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ORIGINAL ARTICLE

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# Phase II study of a fixed dose-rate infusion of gemcitabine associated with docetaxel in advanced non-small-cell lung carcinoma

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**Abstract** *Purpose*: To evaluate the efficacy and toxicity profile of the combination of docetaxel and prolonged gemcitabine infusion in front-line chemonaive patients with advanced non-small-cell lung cancer (NSCLC). *Patients and methods*: A total of 50 chemonaive patients diagnosed with advanced NSCLC according to the AJCC/TNM classification system were included in the present study. Treatment consisted of 1000 mg/m$^2$ gemcitabine given as a 100-min continuous infusion (10 mg/m$^2$ per min) on days 1 and 8 of each course and 75 mg/m$^2$ docetaxel as a 60-min infusion on day 8, repeating each course every 21 days. *Results*: The ECOG performance status of the patients were as follows: 0 (10%), 1 (60%), and 2 (30%). All patients had two-dimensionally measurable disease. Their median age was 63 years (range 41–75 years). Of the 50 patients, 28 (56%) had squamous cell carcinoma, 14 adenocarcinoma (28%), and 8 (16%) large-cell carcinoma, and 40% and 60% of patients presented with stage IIIB and IV disease, respectively. Of those with stage IV disease, 33% had more than one metastatic site. A total of 220 courses were administered with a median of five courses per patient. Of 46 patients assessed for response, 12 (26%) had a partial remission (95% CI 13–39%). In 19 patients (41%) the disease remained stable, while disease progression was observed in 15 (33%). The median time to disease progression was 4 months, and median survival time was 7 months. At 1 year, 25% of patients remained alive, and the main grade 3/4 toxicity (according to the WHO scale) consisted of neutropenia ($n=6$, 12%), asthenia ($n=4$, 8%), peripheral edema ($n=3$, 6%), dyspnea ($n=3$, 6%), and diarrhea ($n=2$, 4%). *Conclusions*: Prolonged gemcitabine infusion combined with docetaxel is well tolerated and its efficacy is similar to that of other chemotherapeutic schemes used for NSCLC treatment. However, the prolonged infusion of gemcitabine did not appear to result in any improvement in outcome or toxicity versus the standard dose rate.

**Keywords** Non-small-cell lung carcinoma · Gemcitabine · Docetaxel · Chemotherapy · Fixed infusion

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## Introduction

Cisplatin-based chemotherapy confers an improvement in overall survival compared with best supportive care and is an effective palliative treatment in patients with

advanced non-small-cell lung carcinoma (NSCLC) [1, 2]. A number of studies have demonstrated that the addition of a new chemotherapeutic agent (gemcitabine [2], vinorelbine [3], and paclitaxel [4]) to cisplatin provides a modest but clinically significant survival advantage over cisplatin alone. However, to date, no regimens have been shown to be clearly better, with response rates below 30%. Responses have been partial and short-term in all cases, with a median survival shorter than 8–9 months. Only 35% of patients remain alive after 1 year, and toxicity is not inconsiderable [5]. In this regard, the employment of a non-platinum-containing chemotherapy regimen could be an attractive alternative, as it may be associated with reduced toxicity and similar activity.

Docetaxel has been shown to exert an outstanding single-agent activity in patients with untreated disease [6, 7], and, when combined with cisplatin, is an active regimen for front-line treatment of patients with advanced NSCLC [8]. Furthermore, docetaxel is the only agent which has proved efficient as a second-line treatment for platinum-resistant NSCLC [9, 10]. Gemcitabine, in turn, is another agent, which has provided a small but significant clinical benefit in advanced NSCLC when administered at a dose of 1000 mg/m$^2$ given over 30 min on a weekly basis [11]. Higher doses could improve clinical results, but pharmacological studies suggest that the augmentation of the dose when administered over a 30-min period does not increase either cytotoxicity or the therapeutic index [12, 13]. This is likely to be due to pharmacological features of gemcitabine, which is activated through several biochemical steps, with a key role for the enzyme deoxycytidine kinase, which is rapidly saturated. Thus, increased doses would not be efficient, while longer infusion times would provide increased intracellular concentrations, thus enhancing the agent's efficacy.

Accordingly, the authors of the present investigation decided to develop a combination regimen of gemcitabine (given at a constant dose rate of 10 mg/m$^2$ per min) and docetaxel in chemonaive patients with NSCLC. This scheme would take advantage of the synergism between gemcitabine and docetaxel and would be expected to be more convenient for patients as far as tolerability is concerned. Accordingly, it was the aim of the present study to assess the chemotherapeutic activity and toxicity of the above scheme involving gemcitabine and docetaxel in patients with advanced NSCLC.

## Patients and methods

The purpose of this phase II study was to evaluate a new combination chemotherapy regimen for the treatment of chemotherapy-naive patients with advanced NSCLC. Patients were given gemcitabine, 1000 mg/m$^2$, days 1 and 8, and docetaxel, 75 mg/m$^2$ day 8. Gemcitabine was administered over 100 min (10 mg/m$^2$ per min) and was followed immediately by docetaxel, which was administered over 60 min. Premedication with 8 mg of dexamethasone was initiated 12 h prior to each docetaxel infusion and continued every 12 h for two doses. All patients received antiemetic prophylaxis with ondansetron or granisetron. This regimen was repeated every 21 days for a minimum of three courses per patient unless disease progression was detected. Treatment was administered on an outpatient basis. All patients had histologically or cytologically proven NSCLC (squamous cell carcinoma, adenocarcinoma, or large-cell carcinoma) and stage IIIB or IV disease according to the staging system proposed by Mountain [14]. All the patients had one or more two-dimensionally measurable or evaluable lesions in accordance with World Health Organization (WHO) guidelines [15]. Pleural effusion, ascites, osteoblastic lesions or previously irradiated lesions were not accepted as measurable disease.

Eligible patients were to meet the following inclusion criteria: (1) aged 18–75 years; (2) ECOG performance status $\leq 2$; (3) life expectancy of at least 3 months; (4) adequate medullar function (i.e., granulocyte count $\geq 2\times10^9$/l and platelets $> 100\times10^9$/l); (5) adequate liver function (i.e., serum bilirubin less than 1.25 times the upper normal limit, glutamic oxaloacetic transaminase values (SGOT) and glutamic pyruvic transaminases (SGPT) less than 3 times the upper normal limit in the absence of hepatic metastases); and (6) adequate renal function (i.e., serum creatinine $< 150$ μmol/l, or creatinine clearance of at least 60 ml/min).

Patients who had undergone radiotherapy were eligible provided that there was at least one measurable lesion outside the radiation field and radiation treatment had been completed at least 4 weeks before enrolment. The presence of brain metastases, significant heart disease (congestive heart failure or unstable angina), and neuropathy greater than grade 2 were considered as exclusion criteria. Patients with tumors other than lung cancer were also excluded, with the exception of radically resected non-melanoma skin cancer or in situ cervical carcinoma. Oral and written informed consents were obtained from all patients according to the local ethics committee guidelines of the participating hospitals.

Diagnostic workup was performed within 3 weeks prior to treatment initiation. It involved comprehensive history, physical examination, blood analysis (complete blood count and blood chemistries), and imaging studies as needed (chest radiograph, chest and abdominal CT scan, and radionuclide bone scan). Brain CT scan was performed in the presence of symptoms suggestive of brain metastases. ECOG performance status and body weight were recorded. Symptom assessment, physical examination, and blood chemistries were repeated before each treatment course. Tumor size was measured every 3 months or sooner if clinically indicated. Patients with stage IIIB disease and with no pleural effusion received chest radiotherapy at a dose of 60 Gy after the third course of chemotherapy. Patients were evaluated for response, survival, and toxicity.

Complete blood count was obtained before each course of chemotherapy. Full doses of the drugs were given if neutrophil and platelet counts on the day of treatment were at least $1.5\times10^9$/l and $100\times10^9$/l, respectively. If WHO grade ≥2 neutropenia or grade ≥1 thrombopenia was found on the day of docetaxel and gemcitabine administration, chemotherapy was delayed for 1 week. If grade 2 neutropenia or grade 1 thrombopenia persisted 1 week later, docetaxel and gemcitabine doses were reduced by 25%, but if a greater degree of toxicity persisted 2 weeks after the scheduled time of recycling, chemotherapy was definitively discontinued. The dose of each drug was reduced by 25% if WHO grade 4 neutropenia/thrombopenia or grade 3/4 nonhematologic toxicity had occurred in the previous course. Patients were allowed to receive granulocyte-colony-stimulating factor (G-CSF) after each cycle at the discretion of the investigator; however, G-CSF was not used routinely.

Toxicity for each course was recorded and graded according to WHO scales [15]. Patients were restaged every three cycles and continued to receive treatment if stable or responsive disease was observed. Response was evaluated using WHO guidelines. Time to tumor progression was estimated by the product-limit estimation from the date of the first course to the first evidence of disease progression. Survival was calculated by the same method from the date of the first course until the date of death or last follow-up visit.

Patients who received at least one course of treatment were evaluable for toxicity. Patients receiving at least two courses of treatment were evaluable for response. Response evaluation was performed after the third course of chemotherapy was completed. Response duration was measured from the day on which it was first documented until confirmed disease progression. Time to disease progression was calculated from study entry until evidence of disease progression, while overall survival was measured from the day of entry until last follow-up or death. Any patient who received radiation therapy was censored from the calculations of progression-free survival following chemotherapy alone. Actuarial survival was estimated in terms of the Kaplan and Meier product-limit.

## Results

### Patient characteristics

A total of 50 patients with advanced NSCLC (46 male, 91%; 4 female, 9%) were entered into the present study. Patient characteristics are shown in Table 1. Their median age was 63 years (range 41–75 years). Stage IV disease was present in 60% of patients, and stage IIIB disease in 20 patients (40%), of whom 4 had malignant pleural effusion and 16 had T4 disease or contralateral mediastinal node involvement. Of the 50 patients, 70% had an ECOG performance status of 0–1, and 56% had squamous cell carcinoma, 28% adenocarcinoma and 16% large-cell carcinoma.

**Table 1** Patient characteristics ($n = 50$)

| | |
|---|---|
| Age (years) | |
| Median | 63 |
| Range | 41–75 |
| Sex | |
| Male | 46 (91%) |
| Female | 4 (9%) |
| Stage | |
| IIIB | 20 (40%) |
| IV | 30 (60%) |
| Performance status (ECOG) | |
| 0 | 5 (10%) |
| 1 | 30 (60%) |
| 2 | 15 (30%) |
| Histology | |
| Squamous cell carcinoma | 28 (56%) |
| Adenocarcinoma | 14 (28%) |
| Large-cell carcinoma | 8 (16%) |
| No. of involved sites | |
| 1 | 20 (67%) |
| 2 | 9 (30%) |
| 3 | 1 (3%) |

A total of 220 courses of chemotherapy were given with a median number of five courses per patient (range one to nine). The median interval between courses was 21 days (range 21–26 days). It was necessary to delay 40 courses (19%) for 3–10 days (median 7 days). The reasons for treatment delay were patient's request unrelated to the disease or treatment (10 cycles), hematological grade 2 or 3 toxicity (18 cycles), and other grade 2 or 3 nonhematological toxicities (12 cycles). All the patients were considered analyzable for toxicity. The median dose intensity was 24 mg/m$^2$ per week (range 13–26 mg/m$^2$ per week) and 631 mg/m$^2$ per week (range 341–705 mg/m$^2$ per week) for docetaxel and gemcitabine, respectively. At least 90% of the scheduled doses were delivered to 45 patients (90%). Chest radiation therapy was carried out in 16 patients after completing three courses of chemotherapy.

### Tumor response and survival

Of the 50 patients, 46 were evaluable for response after three courses of chemotherapy. The remaining four patients were excluded due to death in two and to adverse events in the other two. Partial response (PR) was achieved in 12 patients (26%; 95% CI: 28–52%). Stable disease was seen in 19 patients (41%) and 15 (33%) had disease progression. The median time to progression was 4 months (95% CI 2.6–6 months). Median survival was 7 months (95% CI 2.9–10.3 months), whereas actuarial 1-year survival was 25% (95% CI 5.9–42.5%).

### Toxicity

All 50 patients were evaluable for toxicity (Table 2). The chemotherapy regimen was well tolerated with a low

**Table 2** Treatment toxicities per patient

| Toxicity | WHO grade, no. (%) | |
|---|---|---|
| | 1/2 | 3/4 |
| Anemia | 30 (60%) | 1 (2%) |
| Leukopenia | 16 (32%) | 4 (8%) |
| Neutropenia | 20 (40%) | 6 (12%) |
| Thrombopenia | 2 (4%) | 1 (2%) |
| Nausea/vomiting | 32 (64%) | 1 (2%) |
| Asthenia | 26 (52%) | 4 (8%) |
| Peripheral edema | 15 (30%) | 3 (6%) |
| Diarrhea | 11 (22%) | 2 (4%) |
| Dyspnea | 2 (4%) | 3 (6%) |
| Alopecia | 19 (38%) | |
| Peripheral neurotoxicity | 8 (16%) | |

incidence of grade 3/4 adverse effects. No toxic deaths were seen. While grade 1 or 2 neutropenia was seen in 20 patients (40%), grade 3 or 4 neutropenia was seen in only 6 patients (12%), and febrile neutropenia was not seen in any patient. Although 30 patients had grade 1 or 2 anemia, only one patient showed grade 3 or 4 anemia, and only one had grade 3 or 4 thrombopenia. Grade 3 or 4 asthenia was seen in four patients (8%), and mild asthenia (grade 1–2) was seen in 26 patients. Grade 3 fluid retention was observed in three patients (6%). While three had grade 3 or 4 dyspnea, there was no indication of hypersensitivity pneumonitis in any patient, nor was severe nephrotoxicity seen in any patient. Gastrointestinal adverse effects were mild. Only two patients had grade 3 or 4 nausea-vomiting or diarrhea. Other grade 1/2 toxicities were as follows: leukopenia (32%), thrombopenia (4%), nausea/vomiting (64%), fluid retention (30%), diarrhea (22%), alopecia (38%), and peripheral neurotoxicity (16%).

## Discussion

The combination of docetaxel and gemcitabine as a front-line regimen for advanced NSCLC may be an appealing choice because it has been proved to be synergistic [16], allows cisplatin to be avoided, and, therefore, it can be given to patients with impaired renal function and the elderly. Furthermore, it is likely to present an acceptable toxicity profile.

In the present phase II study involving a combination of docetaxel and gemcitabine, a response rate of 26%, a median survival time of 7 months and a 1-year survival rate of 25% were achieved. These results are comparable to those obtained with conventional platinum-based combination chemotherapy, and are in keeping with those of previous studies in which this chemotherapy combination was given as a front-line treatment to patients with advanced NSCLC. Different investigators have reported response rates ranging from 30% to 50%, with a median survival ranging from 7 months to 13 months [17–23]. However, our dosage, schedule, and combination modality of docetaxel and gemcitabine differ from those used in the previous studies in which docetaxel was given on day 1 [20] or day 8 [18, 21] at doses ranging from 80 to 100 mg/m$^2$ combined with gemcitabine on days 1 and 8 at dose from 900 to 1000 mg/m$^2$. To our knowledge, only Popa et al. used a divided dose of docetaxel of 40 mg/m$^2$ on days 1 and 8 [22]. On the other hand, in the previous studies, all courses were repeated every 21 days, except in the study by Galetta et al. in which a weekly-basis administration was used with docetaxel at 50 mg/m$^2$ and gemcitabine at 2000 mg/m$^2$ [24].

In the present investigation, docetaxel was administered on day 8, as advocated previously, because docetaxel-induced neutropenia generally occurs 5–8 days after administration, so that docetaxel delivery on day 1 may interfere with gemcitabine on day 8. Nonetheless, the most outstanding feature of our schedule as compared to previous studies was prolonged gemcitabine infusion. Gemcitabine is a prodrug, requiring intracellular phosphorylation by the enzyme deoxycytidine kinase and ultimately conversion to the active difluorodeoxycytidine diphosphate (dFdCDP) and triphosphate (dFdCTP) forms. The dFdCTP competes with deoxycytidine triphosphate for incorporation into DNA, which results in DNA synthesis inhibition [25]. The dFdCDP, in turn, can inhibit ribonucleotide reductase [26]. The enzyme deoxycytidine kinase is saturated at gemcitabine concentrations of 15–20 $\mu M$, and such a concentration is reached with doses ≥350 mg/m$^2$ given over 30 min [27]. Alternatively, increasing the infusion time while holding the dose rate constant at 10 mg/m$^2$ per min may result in increased intracellular levels of the active metabolites dFdCDP and dFdCTP, thus enhancing the activity of gemcitabine [28, 29].

With the combination of prolonged gemcitabine infusion and docetaxel used in the present work, a response rate comparable to that obtained in previous studies [21, 22] was achieved, though lower than that reported by Georgoulias et al. and Hejna et al., who showed a response rate of 37% and 50%, respectively [18, 20]. Nevertheless, when comparing the dose intensity reached in the present study (docetaxel 24 mg/m$^2$ per week, gemcitabine 631 mg/m$^2$ per week) with those used in previous studies, only in the studies by Georgoulias et al. and Hejna et al. was docetaxel dose intensity higher than in our study (33 mg/m$^2$ per week); and, on the contrary, gemcitabine dose intensity was lower (600 mg/m$^2$ per week) in the other two studies. Therefore, the discrepancy in response rates may be due to study design differences in phase II studies or issues concerning patient recruitment. In this respect, it should be borne in mind, for instance, that adenocarcinoma has been reported to be more responsive than squamous cell carcinoma. However, we failed to confirm this finding in the present investigation: adenocarcinoma response rates were similar to those for squamous cell carcinoma (33% vs 34%). In contrast, Georgoulias et al. reported a difference in response rates favoring adenocarcinoma [30], and it should be kept in mind that the study by

Hejna et al. included more than 50% of patients with adenocarcinoma.

The toxicity profile in the present study can be considered good, with low grade 3/4 hematologic toxicity rates. While in our study, the rate of grade 3/4 neutropenia was as low as 12%, the rates in the studies by Popa et al., Georgoulias et al., and Rebattu et al. were 19%, 20% and 47%, respectively, despite G-CSF being used systematically in some of these studies. As far as non-hematologic toxicity is concerned, the results of the studies coincide: asthenia was seen in more than 50% of patients, even though only 8% of patients showed grade 3 asthenia. On the other hand, mild peripheral edema was present in 30% of the patients in our study. Gastrointestinal toxicity was low, and grade 1/2 peripheral neurotoxicity was found in only eight patients. Also, it should be stressed that hypersensitivity pneumonitis, found in previous studies, was not found in the present study, possibly because in our series there were no patients undergoing chest radiation, which seems to be a risk factor for this complication [30].

At present, the potential role of prolonged gemcitabine infusion is being addressed in several ongoing studies in an attempt to determine the most appropriate combination and its potential superiority over rapid infusion [31–33]. However, our findings do not suggest that docetaxel combined with prolonged gemcitabine infusion provides an advantage over conventional schemes involving rapid infusion.

In conclusion, the present investigation showed the antitumor activity and safety profile of docetaxel combined with prolonged gemcitabine infusion confirming it as an attractive option for advanced NSCLC treatment [34]. In theory, our scheme would be more appropriate from a pharmacokinetic point of view, even though our findings do not suggest that this scheme provides an advantage over traditional schedules involving docetaxel combined 30- to 60-min infusion of gemcitabine. Nonetheless, the limitations inherent in phase II studies should be borne in mind.

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