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ORIGINAL ARTICLE

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Alternating weekly administration of paclitaxel and gemcitabine: a phase II study in patients with advanced non-small-cell lung cancer

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Abstract *Background*: We sought to evaluate toxicity and efficacy of an alternating week schedule of paclitaxel and gemcitabine in patients with advanced non-small-cell lung cancer (NSCLC). *Methods*: Patients ($n=27$, mean age 56 years, range 27–73 years) received paclitaxel (100 mg/m^2 i.v. infusion over 1 h) on days 1 and 15 alternating with gemcitabine (1000 mg/m^2) on days 8 and 22 of a 36-day cycle. Responses were evaluated after three cycles, and after the proposed six cycles. *Results*: In total, 116 cycles were administered (mean 4.25 cycles per patient). Haematological toxicity was slight: febrile neutropenia ($n=1$) and neutropenia grade III–IV ($n=5$). Non-haematological toxicities included arthromyalgia grade II ($n=6$) and neurotoxicity grade III ($n=1$). Objective response was 29%, stable disease 25% and disease progression 46%. Median duration of response was 8 months (95% CI 5–11 months), median progression-free survival was 7 months (95% CI 4–11 months), median overall survival was 13 months (95% CI 7–17 months) and survival at 1 year was 52%. *Conclusions*: A regimen of alternating weekly paclitaxel and gemcitabine is feasible in patients with advanced NSCLC, showing a lower toxicity profile compared with other platinum-based combinations, which makes this novel scheme attractive for these patients.

Keywords Advanced non-small-cell lung cancer · Chemotherapy · Paclitaxel · Gemcitabine

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Introduction

Non-small-cell lung cancer (NSCLC) shows the highest incidence of tumours in adults. The high mortality rate makes it the principal cause of death from cancer. Unfortunately, only 14% of all the patients diagnosed with NSCLC remain alive at 5 years, and a great proportion of the patients with NSCLC (up to 70%) are diagnosed late at the locally advanced or metastatic stages of the disease [1, 2]. Chemotherapy has been shown in randomized studies and meta-analyses [3] to have a modest, but statistically significant, effect on survival in this group of patients. The standard, classical treatment has been combinations based on cisplatin. Newer chemotherapy agents such as paclitaxel and gemcitabine that have been incorporated in the treatment of NSCLC have shown high activity in the advanced stages of the disease. Their use in combination with platinum derivatives shows higher levels of response [4, 5]. However, the high frequency of haematological, renal and gastrointestinal adverse effects has prompted the search for new combinations that exclude platinum derivatives while maintaining similar efficacy [6–8]. The absence of cross-resistance between paclitaxel and gemcitabine has stimulated their use in combination in the treatment of NSCLC, and the activity observed is similar to that of the older combinations based on platinum derivatives, but with a more acceptable toxicity profile [9–11].

Based on the known activity of paclitaxel and gemcitabine in monotherapy and in combination, we initiated a phase II study using a novel weekly regimen in which paclitaxel and gemcitabine were administered alternately in order to evaluate the efficacy and toxicity profile in patients with inoperable, metastatic or locally advanced NSCLC. Alternating administration of non-cross-resistant drugs would permit the use of paclitaxel and gemcitabine at full doses of weekly administration (paclitaxel 100 mg/m^2 and gemcitabine 1000 mg/m^2) without the need for dose reduction. This form of

administration would avoid the cumulative toxicity associated with the simultaneous administration of both drugs, especially haematological toxicity and the neurotoxicity of paclitaxel.

Patients and methods

Patient eligibility criteria

All patients provided written informed consent to participation in the study. The patients needed to have NSCLC diagnosed histologically or cytologically as being in stage IIIB or IV. Additional patients at early stages were permitted to enter the study in order to assess toxicity and response if they did not have any other therapeutic alternative.

The patients with any metastatic location and those who presented with pleural or pericardial effusion were confirmed cytologically, except in the cases of diffuse bone involvement. All patients needed to have a European Cooperative Oncology Group performance status (ECOG PS) of 0–2, adequate bone marrow reserve (leucocytes not less than $3.5\times10^9\ l^{-1}$; platelets $\geq100\times10^9\ l^{-1}$; and haemoglobin ≥9.0 mg/dl), and adequate renal function (plasma creatinine ≤ 1.5 mg/dl). The patients needed to have at least one measurable lesion.

The patients with a previous neoplasia were excluded except those with basocellular carcinoma of the skin or in situ carcinoma of the cervix. Having had previous radiotherapy was allowed provided that the irradiated zone did not cover the single lesion evaluable for response. For inclusion in the trial, prior chemotherapy was permitted even if treatment contained paclitaxel or gemcitabine, or both in combination in order to evaluate the toxicity profile of the regimen.

Baseline assessment

All patients were staged with respect to the disease on entry into the trial. A complete clinical history was obtained and thorough physical examination performed. Blood analyses included complete blood count, chemistries and coagulation. Baseline data included weight, height, ECOG PS and disease symptoms. Bronchoscopy, radiography of the thorax and CT scan of the chest and abdomen were performed. Those patients with a diagnosis of adenocarcinoma with extensive mediastinal involvement or neurological symptoms had a cranial CT scan performed. A bone scan was performed in the patients with bone pain or blood chemistry alterations such as elevated levels of alkaline phosphatase and/or calcium.

Treatment plan

The chemotherapy schedule consisted of the administration of paclitaxel and gemcitabine on a weekly alternating basis. A treatment cycle was defined as the administration of 4 weeks of treatment, i.e. paclitaxel twice and gemcitabine twice followed by a rest period and the start of the new cycle on day 36. The paclitaxel was administered at a dose of 100 mg/m^2 infused over 1 h on days 1 and 15 of the cycle. The gemcitabine was administered as an infusion over 30 min on days 8 and 22 at a dose of 1000 mg/m^2. Premedication consisted of 16 mg dexamethasone, 50 mg ranitidine and 5 mg dexchlorfeniramine administered 30 min before the paclitaxel administration on days 1 and 15. Intravenous ondansetron 8 mg was provided before each administration of paclitaxel and gemcitabine on days 1, 8, 15 and 22.

Treatment was given on day 1 of every cycle if the absolute neutrophil count (ANC) and platelets were $\geq1.5\times10^9\ l^{-1}$ and $\geq100\times10^9\ l^{-1}$, respectively. For the doses on days 8, 15 and 22 of every cycle, treatment was given if ANC and platelets were $\geq1.0\times10^9\ l^{-1}$ and $\geq75\times10^9\ l^{-1}$, respectively. If non-haematological toxicity (except for grade I nausea/vomiting and alopecia) were observed, treatment was delayed until recovery for a maximum of 3 weeks. If febrile neutropenia, grade IV non-haematological toxicity, or grade III peripheral neuropathy occurred, drugs were reduced by 50%. If grade III non-haematological toxicity (except nausea/vomiting and alopecia), grade II peripheral neuropathy and/or grade II–IV neutropenia occurred, doses were reduced by 25%. The maximum number of cycles envisaged per patient was six. All patients were treated on an outpatient basis.

Objectives

The principal objective of the trial was to evaluate the toxicity profile and the efficacy of the new scheme of chemotherapy (which excluded platinum-based combinations) in patients with advanced NSCLC. Secondary objectives were progression-free survival (PFS) and overall survival (OS).

Toxicity assessment

In each week of the treatment, and prior to the drug administration, a thorough anamnesis was performed and blood taken for a full blood count. Weekly data were recorded on specifically designed data-recording sheets and included haematological and non-haematological toxicity data based on the criteria of the National Cancer Institute Common Toxicity Criteria (NCI-CTC 2.0). The analyses were performed throughout the treatment period, and at 1 week following the conclusion of the treatment.

Response evaluation

Response was evaluated according to the response evaluation criteria in solid tumours (RECIST) [12]. Physical examination was performed before each chemotherapy administration to check for appearance of new symptoms, non-haematological secondary effects and the presence of evaluable lesions. A thorough examination was performed following the first three cycles using CT scan of the thorax and abdomen. Those patients with objective response or stable disease (SD) continued up to the maximum of six cycles, while those patients with disease progression (DP) following the first three cycles were transferred out of the trial.

Statistical considerations

The study was designed to reject a response rate of less than 10% (p0) and provide a statistical power of 80% in assessing the activity of the regimen as 30% (p1) (p1−p0 = 20%) with an alpha error of less than 0.05. Therefore, 25 patients were required with at least six objective responses to reject the null hypothesis. The method of Kaplan and Meier was used to estimate median OS and median PFS. OS was measured from the date of the first chemotherapy administration to the date of death or the last date the patient was known to be alive. PFS was measured from the date of first administration of the chemotherapy up to the date of relapse or onset of DP. All patients alive at the time of the analysis were censored with the date of the last follow-up. Duration of response was calculated from the day of the first demonstration of response until DP was established. The log-rank test and hazard ratios were used to compare differences in survival between patients with an ECOG PS of 0–1 and those with an ECOG PS of 2.

Results

Patient characteristics

A total of 27 patients were recruited into the study between October 2001 and August 2002. Of these, 24 were at stage IIIB or IV, 6 stage IIIB (3 with pericardial effusions and 2 with pleural effusions) and 18 stage IV. The other 3 patients (1 stage II and the other 2 stage IIIA) were treated within the study having been rejected for surgery or radiotherapy because of their baseline pathology and/or poor functional status. Of the 27 patients, 5 (1 stage IIIB and 4 stage IV) had received previous chemotherapy but had DP, four with the paclitaxel–carboplatin–gemcitabine triplet and one with paclitaxel–carboplatin doublet. The principal characteristics of the patients on entry into the trial are summarized in Table 1.

Table 1 Patient characteristics on entry into the trial. Values are number (%) of patients ($n = 27$), except age in years

Age (years)	
Median	56
Range	27–73
Gender	
Male	21 (78)
Female	6 (22)
Histology	
Adenocarcinoma	14 (52)
Large-cell carcinoma	7 (26)
Squamous-cell carcinoma	4 (15)
Bronchoalveolar	2 (7)
ECOG PS	
0	4 (15)
1	19 (70)
2	4 (15)
Stage IV ($n = 18$)	
Lung nodules	12 (44)
Liver metastasis	5 (19)
Lung lymphangitic spread	3 (11)
Bone metastasis	3 (11)
Lymph node metastasis	3 (11)
Adrenal metastasis	1 (4)
Previous therapy	
No chemotherapy	22 (4)
One line of chemotherapy	4 (15)
Two lines of chemotherapy	1 (4)

Delivered chemotherapy

A total of 116 cycles of chemotherapy were administered, representing 466 chemotherapy sessions (235 paclitaxel and 228 gemcitabine). The mean was four cycles per patient (range one to six). Of the 27 patients, 10 (37%) needed a delay in the administration of treatment, and represented 17 of the 466 sessions administered (3%), and 9 (33%) required a dose reduction (14 paclitaxel and 1 gemcitabine) at some time during the course of the treatment, and represented 15 of the 411 sessions administered (4%). Overall, the patients had 93% of the chemotherapy sessions administered at the scheduled time and at the planned dosage.

Toxicity of the chemotherapy

All of the 27 patients were evaluable for toxicity. Two patients had hypersensitivity reaction to paclitaxel in the first cycle. In general, the toxicity was slight, was tolerated by the patients and none opted to withdraw from the study. Only one case of febrile neutropenia grade III was recorded. The patient did not need hospitalization and the febrile neutropenia was resolved with outpatient prescription of antibiotics for a 48 h period. Apart from these, the most frequent haematological toxicity was anaemia grade I which occurred in 44% of the patients. Neutropenia grade III–IV was recorded in five patients (19%). There was no single case of thrombocytopenia nor of anaemia grade III–IV. In relation to non-haematological toxicity, there were only two cases of toxicity grade III (one of peripheral sensitive neuropathy and one of arthralgia–myalgia) and no case of grade IV

toxicity. The two patients with neuropathy grade II–III had not received any chemotherapy previously. The most frequent non-haematological toxicity was arthromyalgia grade II in six patients (22%). The toxicity data, according to the criteria of the NCI-CTC, are summarized in Table 2. In the course of the treatment, eight patients needed some form of treatment support (five with erythropoietin, two with granulocyte colony-stimulating factor, and two with antibiotics). Neither antiemetics nor blood-product transfusions were needed. No patient needed hospitalization for toxicity, and there were no toxicity-related deaths.

Response to chemotherapy

Of the 27 patients included in the study, 24 were evaluable for response (1 stage II, 2 stage IIIA, 5 stage IIIB, and 16 stage IV). Of the 3 who were not evaluable (NE), 2 were withdrawn from the study because of toxicity in the first cycle, as has been commented upon above, and 1 died prematurely in the first cycle from causes unrelated to the disease or its treatment.

There were a total of 7 patients with a partial response (PR) making an objective response rate (ORR) in the group of evaluable patients of 29%. Six patients (25%) had SD and 11 (46%) had DP. There were no complete responses (CR). PR was observed in 1 patient with stage IIIA, 2 with stage IIIB (ORR of 40%) and 4 with stage IV (ORR of 25%). The ORR among the evaluable stage IIIB–IV patients was 29%. One of the patients who had previously received chemotherapy with the paclitaxel–carboplatin–gemcitabine triplet achieved a PR while the other 4 patients with previous chemotherapy did not respond to the new regimen. None of the patients with ECOG PS of 2 achieved a response to the treatment. Among the seven patients who responded, the median duration of response was 8 months (95% CI 5–11 months). All the responses were observed in the first follow-up after three cycles of treatment.

Table 2 Worst-grade toxicities recorded for each patient ($n=27$)

Toxicity	NCI-CTC grade, *n* (%)			
	I	II	III	IV
Leucopenia	3 (11)	6 (22)	1 (4)	1 (4)
Neutropenia	6 (22)	6 (22)	3 (11)	2 (7)
Anaemia	12 (44)	3 (11)	0	0
Thrombocytopenia	0	0	0	0
Anorexia	1 (4)	0	0	0
Nausea/vomiting	5 (19)	4 (15)	0	0
Dysgeusia	3 (11)	0	–	–
Diarrhoea	0	2 (7)	0	0
Constipation	1 (4)	4 (15)	0	0
Fatigue	2 (7)	4 (15)	0	0
Arthralgia/myalgia	2 (7)	6 (22)	1 (4)	0
Alopecia	4 (15)	0	–	–
Nail changes	1 (4)	1 (4)	–	–
Neuropathy[a]	3 (11)	1 (4)	1 (4)	0
Allergic reaction[b]	0	1 (4)	1 (4)	0

[a]Peripheral sensitive neuropathy
[b]Hypersensivity to paclitaxel

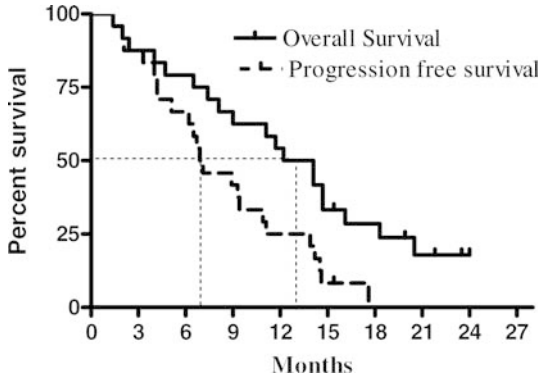

Fig. 1 Kaplan–Meier survival curves for overall survival and progression-free survival

Survival

Survival was analysed on an intention-to-treat basis for stage IIIB–IV patients. At the time of the present analysis, the median follow-up was 21 months (95% CI 19–24 months).

To date, 22 of the 27 patients (81%) had died and 5 remained alive. In relation to the response categories, 5 of 7 patients with PR, 4 of 6 with SD, 10 of 11 with PD, and 3 of 3 in the NE category had died. There were 5 patients still alive (2 stage IIIB and 3 stage IV) and of these 4 had been placed on treatment with a second line of chemotherapy and 1 was without treatment (initially SD and subsequently DP). Among the 4 patients under treatment, 2 achieved an initial PR (1 of them currently showed SD), 1 initially achieved SD and then progressed, and the other initially showed PD.

The median PFS for stage IIIB–IV was 7 months (95% CI 4–11 months). Median OS was 13 months (95% CI 7–17 months) and the rate of survival at 1 year was 52% (Fig. 1).

The patients with an ECOG PS of 2 had a mean survival that was statistically significantly lower than the group of patients with an ECOG PS of 0–1. Median OS for the patients with an ECOG PS of 0–1 and an ECOG PS of 2 were 14 and 3 months, respectively (hazard ratio 0.30; 95% CI 0.02–0.73 months; $P=0.021$).

Discussion

Despite the advances in combination chemotherapy and the advent of new drugs there is no regimen that is clearly superior in the treatment of advanced NSCLC. This has been amply demonstrated in randomized studies evaluating doublets with or without the addition of platinum and its derivatives, and including triplet combinations [13–16]. The studies demonstrate no

statistically significant differences between the treatments with response rates of around 20–40% and mean survivals of around 8–11 months. The combination of paclitaxel and carboplatin was compared with vinorelbine and cisplatin, and ORR of 25% and 29% were shown, respectively, with a median survival of 8 months in both groups [13]. In another phase III randomized trial comparing four different two-drug combinations (paclitaxel + cisplatin, gemcitabine + cisplatin, docetaxel + cisplatin, paclitaxel + carboplatin) again there were no statistically significant differences between the four treatment arms in relation to the ORR (21, 21, 15 and 15%, respectively) or mean survival (8, 8, 7 and 8 months, respectively) [14]. In another study comparing three doublets (gemcitabine + cisplatin, paclitaxel + carboplatin, vinorelbine + cisplatin) no significant differences between the three treatment arms were found with respect to response (30%, 32% and 30%, respectively) and median survival (around 10 months) [15]. In all of these studies, the percentage of patients remaining alive at the end of the first year did not vary significantly at around 30–40%.

Studies performed with drug combinations that excluded platinum and its derivatives appear to indicate equivalence in activity, but with better patient tolerance and with reduced gastrointestinal and renal toxicity [6–8]. A study conducted by the European Organization for the Research and Treatment of Cancer (EORTC) compared three treatment arms (paclitaxel + cisplatin, gemcitabine + cisplatin, paclitaxel + gemcitabine) [6]. No statistically significant differences were seen between the treatment arms in relation to the ORR, median survival, or survival at 1 year. However, the paclitaxel + gemcitabine treatment arm showed a non-significant trend towards inferiority with lower levels of response, OS and survival at 1 year (27%, 7 months, and 26%, respectively), although the study was powered to be significant only for a large difference. In another multicentre randomized phase II trial [7], the combination of docetaxel + cisplatin was compared with docetaxel + gemcitabine and, again, the results were similar in both treatment arms. Similar results were obtained in the study of Satouchi et al. [8] comparing docetaxel + cisplatin with docetaxel + irinotecan.

The paclitaxel + gemcitabine combination (200 mg/m^2 of paclitaxel on day 1 and 1000 mg/m^2 of gemcitabine on days 1 and 8 of a 21-day cycle) has been compared directly with the paclitaxel + carboplatin combination [11]. The study was a phase II randomized trial with 509 patients. The ORR obtained was 35% for the paclitaxel + gemcitabine combination and 28% for the paclitaxel + carboplatin combination, with a survival of around 10 months and survival at 1 year of 41% and 42% for the two treatment arms, respectively. None of the differences were statistically significant. The toxicity was similar in both groups, with 15% neutropenia grade III–IV in both groups, and 8% and 6% neuropathy grade III for the paclitaxel + carboplatin and the paclitaxel + gemcitabine combinations, respectively.

Because of the similarity of these results, the selection of a chemotherapy scheme for use in these patients would need to be based on various other aspects such as familiarity with the regimen, toxicity of the therapy, convenience of administration and the cost of the treatment [17].

Over the past few years there have been several studies exploring the weekly administration of chemotherapy, and these schedules have shown a similar activity but with a lower toxicity, mainly haematological. Paclitaxel has been used at doses of between 80 and 175 mg/m^2 in weekly regimens in several types of tumours including NSCLC. In one study with paclitaxel at the recommended dose of 80 mg/m^2, an objective response of 30% was obtained, with only 9% neutropenia grade III–IV and 6% neuropathy grade II [18]. The toxicity was considerably greater in another phase II trial with paclitaxel at a dose of 150 mg/m^2 per week [19] (33% haematological toxicity grade III–IV, principally neutropenia, and 28% neuropathy grade III), and without any substantial increase in the rates of response.

The combination of paclitaxel + gemcitabine, with both drugs administered weekly, has not been so well investigated to date. In a phase I trial [20], paclitaxel and gemcitabine were employed in a weekly scheme on days 1, 8 and 15 of a 28-day cycle, and with scalable doses. At dose levels corresponding to paclitaxel of 100 mg/m^2 and gemcitabine above 1000 mg/m^2, peripheral neuropathy occurred in 23–39% of the patients. More recent results include a phase II trial [21] with 40 previously untreated patients in whom gemcitabine was administered at a dose of 1000 mg/m^2 and paclitaxel at a dose of 110 mg/m^2, both drugs administered on days 1, 8 and 15 of a 28-day cycle. The ORR was 38.2%, but with an elevated toxicity: neutropenia occurring in 43% of patients, thrombocytopenia grades III–IV in 13% and febrile neutropenia in 13%, and with four toxic deaths (10%). In a dose-optimizing phase II study [22], paclitaxel was administered at a dose of 100 mg/m^2 and gemcitabine at a dose of 1000 mg/m^2. Initial patients received chemotherapy on days 1, 8 and 15 every 4 weeks but the tolerability was poor and the rest of the patients received chemotherapy on days 1 and 8 every 3 weeks. The ORR was 55% with a median survival of 9.8 months.

Our present results with paclitaxel + gemcitabine administered on alternate weeks show that the antitumour activity in advanced NSCLC is maintained within the range obtained for the more toxic combinations. Although our study was a non-randomized phase II trial with a limited number of patients, the ORR of 29% is similar to that expected from combination therapies containing derivatives of platinum as well as combinations involving the newer agents (as commented upon above). The median survival of 13 months for stage IIIB–IV patients obtained in our study is very promising and was higher (14 months) if the patients with ECOG PS 0–1 are considered separately from the other patients. An equally good outcome is that 52% of these patients

were still alive at 1 year. Of considerable note is the survival rate obtained in the 12 patients with stage IIIB–IV who had therapeutic benefit (patients with PR or SD), 5 of these patients being still alive with a mean survival time of 21 months (range 15–25 months). The toxicity observed in our study was slight and compared very favourably with that observed with other schemes of chemotherapy, and without loss of efficacy.

As mentioned earlier, the neurotoxicity associated with the administration of weekly paclitaxel increases up to 38% when a dose of 150 mg/m^2 is used in monotherapy, and is between 20% and 30% when administered in combination with weekly gemcitabine at a lower dose. In our study, the alternating administration of paclitaxel and gemcitabine resulted in only one case (4%) of peripheral sensitive neuropathy grade III. This was very much lower than expected. The absence of gastrointestinal toxicity grade III–IV is another point in favour of this new combination compared to other chemotherapy combinations. The early trials with combinations of paclitaxel and gemcitabine were complicated by the development of drug-induced pneumonitis, as reported particularly by Bhatia et al. [21] (10% pneumonitis with 1 related death), and by Thomas et al. [23] (4 of 12 patients with pneumonitis grade II–III). This was not an issue in our trial.

Haematological toxicity was also slight, and with few repercussions. The occurrence of neutropenia grade III–IV in 19% of the patients did not have a significant influence on the timing of the administration of the treatment nor on the intensity of dose, i.e. 93% of the chemotherapy sessions were administered successfully at the scheduled time and at the planned dosage. The absence of thrombocytopenia and anaemia in our study are also favourable points that need to be born in mind.

Although the number of patients studied was too small to draw definitive conclusions, the results support the hypothesis that weekly chemotherapy with alternating paclitaxel and gemcitabine is feasible for the treatment of advanced NSCLC. This novel schedule shows an activity that compares favourably with other, more toxic, chemotherapy regimens for advanced NSCLC. The very acceptable toxicity profile makes it an attractive option for these patients. Further studies of other two-drug combinations with alternating weekly schedules are warranted so that improved results may be obtained with these low-toxicity chemotherapy regimens.

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