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Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial

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Background: The combination of paclitaxel with cisplatin or carboplatin has significant activity in non-small-cell lung cancer (NSCLC). This phase III study of chemotherapy-naïve advanced NSCLC patients was designed to assess whether response rate in patients receiving a paclitaxel/carboplatin combination was similar to that in patients receiving a paclitaxel/cisplatin combination. Paclitaxel was given at a dose of 200 mg/m^2 (3-h intravenous infusion) followed by either carboplatin at an AUC of 6 or cisplatin at a dose of 80 mg/m^2, all repeated every 3 weeks. Survival, toxicity and quality of life were also compared.

Patients and methods: Patients were randomised to receive one of the two combinations, stratified according to centre, performance status, disease stage and histology. The primary analyses of response rate and survival were carried out on response-evaluable patients. Survival was also analysed for all randomised patients. Toxicity analyses were carried out on all treated patients.

Results: A total of 618 patients were randomised. The two treatment arms were well balanced with regard to gender (83% male), age (median 58 years), performance status (83% ECOG 0–1), stage (68% IV, 32% IIIB) and histology (38% squamous cell carcinoma). In the paclitaxel/carboplatin arm, 306 patients received a total of 1311 courses (median four courses, range 1–10 courses) while in the paclitaxel/cisplatin arm, 302 patients received a total of 1321 courses (median four courses, range 1–10 courses). In only 76% of courses, carboplatin was administered as planned at an AUC of 6, while in 96% of courses, cisplatin was given at the planned dose of 80 mg/m^2. The response rate was 25% (70 of 279) in the paclitaxel/carboplatin arm and 28% (80 of 284) in the paclitaxel/cisplatin arm (P = 0.45). Responses were reviewed by an independent radiological committee. For all randomised patients, median survival was 8.5 months in the paclitaxel/carboplatin arm and 9.8 months in the paclitaxel/cisplatin arm [hazard ratio 1.20, 90% confidence interval (CI) 1.03–1.40]; the 1-year survival rates were 33% and 38%, respectively. On the same dataset, a survival update after 22 months of additional follow-up yielded a median survival of 8.2 months in the paclitaxel/carboplatin arm and 9.8 months in the paclitaxel/cisplatin arm (hazard ratio 1.22, 90% CI 1.06–1.40; P = 0.019); the 2-year survival rates were 9% and 15%, respectively. Excluding neutropenia and thrombocytopenia, which were more frequent in the paclitaxel/carboplatin arm, and nausea/vomiting and nephrotoxicity, which were more frequent in the paclitaxel/cisplatin arm, the rate of severe toxicities was generally low and comparable between the two arms. Overall quality of life (EORTC QLQ-C30 and LC-13) was also similar between the two arms.

Conclusions: This is the first trial comparing carboplatin and cisplatin in the treatment of advanced NSCLC. Although paclitaxel/carboplatin yielded a similar response rate, the significantly longer median survival obtained with paclitaxel/cisplatin indicates that cisplatin-based chemotherapy should be the first treatment option.

Key words: carboplatin, cisplatin, doublets, non-small-cell lung cancer, paclitaxel

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Introduction

Cisplatin is still the backbone of chemotherapy combinations in non-small-cell lung cancer (NSCLC), and several combinations of cisplatin-based chemotherapy are used in the current treatment of this disease. While carboplatin has also been used extensively, especially in the USA in combination with paclitaxel, to date no randomised trial has compared these two drugs at the same dose schedule. A previous trial [1] by the European Organization for Research and Treatment of Cancer (EORTC) combining VP16 with cisplatin (120 mg/m^2) or carboplatin (325 mg/m^2) yielded a slightly higher but not significant difference in response rate and survival in favour of the cisplatin combination; however, renal function impairment and myelotoxicity were significantly higher in the cisplatin arm.

There is ample evidence that cisplatin has a pivotal role in NSCLC management [2]. In the meta-analysis undertaken by the Non-Small-Cell Lung Cancer Collaborative Group, a hazard ratio of 0.73 was observed (27% reduction in the risk of death and 10% improvement in survival at 1 year) when cisplatin chemotherapy was compared with best supportive care [3]. A later British study was also able to confirm the benefit of cisplatin-based chemotherapy [4]. A North American meta-analysis found that only five of 33 (15%) phase III studies showed significant differences in survival in favour of the patient cohort receiving the experimental therapy. Four of these five trials included cisplatin-based regimens [5]. Vinorelbine as a single agent was the first non-cisplatin drug to show a survival advantage, with median survival of 30 weeks, compared with 22 weeks for those who were treated with fluorouracil plus leucovorin [6].

Intriguingly, paclitaxel as a single agent showed a median survival of 6.8 months, in contrast to 4.8 months for supportive care alone. The median time to disease progression was 3.9 months for patients in the paclitaxel arm and 0.5 months for supportive care alone. The Cox regression model showed a hazard ratio of 0.68 in favour of paclitaxel. No responses were observed in patients with poor performance status, which was more frequent in patients ≥65 years old than in younger patients [7]. Other studies have also identified older age as a prognostic factor for response and survival [8–10]. Phase II studies have demonstrated activity for paclitaxel as a 24-h intravenous infusion, both as a single agent and in combination with carboplatin [11–14]. Paclitaxel as a 24-h intravenous infusion plus cisplatin (75 mg/m^2) has been compared with cisplatin/etoposide. The response rate for paclitaxel/cisplatin was ~26%, while that for cisplatin/etoposide was 12.4% (P <0.001). The median survival time was 9.9 months versus 7.6 months (P = 0.04) [15]. However, an EORTC trial of cisplatin/teniposide versus cisplatin/paclitaxel (175 mg/m^2 as a 3-h intravenous infusion) found no significant difference in median survival times (9.9 versus 9.7 months respectively), although response rate was higher in the paclitaxel arm (28% versus 41%; P = 0.01) [16]. Single-agent cisplatin (100 mg/m^2) has been compared with paclitaxel (175 mg/m^2) plus cisplatin (80 mg/m^2). Although there were differences in response rate and progression-free survival in favour of the combination arm, median survival was similar in the two arms (8.6 months in the cisplatin arm and 8.1 months in the paclitaxel/cisplatin arm) [2].

Other studies have explored the administration of paclitaxel given as a 3-h intravenous infusion in combination with carboplatin. Median survival was 30 weeks, but rose to 39 weeks when paclitaxel doses were >175 mg/m^2, with carboplatin doses of 350–400 mg/m^2 [17]. Paclitaxel (175 versus 225 mg/m^2) as a 3-h intravenous infusion has been tested in combination with carboplatin (AUC of 6), with slight differences in favour of the higher paclitaxel dose in terms of response, progression-free survival and median survival [18]. A recent trial by the Southwest Oncology Group (SWOG) epitomised the current outcomes that are achieved with chemotherapy. Vinorelbine/cisplatin (100 mg/m^2) was compared with paclitaxel given as a 3-h intravenous infusion in combination with carboplatin (AUC of 6). The response rates were 28% and 25%, respectively, and median survival was the same in both arms (8 months). However, myelotoxicity and nausea and vomiting were observed more frequently in the vinorelbine/cisplatin arm [19]. In a survey of medical oncologists in the USA, the combination of paclitaxel/carboplatin was the most highly accepted therapeutic option in NSCLC. This may be explained by practical considerations, since administration is easier and toxicity milder than with cisplatin combinations [20].

The present large, randomised, multicentre European trial tested whether paclitaxel/carboplatin induces a similar benefit to paclitaxel/cisplatin in terms of objective response rate. Secondary endpoints were survival, toxicity, quality of life and the analysis of prognostic factors, including histology. Paclitaxel (200 mg/m^2) was administered in both arms as a 3-h intravenous infusion with either cisplatin (80 mg/m^2) or carboplatin (AUC of 6).

Patients and methods

Patients

Eligible patients were required to meet all of the following criteria: (i) a histological or cytological diagnosis of NSCLC; (ii) stage IIIB (malignant pleural/pericardial effusions and/or supraclavicular adenopathy) or IV disease (patients with recurrent stage III or IV disease or restaging after surgery were eligible); (iii) age 18 years or older; (iv) performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) scale with a predicted life expectancy of at least 12 weeks; (v) measurable (or non-measurable but assessable) disease, at least one area of which had not been subject to prior irradiation; (vi) no prior chemotherapy; (vii) any previous radiation therapy completed >3 weeks before enrolment and the patient recovered from any adverse effects; (viii) adequate baseline bone marrow function as documented by an absolute neutrophil count of 1.5 cells × 10^9/l or higher, platelet count of 100 cells × 10^9/l or higher, haemoglobin 9 g/dl or higher; total serum bilirubin level of ≤1.25 times the upper limit of normal, hepatic transaminase <3 times the upper limit of normal, and serum creatinine level of ≤1.25 times the upper limit of

normal. Patients had to be able to understand the EORTC quality-of-life questionnaire C-30, which had previously been validated in several language-cultural groups across Europe.

Patients were not eligible for the study if they had any of the following: (i) a history of prior or concomitant malignancy (except for curatively treated non-melanoma skin cancer or carcinoma *in situ* of the cervix, or other cancer for which the patient had been disease-free for 5 years); (ii) active or uncontrolled infection; (iii) significant cardiovascular disease (uncontrolled hypertension, unstable angina, active congestive heart failure, myocardial infarction within the previous year or uncontrolled serious arrhythmia); (iv) pregnancy, lactation or refusal to use effective contraception; (v) symptomatic brain metastases; (vi) evidence of peripheral neuropathy; (vii) uncontrolled diabetes mellitus; or (viii) other serious medical conditions that would impair the ability of the patient to receive protocol treatment, including prior allergic reactions to drugs containing Cremophor® EL.

Ethics review

The institutional ethics committee of each participating institution approved the study protocol. Written informed consent was obtained from each patient prior to study entry. Patients were informed that although cisplatin-based chemotherapy had been associated with survival benefit compared with best supportive care, it was unknown whether there would be a net or equal benefit from carboplatin instead of cisplatin when combined with paclitaxel.

Randomisation and treatment

Randomisation was performed centrally by Bristol-Myers Squibb Inc., Waterloo, Belgium, using a dynamic balancing algorithm of the Pocock–Simon type [21]. This procedure minimised imbalance in treatment assignment with respect to the following parameters: centre, performance status (ECOG 0–1 versus 2), disease stage (IIIB versus IV) and histology (squamous cell versus non-squamous cell carcinoma).

Paclitaxel, cisplatin and carboplatin (Bristol-Myers Squibb Inc., Princeton, NJ, USA) were provided free of charge. Patients randomised to the paclitaxel/cisplatin arm received on day 1 paclitaxel (200 mg/m^2 as a 3-h intravenous infusion) followed by cisplatin (80 mg/m^2 as a 30-min intravenous infusion). Patients randomised to the paclitaxel/carboplatin arm received on day 1 paclitaxel (200 mg/m^2 as a 3-h intravenous infusion) followed by carboplatin (AUC of 6 as a 30-min intravenous infusion). The carboplatin dose was calculated using Calvert's formula [dose (mg) = area under the concentration time curve (glomerular filtration rate + 25)]. Treatment was administered in 21-day cycles (Figure 1).

Paclitaxel was diluted in a minimum of 500 ml 5% dextrose or normal saline. An in-line cellulose acetate filter of 0.22-μm pore size was used. In both regimens, treatment continued at planned intervals of 3 weeks or upon recovery from haematological and non-haematological toxic effects. There were no dose escalations, and dose reduction was based on toxic effects encountered in the previous treatment cycle. The response in both arms was assessed every two cycles according to World Health Organisation (WHO) criteria. Patients with progressive disease discontinued chemotherapy. Patients with stable disease were treated for a maximum of six cycles or until they had disease progression, developed unacceptable drug toxicity not manageable by dosage modification or withdrew their consent.

Patients who achieved a complete response or a partial response continued treatment for a total of 10 cycles or until disease progression.

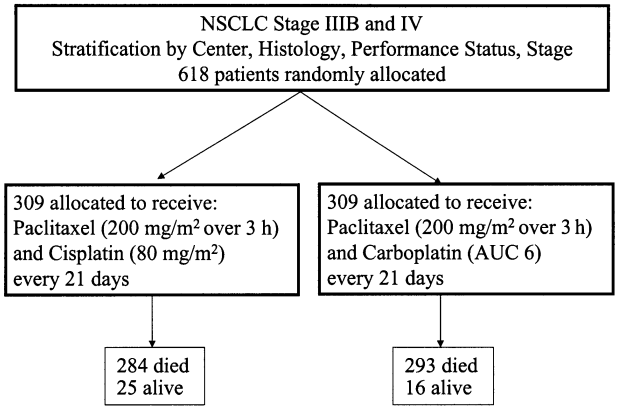

Figure 1. Flow diagram including patient allocation and treatment schema.

Prevention of paclitaxel reactions consisted of dexamethasone (20 mg) given orally on the evening before chemotherapy and again on the morning of treatment, intravenous diphenhydramine (50 mg), and either intravenous cimetidine (300 mg) or ranitidine (50 mg) given 30 min before paclitaxel. Intravenous administration of dexamethasone (10 mg) plus either ondansetron (24–32 mg) or granisetron (10 μg/kg) plus lorazepam (1–2 mg) were suggested as components of the premedication with antiemetic therapy. Oral dexamethasone was used prophylactically if grade II or greater arthralgias/myalgias occurred.

Assessment of patients

The following parameters were assessed at baseline: medical history and physical examination; ECG; blood counts (haemoglobin, granulocytes and platelets); creatinine or EDTA clearance; chemistry (serum creatinine and bilirubin); pregnancy testing for women of childbearing potential; and tumour measurements. Chest X-ray and a computed tomography (CT) scan of the chest and upper abdomen were required. Patients had repeated evaluations at least every 6 weeks. Tumour response was assessed according to WHO criteria (measurable disease; complete response, partial response, stable disease and progressive disease). Tumours were reassessed during treatment with the same imaging method used to establish baseline tumour measurement. Previously irradiated lesions were excluded from evaluation for tumour response. Quality of life was assessed with a validated, cancer-specific instrument that was self-administered at baseline and at the end of each cycle. The EORTC core quality-of-life questionnaire (QLQ-C30) was used [22], together with a lung cancer-specific quality-of-life module (QOL-LC13) [23]. These questionnaires measured global quality of life, five general cancer functional domains (physical, role, cognitive, emotional and social functioning), and 20 symptoms (fatigue, nausea/vomiting, pain, chest pain, shoulder pain, pain elsewhere, pain medication, pain medication help, dyspnea, cough, insomnia, hemoptysis, sore mouth, dysphagia, constipation, diarrhoea, peripheral neuropathy, alopecia, appetite and financial difficulties).

Statistical analysis

The primary goal of this study was to show non-inferiority in response rate for paclitaxel/carboplatin compared with paclitaxel/cisplatin. The target population size for the study was 568 patients. Under the paclitaxel/cisplatin regimen, the expected response rate was ~30%. The primary test on response rate was a non-inferiority test with a null hypothesis that the paclitaxel/carboplatin combination response rate was at least 10% worse.

Therefore, using a significance level of 5%, statistically significant proof of non-inferiority would be obtained if the lower limit of a two-sided 90% confidence interval (CI) of the difference in response rate between paclitaxel/cisplatin and paclitaxel/carboplatin would be –10% or more. Five hundred and twenty response-evaluable patients were needed to obtain 80% power for this test, if the two regimens had the same true response rate of 30%.

As this was a non-inferiority study, the most conservative dataset for this primary analysis was the dataset of all response evaluable patients [24]. This dataset was used for the primary analyses of response rate, survival and progression-free survival. The planned non-inferiority test of survival (as well as progression-free survival) was to conclude non-inferiority if the upper confidence level of the two-sided 90% CI of the hazard ratio (paclitaxel/cisplatin versus paclitaxel/carboplatin) was 1.27 or less. This confidence interval was obtained from a Cox regression stratified for tumour stage, performance status and histology, with treatment as the sole factor.

As a secondary analysis, all randomised patients were included in the analysis of survival and progression-free survival, which was performed strictly according to the intention-to-treat principle. The resulting confidence intervals were interpreted in the context of a non-inferiority test as well as a superiority test.

Progression-free survival was measured from the day of randomisation to the time of progression or last follow-up. In a first definition of progression-free survival, patients who received secondary therapy prior to documented disease progression were censored at the time of the secondary therapy. In a second definition, patients who received secondary radio- or chemotherapy were considered to have an event at that time.

The Cox proportional hazards regression model was used for progression-free survival and survival, stratified by tumour stage, performance status and histology. The model included the following prognostic variables: weight loss during the last 6 months prior to randomisation, gender, prior radiotherapy and baseline haemoglobin. For each of the time-to-event variables (survival, progression-free survival), Kaplan–Meier estimates at 1 and 2 years were calculated per treatment arm with their 95% CIs, as well as median estimates with their 95% CI.

Signs and symptoms of toxicity were reported according to their severity in frequency tables. Toxicity was evaluated considering the worst reported event per patient. For each toxicity, treatment arms were compared using Fisher's exact text for 2×2 tables for occurrence of any toxicity and for occurrence of severe toxicity.

Quality-of-life treatment comparisons over time were assessed by longitudinal analysis curves for the median change from baseline for the global scale, for each of the five functional scales (physical, role, cognitive, social, emotional), and for the 20 symptom scales with the use of the Wei–Johnson test of stochastic ordering.

The final analysis was performed on the database locked on 2 November 1998. In addition to this, a survival update analysis was performed on an updated database locked on 11 September 2001.

Results

Patient characteristics

Between April 1996 and July 1997, 618 patients were randomised from 42 centres in 16 countries. Patient characteristics for all randomised patients are listed in Table 1. Patient characteristics at baseline were well balanced between the two treatment arms. One hundred and seven patients—53 (17%) in the paclitaxel/carboplatin arm and 54 (17%) in the paclitaxel/cisplatin arm—had an ECOG performance status of 2. Among the 618 patients randomised, a total of 616 had histologically proven NSCLC (Table 2). One patient (enrolled in the paclitaxel/cisplatin arm) had histiocytoma and one patient (enrolled in the paclitaxel/cisplatin arm), originally thought to have squamous cell carcinoma of the lung, was later found to have squamous cell carcinoma of the larynx. Histology and tumour stage were equally distributed among treatment arms. A total of 369 (60%) patients had stage IV disease, 49 (8%) patients had either local or metastatic disease and 198 (32%) patients had stage IIIB disease. Two patients in the paclitaxel/cisplatin arm had stage IIIA disease at baseline. Sixty-one patients (10%) had received prior radiotherapy.

Presence of measurable disease was well balanced between the two study arms. At baseline, 573 (93%) patients had bidimensionally measurable disease while five (1%) patients had unidimensionally measurable disease and 40 (6%) patients were found, after review, to have non-measurable disease.

Chemotherapy administration

Of the 618 patients randomised, 10 (2%) never received any study drug. A total of 1311 courses of paclitaxel/carboplatin were administered to 306 patients, and 1321 courses of paclitaxel/cisplatin were administered to 302 patients (Table 2). The median number of courses was four (range 1–10) in both study arms. Twenty-six (8%) patients in the paclitaxel/carboplatin arm received more than six courses of therapy compared with 29 (10%) in the paclitaxel/cisplatin arm. One hundred and fifty-six (51%) paclitaxel/carboplatin patients and 75 (25%) paclitaxel/cisplatin patients had a dose reduction. In the paclitaxel/carboplatin arm, 71 patients had paclitaxel reduced and 144 patients had carboplatin reduced, while in the paclitaxel/cisplatin arm, 47 patients had paclitaxel reduced and 65 patients had cisplatin reduced. The median cumulative dose of paclitaxel administered was similar in both arms: 799 mg/m^2 in the paclitaxel/carboplatin arm and 807 mg/m^2 in the paclitaxel/cisplatin arm. The median paclitaxel dose intensity in both study arms was 65 mg/m^2/week, which is very close to the planned dose intensity of 66.7 mg/m^2/week. In fact, >80% of patients in this study received ≥90% of the scheduled paclitaxel dose intensity. The median dose intensity of platinum agents in both arms was also close to the planned dose intensity. In the paclitaxel/carboplatin arm, the median dose intensity of carboplatin was 1.9 mg/ml·min/week, compared with the planned 2 mg/ml·min/week. In the paclitaxel/cisplatin arm, the median dose intensity of cisplatin was 26 mg/m^2/week, very close to the planned 26.7 mg/m^2/week.

Response rate, progression-free survival and survival

Among the 618 patients randomised, 279 in the paclitaxel/carboplatin arm and 284 in the paclitaxel/cisplatin arm had

Table 1. Patient characteristics (all randomised patients)

	Paclitaxel/cisplatin (n = 309)	Paclitaxel/carboplatin (n = 309)	Total (n = 608)
Gender [n (%)]			
Male	253 (82)	258 (83)	511 (83)
Female	56 (18)	51 (17)	107 (17)
Age (years)			
Median	58	58	58
Range	29–78	27–76	27–78
<65 years [n (%)]	222 (72)	218 (71)	440 (71)
≥65 years [n (%)]	87 (28)	91 (29)	178 (29)
Weight loss [n (%)]			
<5%	151 (49)	159 (51)	310 (50)
5% to 10%	62 (20)	53 (17)	115 (19)
>10%	47 (15)	50 (16)	97 (16)
Not reported	49 (16)	47 (15)	96 (16)
ECOG performance status [n (%)]			
0	50 (16)	52 (17)	102 (17)
1	205 (66)	204 (66)	409 (66)
2	53 (17)	53 (17)	106 (17)
3	1 (<1)	–	1 (<1)
Histology [n (%)]			
Adenocarcinoma	139 (45)	145 (47)	284 (46)
Squamous cell carcinoma	117 (38)	115 (37)	232 (38)
Large cell carcinoma	29 (9)	31 (10)	60 (10)
Other	24 (8)	18 (6)	42 (7)
Tumour stage [n (%)]			
IIIA	2 (1)	0 (0)	2 (<1)
IIIB	108 (35)	90 (29)	198 (32)
IV	178 (58)	191 (62)	369 (60)
Local relapse	8 (3)	9 (3)	17 (3)
Metastatic relapse	13 (4)	19 (6)	32 (5)
Prior radiotherapy [n (%)]			
Yes	28 (9)	33 (11)	61 (10)
No	281 (91)	276 (89)	557 (90)
Tumour measurability [n (%)]			
Bidimensionally measurable	288 (93)	285 (92)	573 (93)
Unidimensionally measurable	4 (1)	1 (<1)	5 (1)
Assessable	17 (6)	23 (7)	40 (6)

response-evaluable measurable disease (Table 3). In this primary data set, the overall clinical response rate was 25% (95% CI 20% to 31%) in the paclitaxel/carboplatin arm and 28% (95% CI 23% to 34%) in the paclitaxel/cisplatin arm. Of note, four complete responses were observed in the paclitaxel/carboplatin arm and two in the paclitaxel/cisplatin arm. The two-sided 90% CI of the difference in response rate ranged from –10% to 3.4%, indicating that paclitaxel/carboplatin is statistically not inferior to paclitaxel/cisplatin. A classical superiority test to compare response rates between the two arms yielded a P value of 0.45. When all randomised patients were considered (intention-to-treat dataset), the response rates were 23% (70 of 309 patients) in the paclitaxel/carboplatin arm and 26% (80 of 309 patients) in the paclitaxel/cisplatin arm.

Table 2. Number of patients treated per cycle (all treated patients)

	Paclitaxel/cisplatin (n = 302)	Paclitaxel/carboplatin (n = 306)
Course number [n (%)]		
1	302 (100)	306 (100)
2	275 (91)	279 (91)
3	226 (75)	220 (72)
4	194 (64)	187 (61)
5	143 (47)	139 (45)
6	118 (39)	123 (40)
7	29 (10)	26 (8)
8	22 (7)	22 (7)
9	9 (3)	6 (2)
10	3 (1)	3 (1)
Total courses	1321	1311
Median number of courses	4	4
Range	1–10	1–10

Table 3. Response rates in response-evaluable patients with measurable tumour

	Paclitaxel/cisplatin (n = 284) [n (%)]	Paclitaxel/carboplatin (n = 279) [n (%)]
Complete response	2 (1)	4 (1)
Partial response	78 (27)	66 (24)
Stable disease	123 (43)	112 (40)
Progressive disease	58 (20)	80 (29)
Early death, toxicity	23 (8)	17 (6)

At the time of the original analysis, 95% of patients in the paclitaxel/carboplatin arm and 93% of patients in the paclitaxel/cisplatin arm had evidence of tumour progression or had received secondary therapy prior to documentation of disease progression. On the intention-to-treat dataset, median progression-free survival was 3 months (95% CI 2.7–3.9 months) for the paclitaxel/carboplatin arm and 4.2 months (95% CI 3.3–4.4 months) for the paclitaxel/cisplatin arm ($P = 0.035$ by log-rank test).

If the start of secondary therapy is regarded as an event, on the intention-to-treat dataset, median progression-free survival was 2.9 months (95% CI 2.7–3.5 months) in the paclitaxel/carboplatin arm and 3.3 months (95% CI 3–4 months) in the paclitaxel/cisplatin arm ($P = 0.36$ by log-rank test) (Figure 2).

More than half of the patients received at least one follow-up therapy: 183 of 309 (59%) patients in the paclitaxel/carboplatin arm and 185 of 309 (60%) patients in the paclitaxel/cisplatin arm (Table 4). Radiotherapy was the most frequent type of secondary therapy. Overall, 44% of the patients received subsequent radiotherapy after completion of the trial. Chemotherapy was used in approximately one-quarter of the patients. Twenty-four per cent of paclitaxel/carboplatin patients and 23% of paclitaxel/cisplatin patients received at least one secondary chemotherapy regimen. The most frequently used second-line chemotherapeutic agents were gemcitabine, vinorelbine, cisplatin, etoposide and mitomycin C (Table 5). Overall, paclitaxel was re-administered in only five patients. Of note, more patients in the paclitaxel/cisplatin arm than in

Table 4. Follow-up therapies (all randomised patients)

	Paclitaxel/ cisplatin [n (%)]	Paclitaxel/ carboplatin [n (%)]
Number of patients with any follow-up therapy	185 (60)	183 (59)
Radiotherapy[a]	139 (45)	131 (42)
Chemotherapy[a]	72 (23)	74 (24)
One regimen	58	67
Two regimens	10	6
Three regimens	4	0
Four regimens	0	1
Other therapies[a,b]	31 (10)	26 (8)

[a]Patients may have more than one type of follow-up therapy.
[b]Includes surgery, hormonotherapy, corticosteroid therapy and non-medically proven therapies.

Table 5. Second-line chemotherapy

	Paclitaxel/cisplatin (n = 72)	Paclitaxel/carboplatin (n = 74)
Gemcitabine	32	33
Vinorelbine	28	29
Cisplatin	12	15
Etoposide	13	7
Mitomycin C	7	4
Cyclophosphamide	4	6
5-Fluorouracil	5	5
Ifosfamide	7	2
Carboplatin	7	3
Methotrexate	1	4
Doxorubicin	1	3
Vindesine	1	3
Docetaxel	1	2
Vinblastine	0	3
Paclitaxel	4	1
Lomustine	0	3
Other agents	5	6

Patients may have received more than one drug.

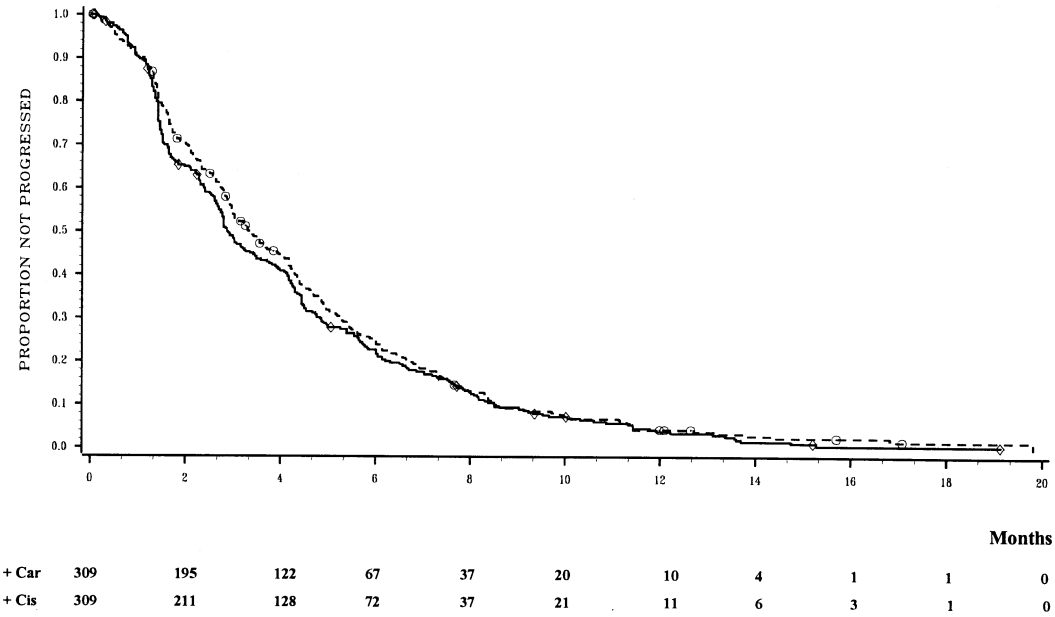

Figure 2. Kaplan–Meier curve of time to tumour progression of patients treated with paclitaxel/cisplatin and paclitaxel/carboplatin (intention-to-treat dataset).

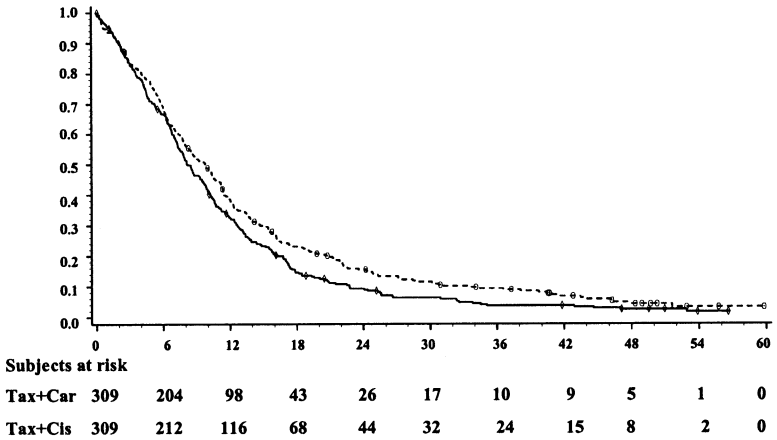

Figure 3. Kaplan–Meier curve of survival of patients treated with paclitaxel/cisplatin and paclitaxel/carboplatin (intention-to-treat dataset, survival update September 2001).

the paclitaxel/carboplatin arm received salvage chemotherapy and/or radiotherapy before disease progression. At the time of this analysis, a total of 479 patients had died (81% of patients in the paclitaxel/carboplatin arm and 74% of patients in the paclitaxel/cisplatin arm). On the intention-to-treat dataset, median survival was 8.5 months (95% CI 7.4–9.6 months) in the paclitaxel/carboplatin arm and 9.8 months (95% CI 8.3–11 months) in the paclitaxel/cisplatin arm. The Kaplan–Meier estimates of survival rate at 1 year were 33% (95% CI 27% to 38%) in the paclitaxel/carboplatin arm and 38% (95% CI 33% to 44%) in the paclitaxel/cisplatin arm.

At the time of the survival update (September 2001), 579 patients had died (95% of patients in the paclitaxel/carboplatin arm and 92% of patients in the paclitaxel/cisplatin arm). In the intention-to-treat analysis, median survival was 8.2 months (95% CI 7.4–9.6 months) in the paclitaxel/carboplatin arm and 9.8 months (95% CI 8.2–11 months) in the paclitaxel/cisplatin arm ($P = 0.019$ by log-rank test) (Figure 3). The stratified hazard ratio between treatment arms was 1.22 (90% CI 1.06–1.40).

Toxicity

All 608 patients who received at least one dose of therapy were included in the toxicity analysis. This included 306 patients in the paclitaxel/carboplatin arm and 302 in the paclitaxel/cisplatin arm. Haematological and non-haematological toxicity data are listed in Tables 6 and 7, respectively.

The combination of paclitaxel/carboplatin caused more severe (grade III and IV) leukopenia and more severe thrombocytopenia than the combination of paclitaxel/cisplatin (Table 6). Severe neutropenia and severe anaemia were reported at a similar rate between the two study arms. Neutropenic fever was reported in 6% of patients in the paclitaxel/carboplatin arm and in 4% of patients in the paclitaxel/cisplatin arm ($P = 0.189$). Severe infections were rare, occurring in 15 (5%) patients in the paclitaxel/carboplatin arm and in 14 (5%) patients in the paclitaxel/cisplatin arm ($P = 1.000$). The combination of paclitaxel/cisplatin caused more nausea and vomiting, diarrhoea and renal toxicity than the paclitaxel/carboplatin combination (Table 7). There was no difference in the incidence or severity between the two study arms in peripheral neuropathy and myalgia/arthralgia. Hypersensitivity reactions were reported in seven (2%) patients in the paclitaxel/carboplatin arm and in 10 (3%) patients in the paclitaxel/cisplatin arm. Overall, three patients, all in the paclitaxel/cisplatin arm, suffered from a severe hypersensitivity reaction. Peripheral neuropathy, mostly grade I or II, was observed in 59% of the patients in the paclitaxel/carboplatin arm and in 58% of the patients in the paclitaxel/cisplatin arm. Severe events (grade III) were reported in 9% of patients in the paclitaxel/carboplatin arm and in 7% of patients in the paclitaxel/cisplatin arm. Arthralgia/myalgia was reported in 62% of patients in the paclitaxel/carboplatin arm and in 57% of patients in the paclitaxel/cisplatin arm. These events were generally mild to moderate in severity, and the incidence of severe events was ~10% in both arms. More patients in the paclitaxel/cisplatin arm (38%) than in the paclitaxel/carboplatin arm (15%) developed renal toxicity. Severe events occurred in three paclitaxel/carboplatin patients and in four paclitaxel/cisplatin patients.

Table 6. Haematological toxicity (all treated patients)

	Paclitaxel/ cisplatin (n = 302) (%)	Paclitaxel/ carboplatin (n = 306) (%)
Leukopenia		
Any	73	74
Severe (grade III–IV)	16[a]	23
Neutropenia		
Any	73	70
Severe (grade III–IV)	51	54
Thrombocytopenia		
Any	13[a]	27
Severe (grade III–IV)	2[a]	8
Anaemia		
Any	95	94
Severe (grade III–IV)	9	7
Febrile neutropenia	4	6
Infections		
Any	16	20
Severe (grade III–IV)	5	5

[a]P <0.05.

Quality-of-life analysis

Quality-of-life evaluation was performed in a large number of patients and at a similar rate in both arms. At baseline, 258 (84%) patients in the paclitaxel/carboplatin arm and 256 (85%) patients in the paclitaxel/cisplatin arm completed quality-of-life questionnaires. Compliance up to day 120 was excellent, with two-thirds of the patients potentially available for quality-of-life evaluation actually participating. From day 120, the number of patients decreased to <50% of all potential patients. When comparing the changes from baseline over all on-study periods (Table 8), significant differences between the treatment arms were noted. Appetite loss was more severe in the paclitaxel/cisplatin arm ($P = 0.084$); hemoptysis was

Table 7. Non-haematological toxicities (all treated patients)

	Paclitaxel/ cisplatin (n = 302) (%)	Paclitaxel/ carboplatin (n = 306) (%)
Hypersensitivity reaction		
Any	3	2
Severe	1	0
Peripheral neuropathy		
Any	58	59
Severe (grade III)	7	9
Arthralgia/myalgia		
Any	57	62
Severe	9	8
Asthenia		
Any	43	42
Severe	10	10
Ototoxicity		
Any	4	3
Severe (grade III)	0	<1
Nausea/vomiting		
Any	70[a]	49
Severe	14[a]	6
Diarrhoea		
Any	19[a]	9
Severe	2	2
Renal toxicity		
Any	38[a]	15
Severe (grade III)	1	1

[a]P <0.05.

Table 8. EORTC QLQ-C30/LC-13 results: longitudinal comparison of differences from baseline (all treated patients)

	P value[a] in favour of:		
	Paclitaxel/ cisplatin	Neither	Paclitaxel/ carboplatin
Functional scales			
Physical functioning		0.419	
Role functioning		0.622	
Emotional functioning		0.466	
Cognitive functioning		0.588	
Social functioning		0.384	
Global health status		0.939	
Symptoms scales			
Nausea and vomiting		0.149	
Trouble swallowing		0.866	
Sore mouth		0.995	
Constipation		0.468	
Diarrhoea		0.252	
Appetite loss			0.084
Fatigue		0.955	
Insomnia		0.985	
Hair loss		0.540	
Peripheral neuropathy		0.792	
Financial difficulties		0.313	
Dyspnea		0.163	
Cough		0.107	
Haemoptysis	0.048		
Pain	0.058		
Pain in chest	0.046		
Pain in shoulder		0.493	
Pain elsewhere		0.488	
Pain medication	0.054		
Pain medication help		0.606	

[a]Wei–Johnson stochastic ordering test.

reported more frequently in the paclitaxel/carboplatin arm (P = 0.048); pain and chest pain were also reported more frequently in the paclitaxel/carboplatin arm (P = 0.058 and 0.046, respectively); and pain medication consumption was higher in the paclitaxel/carboplatin arm (P = 0.054). Of note, no significant differences in global health status or in the functional scales, which are global indices of quality of life, were noted between the two study arms.

Discussion

Between 1984 and 1985, the ECOG carried out a large five-arm randomised trial in 743 metastatic NSCLC patients, comparing iproplatin or carboplatin followed by MVP (mitomycin, vinblastine and cisplatin) at the time of progression, doublets of vinblastine plus cisplatin, triplets of MVP and MVP alternating with CAMP (cyclophosphamide, doxorubicin, methotrexate and procarbazine). Carboplatin stood out as having a significantly longer progression-free survival (29 weeks; $P = 0.01$) and longer median survival (31.7 weeks). The overall median survival for all patients was 25.4 weeks [25]. Carboplatin has also been found to have survival benefit in other tumours. For example, in a study of 1526 ovarian cancer patients, no differences in survival were found between those patients treated with CAP (cyclophosphamide, doxorubicin and cisplatin) and those treated with single-agent carboplatin [26].

This is the first large, randomised trial directly comparing paclitaxel/carboplatin with paclitaxel/cisplatin in the treatment of advanced NSCLC. The significantly superior survival achieved with cisplatin differs from results reported in similar US studies. In a recent four-arm ECOG trial [27], where 1207 patients were randomised to receive paclitaxel (as a 24-h intravenous infusion)/cisplatin, gemcitabine/cisplatin, docetaxel/cisplatin, or paclitaxel (as a 3-h intravenous infusion)/carboplatin, the response rate for all 1155 evaluable patients was 19%, with a median survival of 7.9 months, a 1-year survival rate of 33% and a 2-year survival rate of 11%. The response rate and survival did not differ significantly between patients receiving paclitaxel/cisplatin and those in any of the other three arms [27]. On the other hand, a recent large international randomised trial comparing docetaxel/carboplatin, docetaxel/cisplatin and vinorelbine/cisplatin reported a significantly superior median survival in the docetaxel/cisplatin arm (10.9 months) [28], and a European randomised study also reported a median survival of 10 months in the docetaxel/cisplatin arm [29].

Differences between paclitaxel/cisplatin and paclitaxel/carboplatin found in the present study are not due to an uneven distribution of patient characteristics (Table 1) or to the number of cycles received (Table 2). The only bias was that dose reduction of carboplatin was necessary for 96 of 279 (34%) of evaluable patients; this reduction occurred mainly at course 1, due to a miscalculation of AUC. The average AUC for these 96 patients was 4.9.

The fact that there was no difference in the ECOG study [27] between paclitaxel/carboplatin and paclitaxel/cisplatin leads us to conclude that we must be cautious with the findings of the present study. We can postulate that continuous infusion of paclitaxel could modify the therapeutic efficacy of this combination. In the prior ECOG study [15], the median survival for the paclitaxel/cisplatin arm where paclitaxel was administered by continuous infusion was 9.9 months compared with 7.6 months for the cisplatin/etoposide arm. The recommended dose for further studies was paclitaxel 135 mg/m^2 by 24-h continuous infusion plus cisplatin. In the study by Schiller et al. [27], the control arm received this combination and found no differences in comparison with paclitaxel 225 mg/m^2 by 3-h

infusion plus carboplatin AUC 6. This study is slightly different from the present one, where patients received paclitaxel 200 mg/m^2 by 3-h infusion plus carboplatin AUC 6. This point should be taken into account in future studies and meta-analyses.

This large European randomised study can contribute greatly to resolving the longstanding debate on the superiority of carboplatin- or cisplatin-based chemotherapy in lung cancer. Given the longer median survival achieved with paclitaxel/cisplatin, its use can be recommended in the treatment of patients with advanced and metastatic NSCLC. Paclitaxel/carboplatin represents a viable alternative, with a similar response rate, a good safety profile, manageable toxicity and superior ease of administration.

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References

1. Klastersky J, Sculier JP, Lacroix H et al. A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small-cell lung cancer: European Organization for research and treatment of cancer protocol 07861. J Clin Oncol 1990; 8: 1556–1562.
2. Gatzemeier U, von Pawel J, Gottfried M et al. Phase III comparative study of high-dose cisplatin versus a combination of paclitaxel and cisplatin in patients with advanced non-small-cell lung cancer. J Clin Oncol 2000; 18: 3390–3399.
3. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Br Med J 1995; 311: 899–909.
4. Cullen MH, Billingham LJ, Woodroffe CM et al. Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. J Clin Oncol 1999; 17: 3188–3194.
5. Breathnach OS, Freidlin B, Conley B et al. Twenty-two years of phase III trials for patients with advanced non-small-cell lung cancer: sobering results. J Clin Oncol 2001; 19: 1734–1742.
6. Crawford J, O'Rourke M, Schiller JH et al. Randomized trial of vinorelbine compared with fluorouracil plus leucovorin in patients with stage IV non-small-cell lung cancer. J Clin Oncol 1996; 14: 2774–2784.
7. Ranson M, Davidson N, Nicolson M et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 2000; 92: 1074–1080.
8. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience. J Clin Oncol 1991; 9: 1618–1626.
9. Paesmans M, Sculier JP, Libert P et al. Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1,052 patients. J Clin Oncol 1995; 13: 1221–1230.

10. Hickish TF, Smith IE, Ashley S, Middleton G. Chemotherapy for elderly patients with lung cancer. Lancet 1995; 346: 580.
11. Murphy WK, Fossella FV, Win RJ et al. Phase II study of Taxol in patients with untreated advanced non-small-cell lung cancer. J Natl Cancer Inst 1993; 85: 384–388.
12. Chang AY, Kim K, Glick J et al. Phase II study of Taxol, merbarone, and piroxantrone in stage IV non-small-cell lung cancer: the Eastern Cooperative Oncology Group results. J Natl Cancer Inst 1993; 85: 388–394.
13. Johnson DH, Paul DM, Hande KR et al. Paclitaxel plus carboplatin in advanced non-small-cell lung cancer: a phase II trial. J Clin Oncol 1996; 14: 2054–2060.
14. Langer CJ, Leighton JC, Comis RL et al. Paclitaxel and carboplatin in combination in the treatment of advanced non-small-cell lung cancer: a phase II toxicity, response, and survival analysis. J Clin Oncol 1995; 13: 1860–1870.
15. Bonomi P, Kim KM, Fairclough D et al. Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. J Clin Oncol 2000; 18: 623–631.
16. Giaccone G, Splinter TAW, Debruyne Ch et al. Randomized study of paclitaxel-cisplatin versus cisplatin–teniposide in patients with advanced non-small-cell lung cancer. J Clin Oncol 1998; 16: 2133–2141.
17. Kelly K, Pan Z, Murphy J et al. A phase I trial of paclitaxel plus carboplatin in untreated patients with advanced non-small cell lung cancer. Clin Cancer Res 1997; 3: 1117–1123.
18. Kosmidis P, Mylonakis N, Skarlos D et al. Paclitaxel (175 mg/m^2) plus carboplatin (6 AUC) versus paclitaxel (225 mg/m^2) plus carboplatin (6 AUC) in advanced non-small-cell lung cancer (NSCLC): a multicenter randomized trial. Ann Oncol 2000; 11: 799–805.
19. Kelly K, Crowley J, Bunn PA et al. A randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 2001; 19: 3210–3218.
20. Shyr Y, Choy H, Cmelak A et al. Pattern of practice survey: non-small cell lung cancer in the U.S. Proc Am Soc Clin Oncol 1998; 17: 463a (Abstr 1778).
21. Pocock S, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31: 103–115.
22. Aaronson NK, Ahmedzai S, Bergman B et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365–376.
23. Bergman B, Aaronson NK, Ahmedzai S et al. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. Eur J Cancer 1994; 30A: 635–642.
24. ICH E9 Guideline: Statistical Principles for Clinical Trials, EU: CPMP/ICH/363/96, FDA: Federal Register, Vol. 63, No. 179, September 16, 1998, p. 49583.
25. Bonomi PD, Finkelstein DM, Ruckdeschel JC et al. Combination chemotherapy versus single agents followed by combination chemotherapy in stage IV non-small-cell lung cancer: a study of the Eastern Cooperative Oncology Group. J Clin Oncol 1989; 7: 1602–1613.
26. The ICON Collaborators. ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. Lancet 1998; 352: 1571–1576.
27. Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002; 346: 92–98.
28. Rodriguez J, Pawel A, Pluzanska A et al. A multicenter, randomized phase III study of docetaxel + cisplatin (DC) and docetaxel + carboplatin (DCB) vs vinorelbine + cisplatin (VC) in chemotherapy-naive patients with advanced and metastatic non-small cell lung cancer. Proc Am Soc Clin Oncol 2001; 20: 314a (Abstr 1252).
29. Georgoulias V, Papadakis E, Alexopoulos A et al. Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicentre trial. Lancet 2001; 357: 1478–1484.