each dose level. If one DLT was observed in the first three patients, three more patients were entered at this dose level and dose escalation continued to the next level if fewer than three out of six patients experienced DLT during the

first two cycles. The MTD was defined as the previous level from the level at which DLT was observed in two out of three or in three out of six patients during the first two cycles.

Dose modification was not planned for any patient at any dose level. In cases of severe toxicity, patients were not given treatment. It was planned that each patient should receive six cycles of chemotherapy in cases of response or disease stability. Treatment was discontinued when disease progression or unacceptable toxicity occurred.

Statistical design

Duration of response was calculated from the day of the first demonstration of response until progressive disease. Survival was measured from the date of initial treatment to the date of death. The time to progression (TTP) was calculated from the day of entry into the study until documented disease progression. The median probability of survival and the median TTP were estimated by the Kaplan-Meier method; confidence intervals for response rates were calculated using methods for the exact binomial confidence interval.

Results

A total of 29 patients were enrolled. The results of the dose escalation are summarized in Table 1 and the patients' characteristics are shown in Table 2. All patients were male, with a median age of 65 years (range, 50–78 years). One patient had inoperable stage IIIA disease, thirteen patients stage IIIB, and fifteen had stage IV disease. Twenty-one patients had squamous cell histology, 6 had adenocarcinoma, and 2 had large cell carcinoma. Seven patients (24%) had an ECOG performance status of 2.

Toxicity

The 29 patients were treated in 6 cohorts through 6 dose escalations. A total of 198 cycles were administered (median 7, range 1–13).

In the third cohort, two patients had DLTs: one, myocardial ischemia on day 1 of the first cycle and the other, grade 4 neutropenia on day 15 of the first cycle. At dose level 5, a patient was hospitalized on day 8 of the first cycle for a short-term episode of febrile neutropenia requiring IV antibiotics and G-CSF administration; this patient received the second cycle on schedule, without delay. Three more patients entered this dose level. A second patient in this cohort had grade 4 neutropenia on day 15 of the first cycle and the second cycle was delayed for 1 week. Inadvertently patient number 6, who had a 1-week delay of the third cycle, due to grade 4 neutropenia, received prophylactic G-CSF on days 2–6 in cycles 3 through 10. These cycles were excluded from the analysis and one more patient entered this cohort.

In cohort 6, three out of six patients experienced DLTs during the first two cycles. One patient had the second cycle delayed for a week due to grade 3 neutropenia on day 15 of the first cycle. A 69-year-old patient with metastatic disease, with prior thoracic radiation therapy and an ECOG performance status of 2, was admitted to hospital because of acute respiratory failure on day 15 of the second cycle. This patient presented with dyspnea, tachypnea, dry cough, low-grade pyrexia, bibasal crackles on examination and radiological findings of bilateral interstitial pneumonitis; he died 3 months later of respiratory failure due to interstitial fibrosis, infection and severe myopathy, probably secondary to corticosteroid administration.

One other patient died suddenly at home, 7 days after the second infusion of paclitaxel and gemcitabine. The exact cause of death was unclear. He was a 69-year-old patient with stage IV disease, bulky mediastinal lymph nodes and an ECOG performance status of 2.

Table 1 Schema and results of dose escalation for the first two cycles

Dose level	Paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)	No. of patients	No. of patients with DLT	DLT
1	135	1,500	3		
2	135	2,000	3		
3	150	2,000	6	2	Grade 4 neutropenia, day 15, cycle 1 Myocardial ischemia, day 1, cycle 1
4	150	2,500	4		
5	175	2,500	7	2	Febrile neutropenia, day 8, cycle 1 (2nd cycle on schedule) Grade 4 neutropenia, day 15, cycle 1
6	175	3,000	6	3	Grade 3 neutropenia, day 15, cycle 1 Pneumonitis grade 4 and grade 3 peripheral neuropathy, day 15, cycle 2 Sudden death, day 7, cycle 2
Total			29	7	

Table 2 Patients' characteristics

Number of patients	29
Male	29
Age (years)	
Median	65
Range	50–78
Performance status (ECOG scale)	
0	1
1	21
2	7
Histology	
Adenocarcinoma	6
Squamous cell	21
Large cell	2
Stage	
IIIA	1
IIIB	13
IV	15
Prior surgery	1
Prior RT	2
Disease site	
Lung	29
Nodes	20
Pleura	7
Liver	3
Bones	10
Brain	1
Other	1
Number of sites involved	
1	1
2	19
≥3	9

For three patients from cohorts 4, 5 and 6 the treatment was interrupted due to grade 3 peripheral neuropathy after 3, 8 and 3 cycles, respectively.

The doses of paclitaxel 175 mg/m^2 and gemcitabine 2,500 mg/m^2, are considered as the MTDs in the present study and are recommended for phase II trials.

Table 3 shows grade 3 and 4 hematological toxicity. No patient experienced a thrombocytopenic event (all patients had grade 0-1 thrombocytopenia). Nonhematologic toxicity observed overall in 198 cycles is shown in Table 4. Hepatic toxicity was limited to reversible grade 2 elevations in serum transaminases in two patients from cohorts 3 and 5. In Table 5, nonhematologic toxicity by dose level is presented.

Thirteen courses (6.6%) out of 198 were administered with a delay due to neutropenia. The dose intensity

Table 3 Serious hematologic toxicity (neutropenia): 29 patients/all cycles

Dose level	No. of patients	No. of cycles	Neutropenia	
			Grade 3	Grade 4
1	3	23	0	1
2	3	20	0	1
3	6	48	2	0
4	4	24	0	0
5	7	50	0	3
6	6	33	1	1
Total	29	198	3	6

Table 4 Nonhematologic toxicity (all cycles)

Toxicity	Toxicity Grade (NCI-CTC)			
	1 *n* (%)	2 *n* (%)	3 *n* (%)	4 *n* (%)
Mucositis	5 (17)	1 (3)	–	–
ALT/AST	–	2 (7)	–	–
Diarrhea	2 (7)	–	–	–
Peripheral neuropathy	3 (10)	7 (24)	3 (10)	–
Skin	1 (3)	1 (3)	–	–
Arthralgias/myalgias	6 (21)	7 (24)	–	–
Allergy	1 (3)	3 (10)	–	–
Alopecia	1 (3)	12 (41)	–	–
Fever	3 (10)	3 (10)	–	–
Cardiac	–	–	1 (3)	–
Pulmonary	–	–	–	1 (3)
Infection	1 (3)	1 (3)	1 (3)	–

actually delivered in all cycles for all dose levels was more than 93% of the calculated dose intensity. In the recommended dose level of paclitaxel 175 mg/m^2 and gemcitabine 2,500 mg/m^2, three (6%) out of a total of 50 cycles were postponed due to neutropenia. The actual delivered dose intensity was 98% and the median dose intensity 87.5 mg/m^2/week (range, 58.3–87.5) and 1,250 mg/m^2/week (range, 833–1,250) for paclitaxel and gemcitabine, respectively.

To evaluate whether or not the doses can be administered repetitively, we analyzed the dose intensity of the first four cycles for dose levels 4 and 5. The mean dose intensity at dose level 4 was 75 mg/m^2/week for paclitaxel and 1,250 mg/m^2/week for gemcitabine. The mean dose intensity at dose level 5 for paclitaxel and gemcitabine was 86 mg/m^2/week (range, 43.75–87.5) and 1,229 mg/m^2/week (range, 625–1,250), respectively.

Response

Twenty-eight patients who received more than two cycles of chemotherapy were assessable for response. Ten patients (35.7%; 95% confidence interval [CI], 17.97%-53.47%) achieved partial response on 'an intent-to-treat' basis. With regard to responders, one patient had stage IIIA disease, 5 had stage IIIB and 4 had stage IV. From the subgroup of patients with an ECOG performance status of 2, only one had a partial response. In Table 6 objective responses are presented according to dose level, the patient's ECOG performance status, stage of disease and histology type. Median duration of response was 20 weeks (95% CI, 9–31 weeks). The small number of patients treated and their dose intensity heterogeneity do not permit us to draw any conclusions about the impact of this schedule on survival; with purely exploratory intent, we present the data on survival and time to disease progression. Mean TTP was 22.93 weeks, standard error 2.70, 95% CI, 17.63–28.22; median TTP 23 weeks, standard error 3.97, 95% CI, 15.22–30.78

Table 5 Serious nonhematologic toxicities by dose level for all treatment cycles

	Level 1			Level 2			Level 3			Level 4			Level 5			Level 6		
No. of patients	3			3			6			4			7			6		
No. of cycles	3			3			6			4			7			6		
No. of patients	23			20			48			24			50			33		
	Grade NCI-CTC toxicity																	
	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
	No. of patients																	
Infection	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
ALT/AST	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
Mucositis	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
Peripheral neuropathy	0	0	0	0	0	0	3	0	0	0	1	0	1	1	0	0	1	0
Cardiac ischemia	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Pneumonitis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

(Fig. 1). Mean survival was 41.93 weeks, standard error 4.41, 95% CI, 33.28–50.58; median survival 36 weeks, standard error 6.28, 95% CI, 23.69–48.31 (Fig. 2).

Eight patients received cisplatin-based, second-line chemotherapy at disease progression. A patient with inoperable stage IIIA disease was treated with radiation therapy after completion of chemotherapy.

Discussion

In our study, the every-2-week schedule of the paclitaxel and gemcitabine combination appears to be feasible and safe in chemotherapy-naive patients with NSCLC.

The main DLT was neutropenia. Only one patient at dose level 5 experienced febrile neutropenia on day 8 of the first cycle, requiring IV antibiotics. This episode was short-lived and the second cycle was administered on schedule. Both hematologic and nonhematologic toxicities were manageable and grade 3 cumulative peripheral neuropathy was a cause of treatment discontinuation only at the dose level of paclitaxel 175 mg/m^2 after several cycles of chemotherapy. One patient, who had received prior radiation therapy at the chest, died from respiratory failure due to interstitial fibrosis.

Using the every-other-week schedule in a phase I dose finding study in patients with refractory solid tumors, Rothenberg et al. [14] reported that the MTDs were 150 mg/m^2 over 3 h for paclitaxel and 3,500 mg/m^2 over 30 min for gemcitabine. For phase II, the study recommended the doses of paclitaxel at 150 mg/m^2 and gemcitabine at 3,000 mg/m^2 due to the higher delivered dose intensity achieved for the first three cycles. No respiratory events were observed in this study. However only 7 out of 37 patients had lung cancer and the authors did not report separate data on doses administered and the status of prior radiotherapy for these patients. DLTs in this study were grade 4 neutropenia and grade 3 elevation of alanine aminotransferase. .

No pulmonary toxicity was reported by Isla et al. in a phase II trial of biweekly administration of paclitaxel 150 mg/m^2 and gemcitabine 2,000 mg/m^2. In this study, only 1% of the cycles were delayed due to neutropenia and a high dose intensity was reported: 97.2% for paclitaxel and 96.6% for gemcitabine [12].

In a phase I–II study by Giaccone et al. [10] using the day 1 dose for paclitaxel, and days 1 and 8 for gemcitabine, paclitaxel was escalated up to 200 mg/m^2 in combination with gemcitabine 1,000 mg/m^2 in 14 out of 16 patients who received more than two cycles of chemotherapy. However, the endpoint of this study was not the establishment of the MTD, but the evaluation of

Table 6 Characteristics of responders

Patient	Dose level	Stage	Performance status	Histology	Response duration (weeks)
1	1	IIIB	1	Squamous	27
2	2	IIIB	1	Squamous	44
3	2	IIIA	0	Squamous	68
4	4	IV	1	Adeno	20
5	5	IV	1	Squamous	14
6	5	IIIB	1	Squamous	17
7	5	IV	2	Squamous	18
8	5	IV	1	Adeno	30
9	5	IIIB	1	Adeno	26
10	6	IIIB	1	Adeno	19

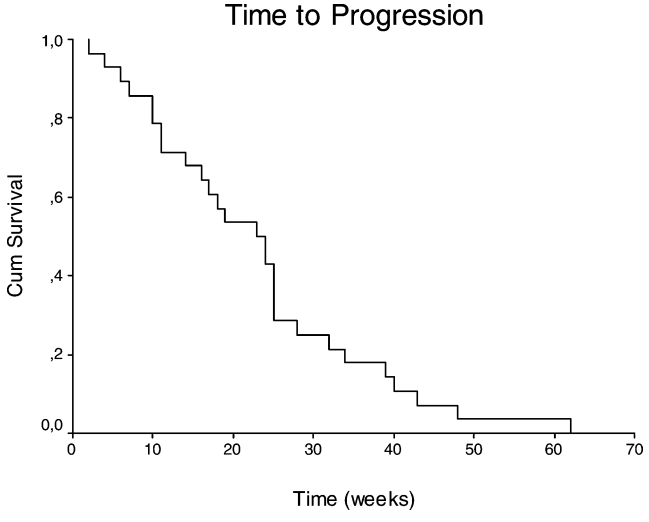

Fig. 1 Kaplan-Meier time to progression

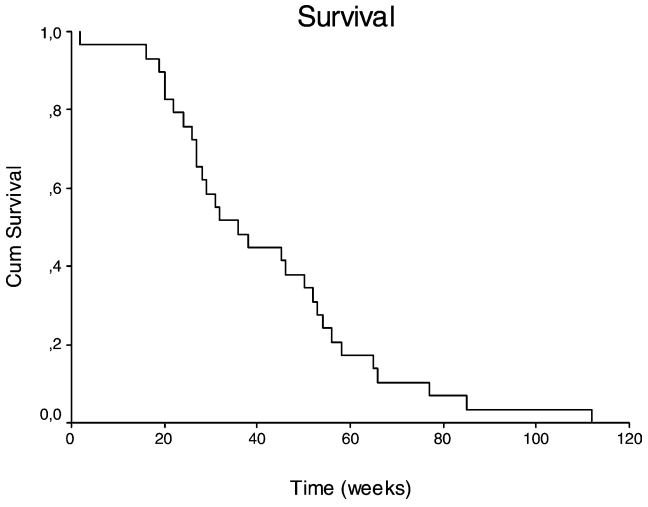

Fig. 2 Kaplan-Meier overall survival

effective doses of the paclitaxel and gemcitabine combination. Pneumonitis was the reason for treatment interruption in one patient in cycle 2 and cumulative grade 2 and 3 neurotoxicity in two patients.

In one of the arms of a phase III randomized trial in patients with advanced NSCLC, Kosmidis et al. administered 200 mg/m^2 paclitaxel on day 1 and 1,000 mg/m^2 gemcitabine on days 1 and 8, every 3 weeks. The relative dose intensity of paclitaxel and gemcitabine was only 0.89 and 17% of the cycles were delayed due to leukopenia [13]. In our study, only 6.5% of the cycles were delayed due to neutropenia, despite the dose schedule used and the higher dose intensity. The higher dose intensity achieved in our study may have been due to the modified treatment schedule we used.

Although efficacy was not a primary endpoint of the present study, 35.7% of our patients achieved a partial response. A 32.2% response rate was reported by Isla et al. using the same schedule of the paclitaxel and gemcitabine combination [12]. The results of the bi-weekly schedule used in these studies are comparable with those reported by other studies using the days-1-and-8 schedule and phase II trials of cisplatin combinations [4, 16–18].

In conclusion, this trial demonstrates that paclitaxel and gemcitabine can be safely administered on a bi-weekly schedule, achieving high dose intensity and efficacy, comparable to that reported by other studies in similar patient populations. The recommended phase II dose, as defined by the study protocol, is paclitaxel 175 mg/m^2 over a 1-h infusion, followed by gemcitabine 2500 mg/m^2 infused over 30 min.

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