Biweekly administration of docetaxel and vinorelbine as second-line chemotherapy for patients with stage IIIB and IV non-small cell lung cancer: a phase II study of the Galician Lung Cancer Group (GGCP 013-02)

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The current report aims to evaluate the efficacy and safety profile of a biweekly administration of docetaxel and vinorelbine to patients with advanced non-small cell lung cancer, who had previously been treated for this disease. In a prospective, multicenter, open-label, phase II trial, patients received 40 mg/m^2 of docetaxel and 20 mg/m^2 of vinorelbine on days 1 and 15, every 28 days. Treatment continued for up to a maximum of six cycles, unless disease progression or unacceptable toxicity occurred, or consent was withdrawn. Fifty patients were enrolled in the study and they received 174 cycles of chemotherapy, with a median of three cycles per patient. All patients were evaluated for efficacy and toxicity in an intention-to-treat analysis. The overall response rate was 10% [95% confidence interval (CI): 1–19], including one complete response (2%) and four partial responses (8%). Previous chemotherapy of 80% of the responders included paclitaxel. Median time to disease progression was 2.7 months (95% CI: 2.2–4.3) and median overall survival was 6.5 months (95% CI: 2.5–9.2). The survival rates at 1 and 2 years were 18% (95% CI: 7–29) and 4% (95% CI: 0–10), respectively. The most frequent severe toxicities were neutropenia (20% of patients) and leukopenia (8% of patients). Other toxicities appeared in 4% or fewer of the patients. Biweekly administration of docetaxel and vinorelbine is feasible as a second-line treatment for non-small cell lung cancer patients, but its level of activity and toxicity does not suggest any advantage compared with the results obtained with single-agent docetaxel in the same setting. ***Anti-Cancer Drugs*** **18:1201–1206 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Lung cancer is one of the leading causes of death in developed countries. The most frequent type of this devastating disease is non-small cell lung cancer (NSCLC), which generally presents with locally advanced or metastatic tumors. First-line chemotherapy based on platinum derivatives has been the standard schedule for many years [1]; however, in recent years, newer cytotoxic agents such as docetaxel, paclitaxel, gemcitabine and vinorelbine have been included in the treatment of NSCLC, either in combination with platinum derivatives or as nonplatinum-containing chemotherapy regimens [2,3].

Unfortunately, advanced NSCLC is often resistant to chemotherapy and requires aggressive second-line treatments. Several trials have been conducted to find a single or a combination chemotherapy regimen with nonplatinum compounds. As advanced NSCLC is not curable, the main objectives for second-line treatments are to prolong survival, as well as to achieve a tolerable toxicity profile and good control of symptoms [4].

Docetaxel is the only cytotoxic agent that is currently approved for both first-line and second-line treatment of advanced NSCLC. In several randomized clinical trials [5–7], this semisynthetic taxane has shown improved efficacy and quality of life when used as first-line treatment, whether in combination with platinum or with nonplatinum schedules [8,9]. As second-line treatment, docetaxel as a single agent has been one of the most extensively studied drugs, also demonstrating significant benefits in survival and quality of life when compared with the standard treatment [10,11].

Vinorelbine is a semisynthetic vinca alkaloid that has been shown to be effective, both as a single agent and in combination with platinum derivatives, in treating NSCLC [12–14]. The effectiveness of docetaxel and vinorelbine in NSCLC, each in combination with other cytotoxic drugs, has been demonstrated in phase III trials. The administration of both drugs together as first-line [15–19] or second-line treatment [20–23] of NSCLC has, however, only been tested in trials in phases II and I. In two of these studies, docetaxel and vinorelbine were given on a biweekly schedule at dosage of 50–60 and 15–45 mg/m^2, respectively, with granulocyte colony-stimulating factor support, and an encouraging antitumor activity along with a low incidence of severe hematological toxicity was observed [15,24]. Apart from these studies, other trials suggested that the efficacy was not improved and that toxicity, mainly in the form of neutropenia and febrile neutropenia, was elevated. More research is needed, therefore, to define an optimal dose and schedule to administer both the drugs together.

In a phase II trial that was performed earlier by our group [25], 50 mg/m^2 of docetaxel was given biweekly, in cycles repeated every 4 weeks, as second-line chemotherapy to treat advanced NSCLC patients. This dosage regimen was well tolerated, with no febrile neutropenia being reported. The main grade 3/4 hematological toxicity was neutropenia (16% of patients, 8% of cycles) and the rates of nonhematological toxicities were low. Nonetheless, one patient suffered a toxic death due to grade 4 neutropenia, with massive hemoptysis. Overall response rate (ORR) was 20% and the median overall survival was 4.0 months with a 1-year survival rate of 23%.

To improve upon these results, we designed a prospective phase II trial in which docetaxel and vinorelbine were administered concomitantly every 2 weeks as second-line treatment to patients with locally advanced or metastatic NSCLC. The primary objective of the study was to determine the response rate to the study treatment. Secondary objectives included evaluating the safety profile, time to progression and overall survival.

Methods

Study design

This was a prospective, multicenter, open-label phase II study performed in six hospitals in Galicia, Spain. Recruitment of patients took place from August 2001 to May 2004. This clinical trial was conducted in accordance with the standards of the Helsinki Declaration of the World Medical Association and Good Clinical Practice guidelines. All patients signed written informed consent. Clinical research forms were specifically designed to record the study data and source-data verification was performed on study information.

Selection criteria

To be included in the study, patients needed to have had a histological diagnosis of advanced or metastatic NSCLC, with bidimensionally measurable disease and progression during or after one earlier chemotherapy regimen. Earlier treatment with other chemotherapies including paclitaxel was allowed, but not with docetaxel and/or vinorelbine. Patients had to be ≥ 18 years old, with an Eastern Cooperative Oncology Group performance status ≤ 2 and a life expectancy of at least 3 months. Adequate bone marrow (neutrophils $\geq 1.5 \times 10^9$/l, platelets $> 100 \times 10^9$/l and hemoglobin ≥ 10 g/dl) and renal and hepatic functions [creatinine ≤ 1.6 mg/dl, total bilirubin < 1.3 mg/dl, aspartate and alanine aminotransferases $\leq 2.5 \times$ upper normal limit (UNL) and alkaline phosphatase $< 5 \times$ UNL] were also required. Patients with aspartate and/or alanine aminotransferases $> 1.5 \times$ UNL, associated with alkaline phosphatase $> 2.5 \times$ UNL, were not included.

Patients were excluded if they had an active infection, other neoplasias (except for nonmelanoma skin cancer, resolved in-situ cervical carcinoma, resolved in-situ or stage A urinary bladder carcinoma or an earlier diagnosis of cancer with no evidence of disease for at least 5 years), leptomeningeal or symptomatic central nervous system metastases, or if the only metastasic lesions were either nonmeasurable bone metastases or malignant pleural effusions. Other exclusion criteria were previous neurotoxicity $\geq$ grade 2, hypersensitivity to study drugs, concomitant chronic corticosteroid treatment or the presence of other concurrent serious illness (such as congestive heart failure or unstable diabetes mellitus). Fertile women were excluded if they were pregnant or lactating and they had to be on adequate contraception.

Chemotherapy regimen and other treatments

Patients received 40 mg/m^2 of docetaxel (Taxotere®, Sanofi-Aventis, Antony Cedex, France) as a 60-min intravenous infusion, and 20 mg/m^2 of vinorelbine (Navelbine®, Pierre Fabre, Barcelona, Spain), in a bolus infusion on days 1 and 15 of each cycle. Cycles were repeated every 28 days. Patients were evaluated after the first two cycles and if either an objective clinical response or stable disease was observed, treatment was continued for up to a maximum of six cycles. Treatment was discontinued if the disease progressed or if unacceptable toxicity occurred. Treatment was also halted in case of withdrawal of consent.

To diminish the incidence and severity of fluid retention and/or hypersensitivity reactions, patients received three doses of dexamethasone (8 mg), twice before (12 and 1 h) and once after (12 h) each infusion. Equivalent doses of methylprednisolone or prednisolone could also be administered.

In the case of a neutrophil count $< 1.5 \times 10^9$/l or a platelet count $< 100 \times 10^9$/l, chemotherapy was delayed, but it was resumed after recovery without dosage modification. If hematological recovery occurred in less than 1 or 2 weeks, treatment dosage was reduced for the remaining cycles; however, if toxicity persisted for more than 2 weeks, the patient was withdrawn from the study. Dosages were also reduced in the cases of grade 2 neurological, grade 3 mucositis, and grade 3 hepatic toxicities. In the event of febrile neutropenia or grade 4 mucositis, treatment was delayed upon recovery and dosage was reduced for the subsequent cycles. Patients were withdrawn from the study in case of grade 4 neurological or hepatic toxicities. When dosage reduction was required, both drugs were reduced by 25%.

Evaluation of safety and response

Baseline evaluation was performed up to 4 weeks before the inclusion. This evaluation consisted of a medical history and a physical examination, measurement of metastases, blood analyses (hematology with cell counts and biochemistry tests), electrocardiography, chest radiography, computed tomography imaging at thoracic and upper abdominal levels, bone scintigraphy, and other examinations as clinically indicated.

Biochemical and hematological analyses were repeated before each infusion, and upon completion of the treatment schedule. After every two cycles, the target tumors were measured by the appropriate imaging methods, depending on the locations of the metastases.

All patients were evaluated for toxicity during each treatment cycle and once again upon completion of the treatment schedule. They were asked to report the occurrence of any adverse experiences to the investigator. Toxicities were recorded and graded according to the Common Toxicity Criteria of the National Cancer Institute Version 2.

Clinical response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria [26]. Target tumors were identified according to size and measurability by clinical and imaging methods. All measurable tumors, up to five per organ and up to a total of 10 per patient, were evaluated for response. The ORR was calculated by the addition of all complete responses (CRs) and partial responses (PRs).

Statistical analysis

The primary objective of this study was to determine the response rate of the study treatment. Secondary objectives were to evaluate the safety profile of this schedule, the time to progression and overall survival.

The sample size was calculated using the Simon method for phase II trials. With a type I error of 5% and a study power of 80%, 14 patients had to be included in the first step. In the event that one or more responses were observed, 36 additional patients were included in the second step for a total sample size of 50 patients.

All efficacy and safety analyses were performed on the intention-to-treat (ITT) population. Objective clinical response rates were calculated with 95% confidence intervals (CIs). Time to progression was defined as the period of time from the start of the treatment to either progression or death, whichever occurred earlier. Overall survival was calculated as the date of first treatment administration to the date of death by any cause. Actuarial survival curves were constructed using the method of Kaplan and Meier.

Results

Patients' baseline characteristics

Fifty patients (80% of whom were men) were enrolled in this trial. Their main baseline characteristics are summarized in Table 1. Disease stages were IIIB (36%) and IV (64%). Tumor histology mainly included squamous-cell carcinomas (48%) and adenocarcinomas (28%). Metastases were found in one (52%), two (32%) or three (16%) locations and the median number of metastatic sites was 1 with a range of 1–3. Metastases were mainly found in the lung (34%), the lymph nodes (26%), the adrenal glands (26%) and bone (20%).

All patients had received one earlier chemotherapy treatment regimen, which had included gemcitabine

Table 1 Patient characteristics at baseline ($n = 50$)

Characteristic	*N*	%
Age (years)		
Median	61	
Range	31–89	
Sex		
Male	40	80
Female	10	20
WHO performance status		
0	10	20
1	28	56
2	12	24
Disease stage		
IIIB	18	36
IV	32	64
Previous cytotoxic agents		
Gemcitabine	41	82
Paclitaxel	33	66
Carboplatin	28	56
Cisplatin	20	40
No. of disease lesions		
1	26	52
2	16	32
>3	8	16
Main metastases locations		
Lung	17	23
Lymph nodes	13	18
Adrenal gland	13	18
Bone	10	14
Liver	9	12
Pleura	8	11
Central nervous system	3	4

Table 2 Clinical responses to study treatment ($n=50$)

	N	%
Complete response	1	2
Partial response	4	8
Stable disease	13	26
Progressive disease	23	46
Nonevaluable	9	18
ORR (95% CI)	5	10 (1–19)

CI, confidence interval; ORR, overall response rate.

(82%), paclitaxel (66%), carboplatin (56%) and/or cisplatin (40%), administered as a two-drug or three-drug combination. After first-line treatment, 10% of patients achieved a CR and 36% a PR.

Treatment

A total of 174 treatment cycles were administered, with a median of three (range 1–6) cycles per patient. Out of these, in 34 cycles, the dosage was reduced owing mainly to neutropenia (74%) and fever (6%). Twenty-four patients (48%) suffered at least one delay in drug administration (two patients with three cycles delayed, six patients with two cycles delayed and 16 patients with one cycle delayed). The median absolute and relative dose intensities for docetaxel and vinorelbine were 18.3 mg/m^2/week (91%) and 9.1 mg/m^2/week (91%), respectively.

The completed treatment of six cycles was given to 16 patients (32%), whereas 34 patients (68%) received between one and four cycles. The reasons for early withdrawal were disease progression ($n=21$), death ($n=6$), patient decision ($n=2$), poor performance status ($n=2$), adverse events ($n=1$), toxic death ($n=1$) and cardiac arrhythmia ($n=1$). Of the six deaths, four were due to disease progression, and two were due to respiratory insufficiency and pneumonia.

Efficacy

Clinical response rates assessed after the completion of chemotherapy are shown in Table 2. On an ITT analysis, one patient (2%) showed a CR and four (8%) showed a PR for an ORR of 10% (95% CI: 1–19). Stable disease was achieved in 13 patients (26%) and the disease progressed in 23 patients (46%). Nine patients (18%) could not be evaluated for response but were included in the efficacy analysis. Eight of them did not complete the first two cycles needed for the efficacy evaluation, and the remaining one, having received three cycles, missed the first efficacy evaluation and died afterwards from disease progression.

The patient who experienced a CR had a stage IIIB disease at the start of the study, and had experienced a PR to an earlier treatment with gemcitabine, paclitaxel and carboplatin. It is interesting to point out that of the four patients with PR, three had previously received paclitaxel. All responders had metastases in only one location.

Table 3 Grade 3/4 treatment-related toxicity ($n=50$)

Toxicity	Per patient ($n=50$) [*N* (%)]	Per cycle ($n=174$) [*N* (%)]
Hematological		
Anemia	2 (4)	6 (3)
Febrile neutropenia	2 (4)	3 (2)
Leukopenia	4 (8)	9 (5)
Lymphopenia	1 (2)	1 (1)
Neutropenia	10 (20)	16 (9)
Thrombopenia	1 (2)	1 (1)
Nonhematological		
Asthenia	2 (4)	6 (3)
Diarrhea	1 (2)	1 (1)
Fever	1 (2)	1 (1)
Mucositis	1 (2)	1 (1)
Nausea	1 (2)	2 (1)
Vomiting	1 (2)	2 (1)

Forty-five patients (90%) died within the follow-up period. With a median follow-up period of 7.2 months (95% CI: 4.5–10.0), the median time to progression was 2.7 months (95% CI: 2.2–4.3) and the median overall survival was 6.5 months (95% CI: 2.6–9.2). Nine patients (18; 95% CI: 6.9–29.1) were alive after 1 year and two patients (4.0; 95% CI: 0.0–9.6) remained alive after 2 years of beginning the treatment.

Safety

Grade 3/4 treatment-related hematological and nonhematological toxicities per patient and per cycle are shown in Table 3. Treatment was generally well tolerated. The most frequent hematological toxicities were neutropenia (20% of patients, 9% of cycles) and leukopenia (8% of patients, 5% of cycles). Febrile neutropenia was observed in two patients (4% of patients). Other hematological and nonhematological toxicities appeared in 4% of patients or fewer.

During the trial, one patient (2%) was withdrawn from the study after 11 infusions, owing to grade 3 thrombopenia and grade 4 asthenia. In addition, one patient suffered a toxic death during the trial. He was a 61-year-old man, who, after the first cycle, suffered a grade 3 neutropenia with sepsis and a pulmonary thromboembolism. The patient died after being hospitalized.

Discussion

This study evaluated the biweekly concomitant administration of docetaxel and vinorelbine to patients with advanced NSCLC, who had been treated previously for this condition (96% of them with platinum-based chemotherapy regimens). Clinical response to this treatment schedule included a CR rate of 2% and a PR rate of 8%, with a median survival time of 6.5 months.

Other phase II trials have been undertaken, in which combinations of docetaxel and vinorelbine were administered as second-line treatment of NSCLC. In one of them, a similar ORR (9.5%) was reported when docetaxel (75 mg/m^2) was administered on day 1 and vinorelbine (20 mg/m^2) on days 1 and 5 in a triweekly schedule [22]. Other studies, however, achieved slightly higher response rates. In one of those studies, an ORR of 18% was achieved when docetaxel (60 mg/m^2) and weekly vinorelbine (15 mg/m^2) were given in a 3-week schedule [21]. In another study, an ORR of 21% resulted from weekly docetaxel (25 mg/m^2) and vinorelbine (20 mg/m^2) administration [20]. The median survival observed in both these studies ranged from 5.8 to 8.0 months, which is within the range of our observations. The combination of docetaxel and vinorelbine has, therefore, resulted in a consistent antitumor action in phase II trials when it was assessed as second-line chemotherapy for advanced NSCLC.

The results observed in this study are in agreement with those from previous phase III trials in which docetaxel was administered as a single agent for second-line chemotherapy of advanced NSCLC [10,11,27,28]. The frequency of docetaxel administration in those studies was once every 3 weeks, with a dosage of either 75 or 100 mg/m^2. The ORR ranged between 5 and 11% (in an ITT analysis), which is in agreement with the results observed in this study (10%). The median survival time ranged between 5.5 and 7.9 months, compared with 6.5 months in this study. The 1-year survival rate in the earlier studies ranged between 19 and 37%, which seems to be higher than the 18% obtained in this study. Radiotherapy was not administered in this study, either during treatment or follow-up, whereas it was used in one of the earlier studies [10]. Our results are very similar to those found in a previous phase II study, in which docetaxel was administered as a single agent in a biweekly schedule, with slightly higher doses than in this study (50 mg/m^2) [25]. Although the ORR observed in the earlier study was (20%) double that found in the current one, the median overall survival was shorter (4.0 vs. 6.5 months).

It has been reported that earlier treatment with paclitaxel decreases neither the likelihood of a response to docetaxel nor the survival advantage seen with a second-line treatment with docetaxel [11]. This is in agreement with our findings here, as the patient who experienced a CR in this study had received chemotherapy with paclitaxel earlier; in three out of the four patients who partially responded to this study treatment, paclitaxel was also one of the drugs administered in earlier chemotherapy.

A favorable toxicity profile was observed in this study. Severe hematological toxicity rates were low, and were mainly due to neutropenia (20% of patients), leukopenia (8% of patients) and febrile neutropenia (4% of patients). Severe nonhematological toxicities appeared in fewer than 5% of the patients. These results compare favorably with other previous phase II trials, in which docetaxel and vinorelbine had been administered concomitantly; however, in these trials, dosages had been higher. In one study [20], severe myelosupression was observed (62% of patients had severe neutropenia and 29% febrile neutropenia) with weekly docetaxel and vinorelbine, whereas, in another study [23], febrile neutropenia was observed in 70% of patients when 30 mg/m^2 of docetaxel and 20 mg/m^2 of vinorelbine were administered once a week. In one study [15], a lower rate of febrile neutropenia was achieved when a biweekly schedule of docetaxel and vinorelbine was administered. In this case, granulocyte colony-stimulating factor was used as primary prophylaxis in all patients, to allow the dosages of 30 and 23 mg/m^2/week for docetaxel and vinorelbine, respectively.

Our results seem to be in agreement with those found in several randomized trials, which could not demonstrate doublets like irinotecan plus docetaxel [29,30], cisplatin [31] or gemcitabine [32] to be superior, as second-line therapy for NSCLC patients, when compared with single-agent chemotherapy. In view of these findings, patients who have progressed with a platinum-containing regimen as first-line treatment are usually treated with monotherapy. Factors to be considered when choosing a single agent as second-line therapy should include efficacy, tolerability profile and patient preference [33].

We conclude that the concomitant administration of biweekly docetaxel and vinorelbine as second-line treatment of NSCLC patients is feasible, but that the level of efficacy, as indicated by our results, does not suggest any advantage compared with results obtained with single-agent docetaxel in this setting.

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