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Paclitaxel by 1-h infusion in combination with carboplatin in advanced non-small cell lung carcinoma (NSCLC)

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Abstract

In our previous study, FCCC 93-024, paclitaxel by 24-h infusion combined with carboplatin yielded a response rate of 62% and median survival of 54 weeks in advanced non-small cell lung cancer (NSCLC). Myelosuppression proved dose-limiting, requiring the routine use of granulocyte-colony stimulating factor (G-CSF). Based on the reported activity of 1-h paclitaxel infusion in NSCLC and minimal myelosuppression at doses of 135 and 200 mg/m^2 every 3 weeks and the suggestion of a dose–response relationship, we launched an intrapatient dose escalation trial of combination carboplatin and 1-h paclitaxel. Chemotherapy-naïve patients with advanced NSCLC received paclitaxel 175 mg/m^2 1-h and carboplatin dosed to a fixed targeted area under the concentration–time curve (AUC) of 7.5 at three weekly intervals for six cycles. In the absence of grade 4 myelosuppression, paclitaxel was escalated by 35 mg/m^2/cycle on an intrapatient basis to a maximum dose of 280 mg/m^2 by cycle 4. G-CSF was not routinely used. 57 patients (pts) were accrued from November 1994 through to April 1996. 44 pts (77%) had Eastern Cooperative Oncology Group (ECOG) performance status 1. Median age was 64 (range: 34–80) years. Cumulative peripheral sensory neuropathy proved dose-limiting and prohibitive in the first 20 evaluable patients (cohort A): grade $\geqslant$1 in 15 patients (75%), grade 3 in 6 (30%), generally occurring at paclitaxel doses $\geqslant$215 mg/m^2 and obligating 3 patients to have treatment halted in the absence of disease progression. The protocol, therefore, was revised and the initial paclitaxel dose reduced to 135 mg/m^2 with intrapatient dose escalation of 40 mg/m^2/cycle to a maximum dose of 215 mg/m^2, recapitulating the original dosing schema used in FCCC 93-024. 35 patients were enrolled in this second cohort (B); 33 proved evaluable. Whilst 17 (52%) experienced peripheral sensory neuropathy, grade 3 neurotoxicity developed in only 3 (9%). Myelosuppression also was less pronounced, with 42% exhibiting grade 4 granulocytopenia and 30% grade $\geqslant$3 thrombocytopenia in cohort B compared with 70% and 50%, respectively in cohort A. Of the first 22 patients accrued to cohort A, 12 (55%) had major objective responses. Median survival was 48.5 weeks, 1-year survival rate 45% and 2-year survival rate 18%. Of 33 evaluable patients in cohort B, 9 (27%) had major objective responses. Median survival was 46 weeks, 1-year survival rate 47% and 2-year survival rate 12%. Combination paclitaxel by 1-h infusion and carboplatin at a fixed targeted AUC of 7.5 is active in advanced NSCLC. Neurotoxicity, not myelosuppression, proved dose-limiting at paclitaxel doses exceeding 215 mg/m^2. Lower doses may be associated with lower response rates, but do not appear to compromise survival.

Keywords: 1-h Paclitaxel; Chemotherapy-advanced; NSCLC; Calvert formula; Carboplatin

1. Introduction

Advanced non-small cell lung cancer (NSCLC) remains a devastating illness. Despite improved systemic therapy and an improvement in median survival to 10 months from 6–8 months over the past 5–7 years, the majority of patients die within 1 year [1,2]. We have previously reported the results of a multi-institutional phase II study in advanced chemotherapy-naïve NSCLC (FCCC 93-024), in which patients received a combination of paclitaxel and carboplatin. Paclitaxel

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was given by 24-h infusion and, in the absence of grade 4 neutropenia or grade $\geqslant 3$ thrombocytopenia, escalated 40 mg/m^2/cycle on an intrapatient basis from 135 mg/m^2 to 215 mg/m^2; carboplatin was dosed at an area under the concentration–time curve (AUC) of 7.5. Treatment was administered at three-weekly intervals [3,4]. In 53 evaluable patients, this combination resulted in a 62% response rate, 9% complete remissions, a median response duration of 6 months (range: 1–30 months), and 1-year and 2-year survival rates of 54% and 15%, respectively. The majority of patients were able to complete all six scheduled cycles. This regimen, however, required overnight hospitalisation for paclitaxel infusion and the obligatory use of granulocyte-colony stimulating factor (G-CSF) during the second and subsequent cycles to prevent neutropenic fever and to permit intrapatient dose escalation of paclitaxel.

Others have demonstrated that 1-h paclitaxel infusions at doses of 135 and 200 mg/^{2} every 3 weeks can produce objective responses in advanced NSCLC [5,6], both in chemotherapy-naïve patients and in those previously exposed to chemotherapy. In addition, data have suggested a dose–response effect. In these trials, myelosuppression has proven to be relatively mild, comparable with that observed with 3-hourly infusions, and there has been no overt increase in the incidence of hypersensitivity reactions.

Therefore, in anticipation of the reduced cost, improved convenience, amelioration of myelosuppression and comparable efficacy, we initiated a phase II intrapatient dose escalation trial at Fox Chase Cancer Center and its network affiliates, combining paclitaxel by 1-h infusion with carboplatin, dosed to a fixed AUC.

2. Patients and methods

2.1. Eligibility

Eligibility was restricted to patients with chemotherapy-naive NSCLC, either stage IV or stage IIIb with malignant pleural effusion, or recurrent, incurable disease after prior surgery or radiation. Patients were required to have measurable tumour, ECOG performance status 0 or 1, absolute neutrophil count $\geqslant 2000$/μl, platelet count $\geqslant 100\,000$/μl, serum creatinine $\leqslant 1.5$ mg/dl, bilirubin $\leqslant 2$ mg/dl, adequate cardiac function with no active arrhythmias or congestive heart failure and restriction of previous radiation to $\leqslant 30\%$ of marrow-bearing bone. A negative serum B-HCG in women of child-bearing potential was required.

Patients with mixed small cell/non-small cell histology were excluded, as were those with prior unrelated invasive malignancy in the preceding 3 years, or completion of radiation or biological therapy within 4 weeks of protocol initiation. Patients with brain metastases were allowed to enroll after craniotomy and resection or whole brain irradiation, as long as brain lesions were radiographically stable or improved and neurological improvement or normalisation was evident. Informed consent was obtained in accordance with the Fox Chase Cancer Center Institutional Review Board or its community affiliates.

2.2. Patient evaluation

Enrolment required full history and physical examination, documentation of ECOG performance status, biopsy or cytological confirmation of NSCLC, complete blood cell count, white cell differential and platelet count, chemistry panel, liver function studies, blood urea nitrogen and creatinine, baseline electrocardiogram, chest X-ray, computerised tomographical (CT) scanning of the chest and abdomen, bone scan and either magnetic resonance imaging (MRI) or CT of the brain.

2.3. Treatment

Patients received paclitaxel 175 μg/m^2 over 1 h, 10–30 min after hypersensitivity prophylaxis consisting of intravenous dexamethasone 20 mg, diphenhydramine 50 mg, and cimetidine 300 mg. We did not routinely administer oral dexamethasone 6 or 12 h prior to paclitaxel infusion.

After completing paclitaxel infusion, carboplatin was administered over 30 min, to a targeted AUC of 7.5. Dosing was based on the method developed by Calvert and colleagues [7] with the total dose calculated by multiplying the sum of the patient's glomerular filtration rate (GFR) and 25 by the targeted AUC of 7.5. The Cockroft–Gault formula for creatinine clearance was substituted for GFR [8]. Antiemetic prophylaxis immediately preceding carboplatin consisted of intravenous ondansetron or granisetron or alternative anti-emetics at the treating physician's discretion.

In the absence of grade 4 neutropenia, grade $\geqslant 3$ thrombocytopenia or grade $\geqslant 2$ neurotoxicity, the paclitaxel dose only was escalated on an intrapatient basis by 35 mg/m^2 per cycle to a maximum dose of 280 mg/m^2 by cycle four. In cases of grade 4 thrombocytopenia lasting $\geqslant 3$ days or requiring transfusion, the paclitaxel dose was decreased by 35 mg/m^2 to a minimum dose of 105 mg/m^2 and the carboplatin dose was reduced by an AUC of 1.5. The carboplatin dose was otherwise fixed. Granulocyte-colony stimulating factor (G-CSF) 5 mcg/kg by subcutaneous injection was administered for 10–14 days only to those who developed grade 4 neutropenia or neutropenic fever during the previous cycle. Treatment was withheld for grade 3 neurotoxicity or fatigue. It was resumed once this toxicity had improved to $\leqslant$ grade 1 and the paclitaxel dose was subsequently reduced by one level from the previous dose.

Because unacceptable neurotoxicity was observed in 6 of the first 22 patients accrued (cohort A), the protocol was subsequently revised, and the starting dose of paclitaxel reduced to 135 mg/m^2 (cohort B). In the absence of grade 4 neutropenia, grade $\geqslant 3$ thrombocytopenia and grade $\geqslant 2$ neuropathy, the paclitaxel dose was increased by 40 mg/m^2 per cycle to a maximum dose of 215 mg/m^2 by cycle three, recapitulating the dosing schema used in FCCC 93-024 [3,4] our original 24-h paclitaxel–carboplatin study. The carboplatin dose was maintained at a targeted AUC of 7.5. The same parameters for implementation of granulocyte colony-stimulating factor applied to both cohorts A and B.

Treatment was repeated at three-weekly intervals and was discontinued only by patient request or for unequivocal disease progression or unacceptable toxicity. Reassessment of measurable lesions generally by CTs occurred every two cycles at six weekly intervals. At the conclusion of six cycles (18 weeks), patients were generally observed off-therapy, although treating physicians at their discretion could continue treatment beyond six cycles. In patients no longer receiving systemic therapy, follow-up studies at Fox Chase Cancer Center occurred at 8 to 12 weekly intervals and included imaging of measurable indicator lesions. The time of clinical progression was recorded in each patient, though details regarding site(s) of disease progression were not routinely available.

2.4. Statistical analysis

Standard ECOG criteria were used to evaluate response to therapy [9]. Patients were monitored for treatment-related toxicity, response, duration of response, time to disease progression, time to death and sites of failure. All patients receiving one or more cycles were evaluated for response, toxicity and survival. Those patients in whom treatment was curtailed after one cycle only, in the absence of disease progression, were considered inevaluable for response, but were included in the toxicity and survival data.

We targeted an initial accrual of 26 patients, and projected a response rate of $\geqslant 50\%$ based on our previous study (FCCC 93-024). The null hypothesis projected a response rate of 30% or less. We, therefore, were prepared to abandon this trial if 8 or fewer of the first 26 patients responded to treatment. However, because of the development of unacceptable peripheral sensory neuropathy in 6 of the first 22 patients, the study was interrupted and the paclitaxel dose reduced. The identical statistical analysis based on response applied to subsequent enrolling patients (cohort B).

Event-free survival and overall survival rates were estimated by the method of Kaplan and Meier [10]. Confidence bounds and response rates used the usual large-sample estimates for binomial distribution.

3. Results

Demographic data are summarised in Table 1. From October 1994 to April 1996, 57 patients were enrolled. The first 22 patients enrolled comprised cohort A. 35 patients were included in cohort B, the group receiving the lower starting doses of paclitaxel. 30 patients were male, 27 female. The median age was 64 years with a range of 34–80 years. 14 patients each had previously received radiation therapy or had undergone definitive pulmonary resections. 44 (77%) had an ECOG performance status of 1 and 44 (77%) had stage IV disease. Histologies included adenocarcinoma in 36 (63%), bronchoalveolar carcinoma in 3 (5%), squamous cell carcinoma in 7 (12%), mixed adenosquamous carcinoma in 3 (5%), and NSCLC, not otherwise specified in 8 (14%). Cohorts A and B were well balanced with regard to demographics, prior treatment, histological diagnosis and baseline performance status. 30 patients were enrolled at Fox Chase Cancer Center, 27 through its community network affiliates.

3.1. Cohort A

96 cycles of treatment were administered to this group. 20 of 22 patients (91%) were fully evaluable for toxicity. One patient in the absence of symptomatic or radiographical progression was removed from study by the treating physician within 10 days of initiating therapy to receive palliative chest radiation and was considered a non-responder. Another patient was compliant with the study schedule, but failed to obtain nadir labs and to consistently report toxicity. Table 2a details the maximum toxicities observed in the 20 fully evaluable patients. Grade 4 granulocytopenia occurred

Table 1
Patient demographics FCCC 94-064 paclitaxel/carboplatin: NSCLC

Cohort	A	B	Total
No. of patients	22	35	57
Age: Median (range, years)	63 (34–80)	65 (41–77)	64 (34–80)
Gender male/female	12/10	18/17	30/27
Prior RT	7	7	14
Histologies	*n* (%)	*n* (%)	*n* (%)
Bronchoalveolar	2 (9)	1 (3)	3 (5)
Adenocarcinoma	13 (59)	23 (66)	36 (63)
Squamous	4 (18)	3 (9)	7 (12)
Adenosquamous	1 (5)	2 (6)	3 (5)
Carcinoma NOS	2 (9)	6 (17)	8 (14)
Stage			
IIIb	3 (14)	10 (29)	13 (23)
IV	19 (86)	25 (71)	44 (77)
Performance status			
0	3 (14)	10 (29)	13 (23)
1	19 (86)	25 (71)	44 (77)

RT, radiotherapy; NOS, not otherwise specified.

in 70% of patients, but there were only two admissions for neutropenic fever (2% of treatment cycles). G-CSF use rose to 30% by cycle 3 in those remaining on-study and to 57% by cycle 6 and was required during 28% of treatment cycles. Anaemia proved cumulative with grade $\geqslant 2$ incidence rising from 23% during the first cycle to a peak of 83% by the fourth cycle. Grade $\geqslant 2$ anaemia occurred in 85% of pts overall. Grade $\geqslant 3$ anaemia occurred in 40% of pts; grade $\geqslant 3$ thrombocytopenia occurred in 50% of pts. 7 patients (35%) required 24 units of packed red blood cells over 12 separate treatment courses. 5 pts (25%) required platelet transfusions. An apparent abscopal effect was observed: whereas 50% of those previously radiated required either red cells or platelets, only 25% of those who were radiation-naïve required red cells and only 13% of radiation-naïve patients needed platelets.

Non-haematological toxicities were protocol-limiting. Grade $\geqslant 1$ peripheral sensory neuropathy occurred in 15 pts (75%); grade $\geqslant 2$ in 12 (60%) and grade 3 in 6 (30%), predominantly at paclitaxel doses in excess of 210 mg/m^2. Cumulative peripheral neuropathy (Fig. 1a) obligated 3 pts to be removed from protocol in the absence of disease progression, and in 2 of these patients, this side-effect did not substantially reverse in their lifetimes. Grade 3 nausea and vomiting occurred in 2 pts (10%), grade 3 fatigue in 5 pts (25%). Myalgias and arthralgias occurred in 15 pts (75%); these symptoms were grade $\geqslant 2$ in 10 pts (50%), but were grade 3 in only 2 pts (10%). The incidence of arthralgias and myalgias rose during sequential treatment cycles (Fig. 1b). There was one grade 3 allergic reaction, which was successfully prevented during subsequent cycles by the prophylactic administration of oral dexamethasone, 10 mg every 6 hours for 24 h prior to treatment. In addition, one older, relatively thin female patient experienced apparent 'intoxication' manifested as transient disorientation, confusion, drowsiness and ataxia, which resolved within 6 h and was attributed to alcohol in the paclitaxel formulation.

9 separate, unanticipated hospitalisations occurred in 7 evaluable pts (35%). The cycle-specific incidence was 9%. In 5 pts, the complications of treatment were directly responsible; these included neutropenic fever in

Table 2
FCCC 94-064

	Grade *n* (%)				
	0	1	2	3	4
(a) Cohort A[a]					
Anaemia	0	3 (15)	9 (45)	7 (35)	1 (5)
Granulocytopenia	1 (5)	1 (5)	2 (10)	2 (10)	14 (70)[b]
Thrombocytopenia	5 (25)	4 (20)	1 (5)	6 (30)	4 (20)
Emesis	10 (50)	5 (25)	3 (15)	2 (10)	0
Fatigue	3 (15)	4 (20)	8 (40)	5 (25)	0
Myalgias/arthralgia	5 (25)	5 (25)	8 (40)	2 (10)	0
Neuropathy	5 (25)	3 (15)	6 (30)	6 (30)[c]	0
(b) Cohort B[d]					
Anaemia	2 (6)	10 (30)	13 (40)	8 (24)	0
Granulocytopenia	4 (12)	3 (9)	2 (6)	10 (30)	14 (42)[b]
Thrombocytopenia	13 (40)	4 (12)	6 (18)	5 (15)	5 (15)
Emesis	16 (48)	14 (42)	3 (9)	0	0
Fatigue	17 (52)	6 (18)	3 (9)	7 (21)	0
Myalgias/arthralgia	16 (48)	10 (30)	5 (15)	2 (6)	0
Neuropathy	16 (48)	11 (33)	3 (9)	3 (9)	0

[a] Maximum toxicity/20 evaluable patients (96 cycles).
[b] Two episodes each of neutropenic fever.
[c] 3 patients removed from study in absence of disease progression due to cumulative sensory neuropathy.
[d] Maximum toxicity/33 evaluable patients (150 treatment cycles).

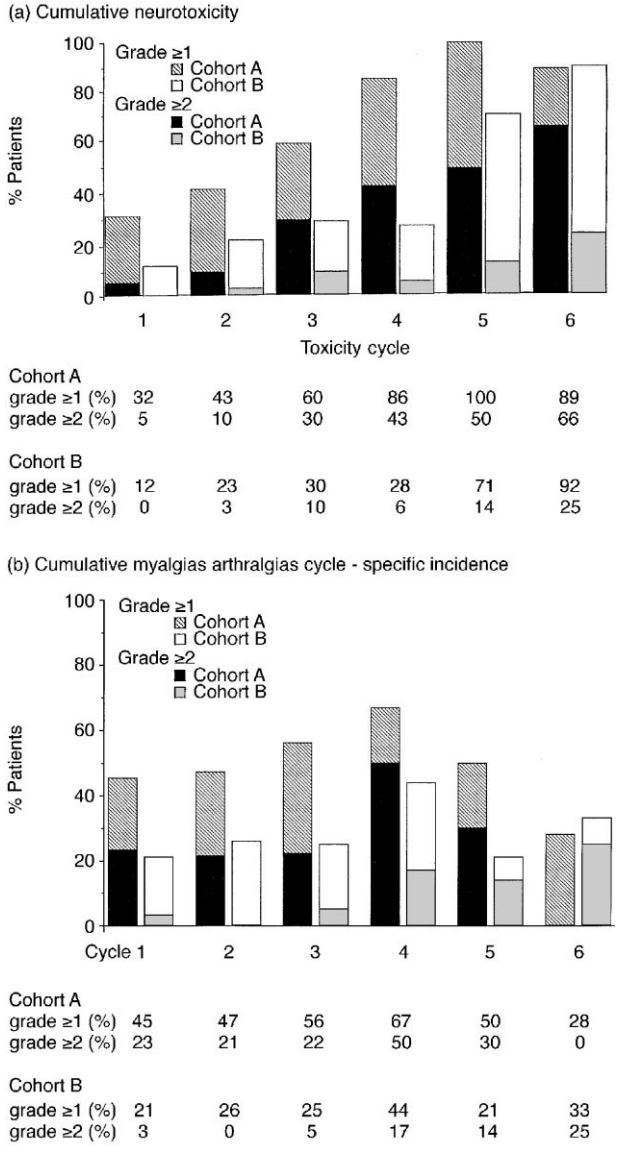

Fig. 1. (a) Cumulative neuropathy was more frequent and more severe in cohort A compared with cohort B. (b) Myalgias and arthralgias were cumulative in both cohorts of the study, but were consistently worse in cohort A through the fifth cycle, peaking during cycle 4. By cycle 6, the overall incidence in both cohorts was roughly comparable due largely to toxicity-mandated dose reductions in cohort A.

Table 3
FCCC 94-064: paclitaxel dose delivery, treatment delays and G-CSF use

Cohort A

Cycle (*n*)	1 (22)	2 (21)	3 (20)	4 (14)	5 (12)	6 (7)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Paclitaxel dose no. (%) (mg/m^2)						
175 mg/m^2	22 (100)	5 (24)	4 (20)	2 (14)	3 (25)	2 (29)
210 mg/m^2	–	16 (76)	7 (35)	4 (29)	5 (42)	1 (14)
245 mg/m^2	–	–	9 (45)	5 (36)	3 (25)	2 (29)
280 mg/m^2	–	–	–	3 (21)	1 (8)	2 (28)
Treatment delays no. (%)	–	0	1 (5)	3 (21)	8 (67)	3 (42)
G-CSF no. (%)	1 (5)	3 (14)	6 (30)	6 (43)	7 (58)	4 (57)

Cohort B

Cycle (*n*)	1 (34)	2 (31)	3 (25)	4 (24)	5 (19)	6 (17)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Paclitaxel dose no. (%) (mg/m^2)						
135 mg/m^2	34 (100)	4 (13)	1 (4)	3 (13)	3 (16)	2 (12)
175 mg/m^2	–	27 (87)	6 (24)	2 (8)	1 (5)	3 (18)
215 mg/m^2	–	–	18 (72)	19 (79)	15 (79)	12 (71)
Treatment delays no. (%)	–	1 (3)	3 (12)	5 (21)	4 (21)	10 (59)
G-CSF no. (%)	0	1 (3)	6 (24)	8 (33)	9 (47)	9 (53)

2, nausea and vomiting in 2, and hyperglycaemia ascribed to steroid prophylaxis with coincident altered mentation in 1 patient. One patient was admitted for chest pain to rule out myocardial infarction; this admission was not temporally connected to treatment. 2 were admitted for unrelated infections, in the absence of neutropenia, 1 for pneumonia and one for *Escherichia coli* bacteraemia; and 1 patient was admitted for probable small bowel obstruction.

The median first cycle carboplatin dose using conventional body surface area (BSA) dosing was 466 mg/m^2 with a range of 358 mg/m^2 to a maximum of 655 mg/m^2. One patient only required dose reduction of carboplatin to an AUC of 6.0 because of myelosuppression, and this did not occur until cycles 5 and 6. Table 3 delineates the percentage of patients receiving specific paclitaxel dose(s) each cycle. Whilst 76% of pts during cycle 2 were able to achieve the targeted paclitaxel dose of 210 mg/m^2, a progressive inability to administer the targeted paclitaxel dose was observed during subsequent cycles: only 45% were able to tolerate dose escalation to 245 mg/m^2 during cycle 3, and only 21% were able to achieve the targeted dose of 280 mg/m^2 during cycle 4.

The received dose intensity of paclitaxel calculated in mg/m^2/wk is shown in Fig. 2. The median number of cycles received was five (range: 1–6). The incidence of treatment delays was 20%. Seven per cent of cycles were delayed $\geqslant$2 weeks. With successive courses of treatment, thrombocytopenia (57%) or neuropathy (40%) resulted in an increasing frequency of treatment delays: by cycles 5 and 6, 75% of those remaining on study had their treatment intervals prolonged for 4 weeks or more.

3.2. Response and survival data

12 of 22 patients (55%) had major objective responses (95% confidence intervals (CI) of 32–76%). One patient

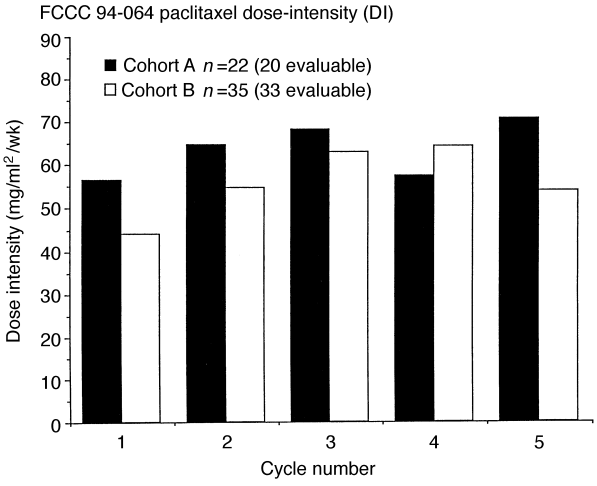

Fig. 2. The dose intensity by trial design was initially higher in cohort A, but because of difficulties achieving the targeted dose (280 mg/m^2) in cohort A and obligatory treatment delays, the dose intensity of cohorts A and B by cycles 3 and 4 was roughly equivalent (68.4 mg/m^2/wk and 57.6 mg/m^2/wk, respectively, for cohort A and 63.2 mg/m^2/wk and 64.5 mg/m^2/wk for cohort B). The dose intensity for cycle 6 could not be determined because there were no further scheduled treatment cycles and hence no denominator.

Table 4
FCCC 94-064: reasons for treatment discontinuation

	n (%)	
Cohort	(A)	(B)
Disease progression	6 (27)	12 (34)
Cumulative toxicity	5 (23)	1 (3)
Neuropathy	3	0
Neuropathy/leucopenia	1	0
Thrombocytopenia	1	1
Death	1 (5)[a]	2 (6)[b]
Allergic reaction	0	1 (3)
Intercurrent illness	0	2 (6)
Protocol completion	10 (45)	17 (49)

[a] Perforated viscus; peritonitis.
[b] Cardiac arrest, not attributable to paclitaxel.

who had previously undergone resection of a discrete rib metastasis at an outside institution had a radiographic partial remission (PR) of the primary lesion; at subsequent thoracotomy, the residual lesion was resected and proved to contain no viable tumour. 2 patients had minor regressions of 25–50%; 5 had stable disease; and 2 had clear-cut progressive disease obligating treatment termination after two cycles. Another patient was removed from study for palliative radiation before the completion of the first cycle, and was also categorised as having progressive disease, even though her disease was radiographically stable. The reasons for termination of therapy are shown in Table 4. At a median potential follow-up of 42 months, with a range of 39–45 months, 3 patients (14%) remain alive. The median survival is 48.5 weeks with a range of 14–190 weeks. The one-year survival rate is 45% and two-year survival rate is 18% (Table 5) (Fig. 3). The median event-free survival, defined as freedom from progression or time to death in the absence of progression, is 25 weeks (Fig. 4). 14%

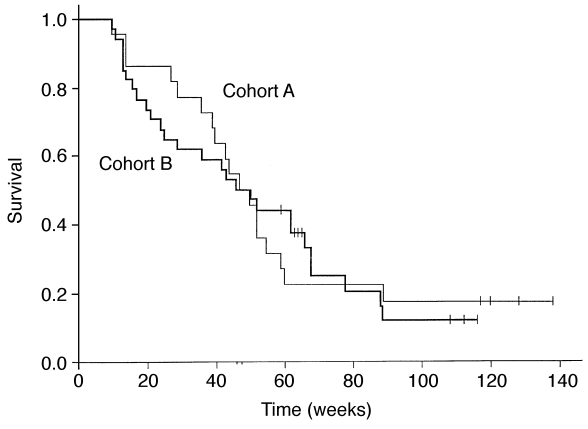

Fig 3. Survival was comparable for cohorts A and B. The median survival in cohort A was 48.5 weeks and in cohort B 46 weeks. The respective 95% confidence intervals were 40–89 weeks and 29–68 weeks. The 2-year survival rate was 18% and 12%, respectively. 5 patients (9%) remain alive from 104 to 190 weeks.

Table 5
Combination paclitaxel and carboplatin in advanced NSCLC: 24-h vs 1-h paclitaxel infusions — a comparative analysis

	Study		
	93-024	94-064 (A)	94-964 (B)
Carboplatin (AUC)	7.5	7.5	7.5
Paclitaxel (mg/m^2)	135–215	175–280	135–215
Paclitaxel (duration)	24-h	1-h	1-h
No. patients enrolled	54	22	35
Cycles	268	96	150
Toxicities (%)			
Granulocytopenia grade 3–4 (4)	71 (45)	80 (70)	72 (42)
Platelets grade 3–4 (4)	48 (23)	50 (20)	30 (15)
Myalgias grade 1–3 (3)	35 (6)	75 (10)	52 (6)
Neuropathy grade 1–3 (3)	38 (2)[a]	75 (30)	52 (9)
Fatigue grade 1–3 (3)	79 (21)	85 (25)	48 (21)
G-CSF cycles/pts (%)	80/100	28/55	22/32
Major response (%)	62	55	27
1-year survival (%)	54	45	47
2-year survival (%)	15	18	12

AUC, area under concentration–time curve.
[a] $P = 0.037$ (93-024 versus 94-064A).

were free from progression at 1 year. One patient (5%) remains free from progression at 44 months.

3.3. Cohort B

From April 1995 to April 1996, 35 patients were accrued to cohort B, of whom 33 were fully evaluable for haematological and non-haematological toxicity. One patient had an anaphylactic reaction to paclitaxel after less than one-tenth of the dose had been infused; this toxicity recurred four days later despite protracted oral corticosteroid prophylaxis and slower infusion, obligating her removal from study. Another patient treated at a network affiliate was neither treated nor followed properly according to protocol guidelines and was, therefore, deemed ineligible for toxicity, response

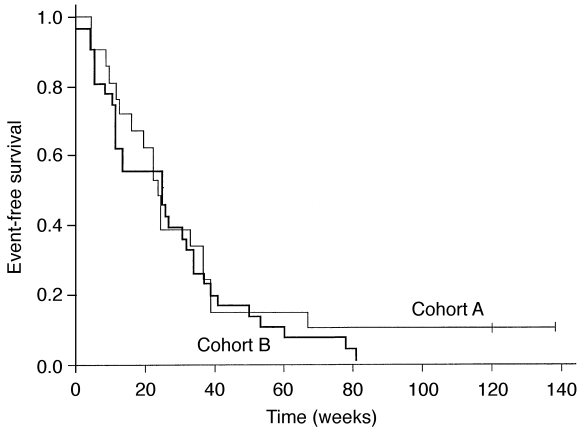

Fig. 4. Median event-free survival was virtually identical in both cohorts at 24–25 weeks.

or survival analysis. The remaining 33 patients completed therapy, 150 cycles total, with a median of six cycles per patient (range: 1–6).

At an initial paclitaxel dose of 135 mg/m^2 with intrapatient escalation to a top dose of 215 mg/m^2, myelosuppression proved less pronounced compared with cohort A. The patient-specific incidence of grade $\geqslant 3$ granulocytopenia was 72%; grade 4 granulocytopenia occurred in 42% of patients and the patient-specific incidence of grade $\geqslant 3$ thrombocytopenia was 30% (Table 2b). There were two episodes of neutropenic fever. G-CSF use was cumulative, rising from 3% during cycle 2 to 53% by cycle 6 (Table 3), but was required in only 22% of cycles overall; fewer than one-third of patients in cohort B required G-CSF at any point. Both thrombocytopenia and anaemia, whilst relatively mild, were cumulative. The incidence of grade $\geqslant 2$ anaemia rose from 6% during cycle 1 to 43% by cycle 4 and to 82% by cycle 6. Grade $\geqslant 3$ thrombocytopenia rose from 3% during cycle 1 to 17% during cycle 4 and to 47% by cycle 6. 6 pts required packed red cell transfusions; 2 needed platelet transfusions.

12 unanticipated hospitalisations occurred during 150 treatment courses. 6 hospitalisations were linked to treatment: 2 for neutropenic fever; 2 for diarrhoea and dehydration; 1 for nausea and vomiting; and 1 for steroid-induced hyperglycaemia with secondary lethargy and altered mentation. 2 were due to unrelated infections, 1 for pneumonia and 1 for an unspecified febrile illness. 4 hospitalisations were prompted by symptoms of disease progression: inadequate pain control in 1 patient; confusion and cachexia in a second; dehydration and syncope in a third; and progressive malignant pleural effusion, hypoxaemia and respiratory insufficiency in a fourth.

Grade 3 fatigue occurred in 21% of patients (Table 2b). Myalgias-arthralgias occurred in 52% of patients, but proved to be $\geqslant$grade 2 in only 21% and grade 3 in only 6%. 17 of 33 evaluable patients (52%) experienced some degree of peripheral sensory neuropathy. The incidence proved cumulative, rising from 11% during the first cycle to 28% by cycle 3 and ultimately to 76% of those remaining on study by cycle 6. Unlike cohort A, there were only three instances of grade 3 neuropathy (9%), and neuropathy did not obligate termination of therapy in any patient.

The median carboplatin dose in cycle 1 using conventional BSA criteria was 446 mg/m^2 (range 336–881 mg/m^2). The targeted paclitaxel dose of 175 mg/m^2 was achieved in 87% of patients by cycle 2. The targeted maximum dose of 215 mg/m^2 was realised in 72% of patients by cycle 3 and was ultimately achieved in 21 of 25 (84%) of patients who received three or more cycles (Table 3). The respective paclitaxel dose intensifies of cohorts A and B are detailed in Fig. 2. Treatment delays occurred during 15% of cycles in cohort B, and the incidence, similar to cohort A, was cumulative, with 59% of those still receiving treatment by cycle 6 delayed 1 week or more. Unlike cohort A, only 1% of cycles were delayed $\geqslant 2$ weeks. Neuropathy was a less frequent cause of treatment delays, accounting for only 22%. Thrombocytopenia accounted for 48%. Other reasons including delayed recovery of WBC, fatigue and patient request were responsible for 30%.

Accrual to this portion of the study is completed. Of 33 evaluable pts, 9 (27%) had major objective responses (95% CI of 12–43%), 8 (24%) had minor responses, 7 (21%) had stable disease, and 7 (21%) had progressive disease. 2 pts who received one cycle only were considered non-responders and are included in the denominator: 1 experienced declining performance status in the absence of objective disease progression; another was removed from treatment due to toxicity and patient request. Median freedom from progression was 24 weeks (Fig. 3). At 1-year, 3 (9%) were free from progression. At a median potential follow-up of 30 months (range: 24–36 months), 4 (12%) remain alive. Median survival is 46 weeks (range: 14–116+), and the 1-year survival rate is 47%. The 2-year survival rate is 12%.

4. Discussion

In comparison with our previous 24-h paclitaxel combination study (FCCC 93-024), there are clear advantages to shorter paclitaxel infusion (1–3 h) in combination with fixed-dose carboplatin (AUC 7.5). Myelosuppression proved either comparable or less severe, without the obligatory use of G-CSF. Abbreviated paclitaxel infusion also avoided the cost and inconvenience of overnight hospitalisation and routine use of G-CSF. Although a comprehensive discussion of cost-effectiveness and utility is beyond the scope of this study, we have computed the relative costs of both protocols. At comparable doses, we have estimated a 35% cost-reduction for the outpatient study, compared with the initial trial using 24-h paclitaxel infusion (Table 6).

There are drawbacks to short infusion as well. The incidence of neurotoxicity in cohort A was unacceptable, its severity clearly worse than that observed in our previous study of 24-h paclitaxel infusion in combination with carboplatin ($P = 0.037$). In retrospect, the dose escalation schema we employed proved overly aggressive and confirmed the dose-limiting toxicity of short-infusion paclitaxel, specifically peripheral neuropathy, not myelosuppression [11]. In cohort B, using reduced doses of paclitaxel compared with cohort A with an intrapatient dose escalation schema and eligibility identical to FCCC 93-024, the incidence of neurotoxicity remained slightly higher compared with our 24-h infusion (Table 5); but its severity proved much less

Table 6
Relative per capita costs ($) of carboplatin and paclitaxel for six cycles by 24-h or 1-h infusion

Infusion duration	24-h[a]	1-h[a]
Hospitalisation for treatment	6000	0
Hospitalisation for neutropenic fever	389[b]	211[c]
Drug costs		
Paclitaxel	11 029.50	11 029.50
Carboplatin	6718.40	6718.40
G-CSF	8550.40[d]	2341.00[d]
Supportive treatments	802.00	802.00
Total	33 489.30	21 101.10

[a] Pro-rated to 215 mg/m^2.

[b] Seven episodes of neutropenic fever with average hospitalisation of 3 days apiece at $1000/day; divided by total number of patients ($n = 54$).

[c] Four episodes of neutropenic fever with average hospitalisation of 3 days apiece; divided by total number of patients ($n = 57$).

[d] The cost of 14 days of G-CSF for six cycles is $10 688. G-CSF was used during 80% of treatment cycles during the 24-h protocol. It was used during 22% of treatment cycles during the 1-h study.

pronounced compared with cohort A, and, unlike cohort A, there were no treatment terminations linked to neuropathy. Adherence to targeted dose escalation was more successful in cohort B compared with cohort A, and treatment delays in arm B, whilst no less frequent, were shorter. As a result, the received dose intensity of paclitaxel (mg/m^2/wk) by cycles 3 and 4 proved similar in both cohorts (Fig. 2), even though the starting dose of paclitaxel and the targeted dose in cohort A were higher. It is not clear if the apparent increase in incidence of neuropathy in cohort B, compared with the original 24-h study, was real or if it reflected our increased sensitivity to this toxicity and, consequently, our more rigorous questioning and elicitation of this symptom. Moreover, a comparative analysis of the relative incidence of neurotoxicity in cohort B and the incidence in the original 93-024 study yielded a two-sided P value of 0.276 by the Fisher's exact test. It should be emphasised that a statistical comparison of toxicities in two separate studies evaluating different infusion durations of paclitaxel has only an exploratory value outside of a randomised trial, and remains subject to caution. Assuming a power of $\geqslant 80\%$ and a type 1 error of $\leqslant 5\%$, we would require an enrolment of more than 380 pts (190 pts per arm) in a randomised trial of 24-h versus 1-h infusion to determine if this apparent increase in neurotoxicity (an escalation from 38 to 50%) was statistically significant by two-sided test. None the less, the incidence observed should compel investigators to evaluate further the prophylactic role of putative neuroprotectants such as amifostine or alternative regimens.

The non-haematological toxicities recorded in cohorts A and B suggest that their severity is linked to paclitaxel dose, rather than infusion duration. In addition, the lower initial and targeted paclitaxel dose in cohort B translated into somewhat less neutropenia, and decreased global use of G-CSF: fewer than one-third of patients in cohort B required G-CSF compared with more than half in cohort A, although the cycle-specific use was similar. There is concern, however, that the improved tolerance observed in cohort B may have been obtained at the cost of reduced efficacy. The overall response rate in cohort B at 27% was lower than the response rates observed in cohort A (55%) and in our original 24-h paclitaxel–carboplatin study (62%). This drop in response rate was observed despite a substantially higher percentage of patients in cohort B having better performance status or stage IIIb disease (29 versus 14%) compared with cohort A.

This difference suggests that initial dose intensity may translate into higher response rates for short infusion paclitaxel combinations; and it raises the question of whether comparable doses of paclitaxel given by longer infusion are more effective using response rate as a primary parameter. Conceivably, patient selection parameters, including investigator bias or reluctance to enrol patients or pretreatment weight loss, might have explained differences in outcome but there was absolutely no difference in eligibility criteria between the original 24-h study and our subsequent 1-h combination study. In addition, all patients at FCCC with advanced NSCLC who met eligibility criteria and who consented to enrolment were entered during the study period, except for the 4-month hiatus during which the trial was suspended and revamped. There is no way to accurately determine the percentage of patients at outside network institutions who might otherwise have been eligible, but who were not enrolled for reasons unrelated to inclusion criteria or because of investigator bias. We do not have access to their tumour registries, individual physician office records or their respective tumour boards, which would potentially give us a true denominator.

A randomised trial to distinguish a 62% response rate from a 27% response rate would require a minimum of 27 patients per arm to yield a type I error of 80% by two-sided test. However, the assessment of survival in the original 24-h study and in both cohorts of the 1-h study suggest minimal, if any, compromise in ultimate outcome (Table 5). Moreover, the confidence intervals of response rate in these relatively small phase II protocols clearly overlap. Many others have reported on the efficacy and relative safety of 3- or 24-h infusion paclitaxel in combination with carboplatin in advanced NSCLC. The results of these studies are updated in Table 7 [3,4,12–18].

The Eastern Cooperative Oncology Group has recently reported an update of a randomised trial of fixed dose cisplatin in combination with either etoposide, low-dose paclitaxel (135 mg/m^2/24 h) or high-dose paclitaxel (250 mg/m^2/24 h) with G-CSF support [1].

Table 7
Selected paclitaxel-CBDCA combinations: NSCLC

Centre (first author)	Phase	Paclitaxel[a] mg/m^2	Duration (h)	Interval (wks)	Carboplatin (CBDCA)[a] mg/m^2 or AUC	G-CSF	N (@MTD)	RR (%) at MTD	MS (wk)	1 YS
FCCC (Langer)	II	135→175→215[b]	24	(3)	AUC 7.5	(+)	54	62%	54	54%
Vanderbilt (Johnson)	I/II	135→175	24	(4)	300 mg/m^2→AUC 6	(−)	51 (23)	39%	38	32%
Maryland (Belani)	I/II	135→175→200[c]	24	(3)	AUC 5→7→9→11	(−/+)	30 (16)	56%	44	41%
									MTD	
USC (Natale)	I/II	150→250 (225)	3	(3)	AUC 6	51 (28)	(−)	61%	40+	38%
Colorado (Bunn)	I/II	135→225	3	(3)	250→400 mg/m^2	(−)	29	50%	ND	ND
Hopkins (Rowinsky)	I/II	175→225	3	(3)	AUC 7→9	(−)	23 (15)	47%	ND	ND
EORTC (Giaccone)	I/II	100–175	3	(4)	300→400 mg/m^2	(−)	19	5%	ND	ND
	I/II	>175–250	3	(4)	300→400 mg/m^2	(−)	30	20%	ND	ND

[a] Maximal tolerated doses (MTD) underlined.
[b] Intra-patient dose escalation (other studies escalated doses across separate patient cohorts).
[c] MTD determined first without, then with G-CSF support.
AUC, area under the concentration–time curve; G-CSF, granulocyte-colony stimulating factor; N, number enrolled; @MTD, number enrolled at MTD; RR, response rate; MS, median survival; 1 YS, 1-year survival rate; ND, not determined/unknown.

Both paclitaxel arms proved superior in terms of response rate and, evaluated together, yielded superior survival rates compared with the etoposide arm. Paclitaxel dose intensification, however, did not enhance outcome. However, similar studies in NSCLC formally comparing dose intensification with shorter paclitaxel infusions (1–3 h) have not yet been formally reported. The work of Akerley and others would suggest that initial dose density of short-infusion paclitaxel might translate into higher response rates and survival rates. Akerley observed a response rate of 54% and 1-year survival exceeding 50% in advanced NSCLC patients receiving paclitaxel 175 mg/m^2 weekly for 6 weeks [19], a dose intensity (525 mg/m^2/3 wk) 2- to 3-fold higher than that conventionally obtained with cyclic three weekly regimens. Others have employed lower doses of single-agent paclitaxel (50–100 mg/m^2) on a weekly basis and have observed lower response rates, but considerably less toxicity, in particular, decreased sensory neuropathy and myalgias/arthralgias [20–22].

Nor have investigators formally compared the relative utility of short versus long infusions in advanced NSCLC. This is an especially important issue since there are compelling preclinical data that demonstrate enhanced cytotoxicity in NSCLC cell lines with protracted infusion up to 96 h [23]. Thus, the underlying question of whether abbreviated paclitaxel infusion is better than or at least equivalent to protracted infusion in advanced NSCLC cannot yet be answered.

Criticism has been levelled at the somewhat unorthodox trial design which employed intrapatient dose escalation, rather than interpatient dose escalation across sequential cohorts. At the time this trial was designed and mounted, the combination of carboplatin and paclitaxel (1-h infusion) had not been studied. Because this study was multi-institutional, with both a research centre and its community affiliates participating, it was deemed impractical to mount a formal phase I study. Hence, patients acted as their own controls. Our goals were 2-fold: (1) to escalate paclitaxel in combination with full-dose carboplatin, toward its single-agent maximum tolerated dose (MTD) that is, into a dose range, which, as a single agent, had proven active; (2) to introduce appropriate safety precautions, by providing investigators an opportunity to stop paclitaxel dose escalation in specific individuals in order to prevent unacceptable, cumulative toxicity. This approach proved unsuccessful in cohort A, but fruitful in cohort B. 84% of pts in this cohort tolerated paclitaxel dose escalation to 215 mg/m^2 without untoward cumulative neurotoxicity. Certainly, one could argue that doses slightly higher than 215 mg/m^2 (e.g. 225 mg/m^2) might be reasonable, but the non-haematological toxicity observed in our trial was still substantial and would probably persuade clinicians to avoid paclitaxel doses much higher than the target dose of 215 mg/m^2 and carboplatin AUC of 7.5. Moreover, our technique using intrapatient dose escalation is not unprecedented: the same approach was instituted in our original 24-h paclitaxel–carboplatin study [3,4]. In both studies, nearly half the patients accrued came from community network affiliates. Despite the non-academic setting, patients were nearly always followed according to protocol: nadir blood counts were obtained on schedule; dose modifications were adhered to; and neither the quality of care, nor the quality of research reportage appeared to be adversely affected.

Based on our data, a formal phase II trial of fixed-dose paclitaxel 215 mg/m^2 and carboplatin (AUC 7.5) administered every 3 weeks could be mounted. Some concern has been raised about the three weekly cycle intervals, particularly if this regimen is to be evaluated further in phase II and phase III trials. An arbitrary decision to administer treatment at 4-week intervals would clearly reduce the dose intensity of paclitaxel and could potentially compromise treatment efficacy.

Table 8
1-h paclitaxel–carboplatin (CBDCA) in NSCLC: mature studies

First author [Ref.]	*n*	CBDCA	Paclitaxel	Cycle length (weeks)	Neuropathy (%)		Cytopenia grade 4 (%)		OR (%)	Median survival rate (months)	1 year survival rate (%)
					grade $\geqslant 1$	grade 3	ANC	Plts			
Langer A	22	7.5	175–>280	3	75	30	70	20	55	10.8	45
Langer B	35	7.5	175–>215	3	52	9	44	15	27	11.2	49
Evans [24]	35	6	175–225	3	53	15	NA	NA	29	6.5	31
Hainsworth [26]	155	6	255	3	–	15	NA	NA	36	8	40
Jagasia/De Vore [25]	63	6	175–200	4	41	NA	3	<1	25	7.7	–

n, number of patients; ANC, absolute neutrophil counts; plts, platelets; OR, overall response rate; NA, not determined.

Although cycle delays in cohort B were cumulative, only 20% of second and subsequent cycles were delayed for 1 week or more. Moreover, cooperative group randomised trials evaluating combination paclitaxel (3-h infusion) and carboplatin have routinely cycled this regimen at three weekly intervals without untoward toxicity [27,28]

Others have also investigated the combination of carboplatin and paclitaxel by 1-h infusion (Table 8). Evans and colleagues [24] observed a response rate of 29% in 35 evaluable pts receiving paclitaxel at a dose of 175 mg/m^2 in combination with carboplatin (AUC of 6) every 3 weeks. The paclitaxel dose was escalated to 225 mg/m^2 in the absence of grade $\geqslant 3$ granulocytopenia or grade $\geqslant 1$ thrombocytopenia, but only 19% of pts were able to have doses escalated to this level. Median time to progression was 3.4 months. Median survival was 6.5 months, and the 1-year survival rate 31%. Myelosuppression was minimal with only four episodes of febrile neutropenia during 131 treatment cycles. Grade 3 neuropathy occurred in 15%, a rate comparable with that observed in our lower dose cohort. Jagasia and colleagues have also reported the results of a phase II evaluation of paclitaxel 200 mg/m^2 over 1 h with carboplatin at an AUC of 6 at 4 weekly intervals [25]. 63 patients were accrued and the overall response rate was 25%, including three complete remissions. Median survival was 32.4 weeks. Myelosuppression was minimal. Grade 3 or 4 neutropenia occurred during only 3% of cycles in contrast to 47% of cycles during their previous experience with 24-h paclitaxel infusion. Neurotoxicity, however, occurred in 41% of patients versus only 7% in their previous study and myalgias and arthralgias in 28 versus 7%. A larger, multi-institutional phase II study orchestrated by Hainsworth and colleagues has tested the utility of paclitaxel at a higher fixed dose of 225 mg/m^2 over 1 h in combination with carboplatin at a lower calculated AUC of 6 every 3 weeks [26]. 155 pts have been accrued. The response rate to date is 36% including 3% CR. Median survival is 8 months and the 1-year survival rate 40%, with no apparent difference between stage IIIb and IV disease. Grade 3 neuropathy, however, has occurred in 15%, and it is not yet clear how many patients have been obligated to terminate therapy in the absence of disease progression because of non-haematological toxicity. This trial has completed accrual and will probably be reported fully in the near future. These data, once fully mature, will further elucidate the safety, efficacy and ultimate utility of 1-h paclitaxel in combination with carboplatin. Hainsworth and colleagues have already proceeded to add gemcitabine to the paclitaxel and carboplatin combination at doses of 225 mg/m^2 and AUC 6, respectively, and plan to launch a phase III study comparing paclitaxel (1-h) infusion and carboplatin, their reference regimen, to the three-drug combination are underway.

In summary, as delineated in our study, combination paclitaxel by 1-h infusion and carboplatin at a fixed targeted AUC of 7.5 is active and feasible in advanced NSCLC. Neurotoxicity, not myelosuppression, appears dose-limiting at paclitaxel doses exceeding 215 mg/m^2. Lower starting and targeted doses of paclitaxel are associated with lower response rates, but do not appear to adversely affect survival rates. Formal phase II testing of paclitaxel 215 mg/m^2/1 h and carboplatin (AUC 7.5) is indicated.

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