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Clinical report

Dose-finding study of paclitaxel and carboplatin in patients with advanced non-small cell lung cancer

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This dose-finding study was designed to determine the maximum tolerated dose (MTD), efficacy and toxicity of combined paclitaxel and carboplatin in 35 previously untreated patients with advanced non-small cell lung cancer (NSCLC). Paclitaxel was given as a 3-h infusion at escalating dose levels (100–250 mg/m^2) immediately followed by carboplatin as a 30-min infusion (325 or 350 mg/m^2) every 3 weeks. The dose-limiting toxicity, paresthesia, occurred at the highest dose level, therefore the recommended dose was established one level below (paclitaxel 225 mg/m^2 with carboplatin 325 mg/m^2). Neutropenia was the most common hematotoxicity; dose dependency was not apparent. Two patients, at different dose levels, had febrile neutropenia. Thrombocytopenia was rare. Non-hematological toxicities grade 3 or higher included infection, anorexia, alopecia and paresthesia. One patient had a hypersensitivity reaction (transient hypotension). The overall response rate was 23% and median survival time was 7.5 months. Promising activity and acceptable toxicity supports the development of this combination as a useful chemotherapeutic option in advanced NSCLC. [© 2000 Lippincott Williams & Wilkins.]

Key words: Carboplatin, dose finding, non-small cell lung cancer, paclitaxel, response rate, survival.

Introduction

Encouraged by single-agent paclitaxel achieving response rates of 21–24% and 1-year survival rates of up to 42% in non-small cell lung cancer (NSCLC),[1] combinations of paclitaxel with other agents of known activity in NSCLC are under extensive investigation. Indeed, phase II studies of combined paclitaxel and cisplatin have produced response rates of 35–47%,[2,3] and a three-arm comparative trial of low- or high-dose paclitaxel plus cisplatin versus a standard combination of etoposide plus cisplatin showed superior response and a trend towards improved survival in the paclitaxel–cisplatin arms.[4] However, the major dose-limiting toxicity (DLT) of this combination is neuropathy, which is both dose related and cumulative.

Response rates of single-agent carboplatin range from 12 to 20%,[5,6] with carboplatin-based combinations achieving response rates of 17–40%.[7,8] Importantly, however, carboplatin is a less toxic analog than its parent cisplatin, and has less nausea, vomiting, nephrotoxicity, ototoxicity and neurotoxicity associated with its administration.[7,8]

Combined paclitaxel and carboplatin in a phase II study of escalating doses of paclitaxel (135–215 mg/m^2 as a 24-h infusion) combined with a fixed dose of carboplatin (AUC 7.5) gave a response rate of 62% and a 1-year survival rate of 54%.[9] Interestingly, however, the DLT of myelosuppression observed for 24-h infusions of paclitaxel was significantly reduced with shorter infusion schedules over 1 or 3 h.[10–12] Also, there appears to be a dose–response effect, with greater anti-tumor activity observed for paclitaxel doses above 175 mg/m^2.[11,13]

This study was designed primarily to establish the maximum tolerated dose (MTD) of paclitaxel given as a 3-h infusion when combined with carboplatin, and, secondly, to determine the efficacy and toxicity of this regimen in previously untreated NSCLC.

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Patients and methods

Patient selection

Eligibility for entering this study required previously untreated, histologically proven NSCLC (stage IIIB or IV), relapsing or metastatic (local or distant) disease with at least one clinically and/or radiologically measurable lesion. Additional patient eligibility criteria included age of 18–75 years inclusive, WHO performance status $\leqslant 2$, life expectancy $\geqslant 12$ weeks, adequate bone marrow function (absolute neutrophil count $\geqslant 1500/\mu l$, platelet count $\geqslant 100\,000/\mu l$), adequate liver function (total bilirubin level $\leqslant 1.25$ times normal), and adequate renal function (serum creatinine $\leqslant$ normal upper limit). Patients with a psychiatric condition, a history of cardiac disease (arrhythmias, congestive heart failure, myocardial infarction in previous 6 months, second- or third-degree heart block), motor or sensory neurotoxicity (WHO grade 2 or greater) were not eligible. Further criteria for exclusion were an additional malignant disease during the previous 5 years, a documented gastrointestinal ulcer in the previous 6 months, any active infection or a co-existing medical condition. During the study other anticancer drugs, hormonal agents, corticosteroids or immunotherapy were prohibited. Women of childbearing potential had to use adequate contraception during treatment and those who were pregnant or lactating were excluded. Investigations before treatment included a medical history, physical examination, electrocardiogram (ECG), laboratory data (including white blood cell count with differential and platelet count, electrolytes, liver function tests and serum creatinine), radiological disease assessment (chest X-ray and, according to sites, site-specific X-ray, ultrasound, computed tomography or magnetic resonance imaging) and bronchoscopy. All patients gave informed consent and the study was approved by local ethical standard committees.

Treatment

Initially, paclitaxel was administered at a dose of 100 mg/m^2 as an i.v. infusion over 3 h, followed immediately by carboplatin at a dose of 325 mg/m^2 as an i.v. bolus infusion over 30 min. Treatment was repeated every 3 weeks (or upon full hematologic recovery). Eight dose levels of paclitaxel were planned (100, 125, 150, 175, 200, 225, 250 and 250 mg/m^2) concurrent with two dose levels of carboplatin (325 mg/m^2 for the first seven levels of paclitaxel and 350 mg/m^2 for the final level). Treatment modifications were based on hematologic and non-hematologic toxicity. All patients received premedication with prednisolone 130 mg given orally at 12 and 6 h before the paclitaxel infusion, and dexchlopheniramine 5 mg and cimetidine 300 mg both given i.v. 30 min before the paclitaxel infusion. Antiemetics were administered as required. Patients were treated for at least three cycles. Treatment was continued further depending on tumor response and stopped after three supplemental cycles following stable disease documentation or maximal disease response, unless the patient or investigator chose otherwise or toxicity became intolerable.

A physical examination preceded every treatment and tumor sites were assessed by physical examination every week and by imaging and bronchoscopy, if required, every three cycles. Laboratory data were collected on the first day of each cycle and twice a week for hematology, and, generally, once a week for biochemistry. An ECG was repeated when clinically indicated. Hypersensitivity reactions were recorded and adverse events were evaluated according to WHO criteria.

DLT and MTD

The DLT was defined as any one of the following: absolute neutrophil count $<500/\mu l$ for more than 7 days, absence of recovery of neutrophils (i.e. absolute neutrophil count $\leqslant 1500/\mu l$) or platelets ($<100\,000/\mu l$) at day 35, any febrile neutropenia (i.e. temperature $\geqslant 38.2^{\circ}C$, and neutrophil count $<500/\mu l$ requiring antibiotics and hospitalization), thrombocytopenia (WHO grade 4), mucositis WHO grade $\geqslant 3$ for more than 7 days, and non-hematological toxicity WHO grade $\geqslant 3$ or persistent grade $\geqslant 2$ (excluding alopecia grade 3 or 4, vomiting grade 3 and musculoskeletal pain grade 3).

Three patients were included at each dose level. In the presence of DLT in one patient, at least six patients were to be entered at that dose and at all future dose levels. If two or more of the six patients developed DLT in the first cycle of a given dose level then we considered the MTD to have been reached and this dose level was not used thereafter.

Response evaluation

All patients who received at least two courses of paclitaxel treatment were evaluated for a response. A complete response was defined as the disappearance of all measurable disease, signs, symptoms and chemical changes related to the tumor that lasted for at least 4 weeks without the appearance of new disease. A partial response was defined as a decrease of

at least 50% in the tumor size (the sum of the products of the perpendicular diameters of measured lesions) for at least 4 weeks without the appearance of new lesions. Stable disease was defined as a regression of measurable disease less than that of a partial response and no progression for at least 4 weeks. Progressive disease or relapse was defined as an increase of at least 25% in the product of two perpendicular diameters or the appearance of new lesions.

Statistical considerations

To estimate the MTD, six patients were to be entered at the toxic dose and at all future dose levels. It was anticipated, therefore, that 25–30 patients should be entered into the trial and 12 months would be required to complete the study. Estimation of the MTD was a primary evaluation. Secondary analyses were response rates, time to response and duration of response, time to progression, and overall survival time. All patients who received at least two courses of paclitaxel and those patients who developed rapid tumor progression after at least one course of therapy were considered evaluable for response. The time to response was calculated from the first day of treatment to the date of first observation of response. The duration of response in responding patients was measured from the first day of treatment to the date of first observation of progressive disease. The time to progression was defined as the time between the first day of treatment and the date of the first observation of progression. All were estimated using the Kaplan–Meier product limit method. The 95% confidence intervals for medians of time to progression and survival time were calculated using the method of reflected intervals.

Retrospectively, the AUC of carboplatin was calculated based on the Cockroft formula and the Chatelut formula.[14,15] Comparisons, by the method of analysis of variance, were made between responders and non-responders, and between patients with and without hematological toxicity.

WHO criteria were used in all patients to assess toxicity and adverse events (nature, severity and duration) from the time of the first dose of paclitaxel.

Results

Patient characteristics

Thirty-five patients, mainly male (91%), entered the study (Table 1). Most of the patients (94%) had a good performance status (WHO grade 0 or 1), stage IIIB or IV disease (97%) and histologically proven adenocarcinoma or squamous cell carcinoma (83%). Two patients showed violations of the study inclusion criteria (operable stage IIIA disease in one patient and history of cardiac disorders in a further patient) but their data were not excluded.

Treatment administration

The number of patients entered at each dose level and the number of cycles administered at each dose level is shown in Table 2. At dose levels 1 and 4, it was necessary to include a fourth patient because one patient in these levels did not receive the second course within 21 days (due to grade 3 abdominal pain/fever in one patient, and convulsions in a second patient). At each of dose levels 6, 7 and 8, six patients were entered because one patient had a DLT (neutropenia) at dose level 6. A total of 160 treatment

Table 1. Patient characteristics

Characteristic	No. of patients (%)
Total number entered	35
male	32 (91)
female	3 (9)
Age (years)	
median	56.0
range	37–70
WHO performance status	
0	10 (29)
1	23 (66)
2	2 (6)
Histology	
squamous cell	14 (40)
adenocarcinoma	15 (43)
large cell	6 (17)
Stage	
IIIA	1 (3)
IIIB	13 (37)
IV	19 (54)
metastatic relapse	2 (6)

Table 2. Number of patients and cycles by dose level

Dose levels	No. of patients	No. of cycles [Median (range)]
1	4	2.5 (2–6)
2	3	2.0 (1–4)
3	3	8.0 (4–10)
4	4	4.5 (3–9)
5	3	8.0 (4–9)
6	6	4.0 (2–9)
7	6	4.5 (1–9)
8	6	3.0 (1–6)
All	35	4.0 (1–10)

cycles were administered. All 35 patients received at least one cycle of treatment and the median number of cycles was 4 (range 1–10); four patients received one cycle, 19 patients received at least four cycles and 13 patients received at least six cycles. Treatment dose was reduced in six cycles, delayed in 28 cycles, and both modified and delayed in four cycles.

Treatment toxicity

Hematologic toxicities at each dose level are shown in Table 3. Although, the most common hematologic toxicity (grade 3 or 4) was neutropenia (64 cycles, 40%), there was no obvious dose-related effect (Figure 1). Grade 4 thrombocytopenia was absent, but grade 3 was reported in six cycles (4%). Twelve patients had fever, including two with febrile neutropenia; one patient for 4 days following the first cycle at dose level 6 (together with grade 3 infection) and one patient for 2 days following the first cycle at dose level 8.

Major non-hematological toxicities were infection, anorexia, alopecia and peripheral neurotoxicity (paresthesia); however, none occurred at grade 4 and their incidence at grade 3 is shown in Table 4. Other grade 3 toxicities included cardiac failure in one patient, cardiac arrhythmia in one patient and dyspnea in three patients. Additional adverse events were mostly of mild or moderate intensity, and included mucositis (one patient), fatigue (one patient), pain (arthralgia in eight patients, myalgia in five patients) and nausea/vomiting (10 patients). One patient had a hypersensitivity reaction at the highest dose level (i.e. paclitaxel 250 mg/m^2 and carboplatin 350 mg/m^2). The reaction was transient hypotension (for 25 min at cycle 4).

Table 3. Hematologic toxicity (WHO grade 3 or 4)

Dose levels	No. of cycles	No. (%) of cycles			
		Neutropenia	Anemia	Thrombocytopenia	Febrile Neutropenia
1	13	1 (0.6)	1 (0.6)	0	0
2	7	0	0	0	0
3	22	13 (8.2)	0	1 (0.6)	0
4	20	11 (6.9)	6 (3.8)	1 (0.6)	0
5	21	11 (6.9)	1 (0.6)	1 (0.6)	0
6	31	12 (7.5)	3 (1.9)	2 (1.3)	1 (0.6)
7	26	7 (4.4)	1 (0.6)	1 (0.6)	0
8	19	9 (5.7)	1 (0.6)	0	1 (0.6)
Total cycles (%)	159[a]	64 (40.3)	13 (8.2)	6 (3.8)	2 (1.3)
Total patients (%)	35	16 (45.7)	8 (22.9)	6 (17.1)	2 (5.7)

[a]Total number was 159 (not 160) because one patient had no hematology assessment at cycle 2.

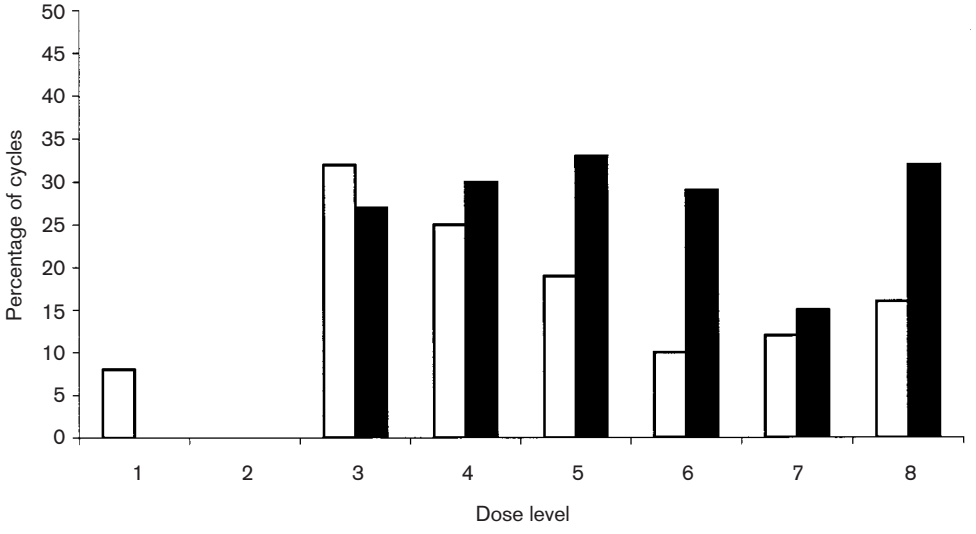

Figure 1. Percentage of cycles with grade 3 (□) and grade 4 (■) neutropenia at all dose levels.

Table 4. Non-hematologic toxicity (WHO grade 3, no grade 4 events were recorded)

Dose levels	No. of patients	No. (%) of patients			
		Infection	Anorexia	Alopecia	Paresthesia
1	4	0	0	0	0
2	3	0	0	0	0
3	3	0	0	2 (5.7)	0
4	4	0	0	3 (8.6)	0
5	3	0	1 (2.9)	2 (5.7)	0
6	6	1 (2.9)	0	4 (11.4)	0
7	6	0	0	3 (8.6)	0
8	6	1 (2.9)	0	4 (11.4)	3 (8.6)
Total patients (%)	35	2 (5.7)	1 (2.9)	18 (51.4)	3 (8.6)

DLT and MTD

During cycle 1, there were two DLTs. Both these patients had febrile neutropenia, as described earlier, but at different dose levels and therefore not satisfying the criteria for the MTD. Three out of six patients at dose level 8 experienced the DLT, paresthesia, although not in the first cycle of treatment.

Treatment response, time to progression and survival

Of 35 enrolled patients, 34 were evaluable for response (one patient had surgery after one cycle of treatment). The overall response rate was 23% (eight of 35) [95% confidence interval (CI): 10–40]. There were no complete responders. Partial response only occurred with paclitaxel doses of at least 175 mg/m^2 (the generally accepted minimum active dose with the 3-h perfusion) (Table 5). Of patients receiving paclitaxel doses of 175 mg/m^2 or more, the partial response rate was 32% (eight of 25) [(95% CI): 15–53]. The median time to response was 62 days (range 39–124) and the median response duration was 460 days (range 155–813). Six patients had a response duration of at least 348 days. Of these patients, one was in remission for more than 4 years. The median time to progression was 85 days (95% CI: 63–155). Figure 2 shows the overall survival for all patients (Kaplan–Meier method). The median survival time was 7.5 months.

AUC of carboplatin

The median AUC in patients receiving carboplatin at a dose of 325 mg/m^2 was 4.2 mg/ml·min (Chatelut formula). Responders had a larger median AUC than non-responders [6.2 (range 4.0–7.4) versus 4.8 (range 3.1–7.7) mg/ml·min (Cockroft formula, p=0.017); 5.1 (range 2.7–5.7) versus 3.7 (range 2.2–6.0) mg/ml·min (Chatelut formula, p=0.036)]. Patients with hematological toxicity had a larger median AUC than patients without haematological toxicity [5.4 (range 3.8–7.7) versus 4.6 (range 3.1–5.6) mg/ml·min (Cockroft formula, p=0.012); 4.3 (range 2.7–6.0) versus 3.7 (range 2.2–4.9) mg/ml·min (Chatelut formula, p=0.051)].

Discussion

Paclitaxel has emerged over the past few years as a significant new agent in the chemotherapeutic treatment of NSCLC and recent effort has focussed on developing combinations of paclitaxel with other agents of known activity in NSCLC.

This dose-finding study was designed to investigate the MTD of paclitaxel given as a 3-h infusion combined with carboplatin in patients with advanced NSCLC. Even though the MTD was not reached after the first cycle at any dose level, in subsequent cycles dose-limiting neurological toxicities (paresthesia) were observed in three out of six patients at the highest dose level (paclitaxel 250 mg/m^2 and carboplatin 325 mg/m^2). Consequently, our study recommends a dosing schedule of paclitaxel 225 mg/m^2 combined with carboplatin 325 mg/m^2 every 3 weeks. These doses are consistent with previous studies that proposed paclitaxel doses of 200–225 mg/m^2 as 1- or 3-h infusions combined with carboplatin AUC 6 or 7,[16–18] and a recent study suggesting a schedule of paclitaxel 225 mg/m^2 as a 3-h infusion and carboplatin 375 mg/m^2 every 4 weeks.[19]

Although neutropenia grade 3 or 4 was common in this study, occurring in 40.3% of cycles and 45.7% of patients, there was no evidence of a dose-related effect. However, this incidence was higher than that previously reported in another dose-finding study

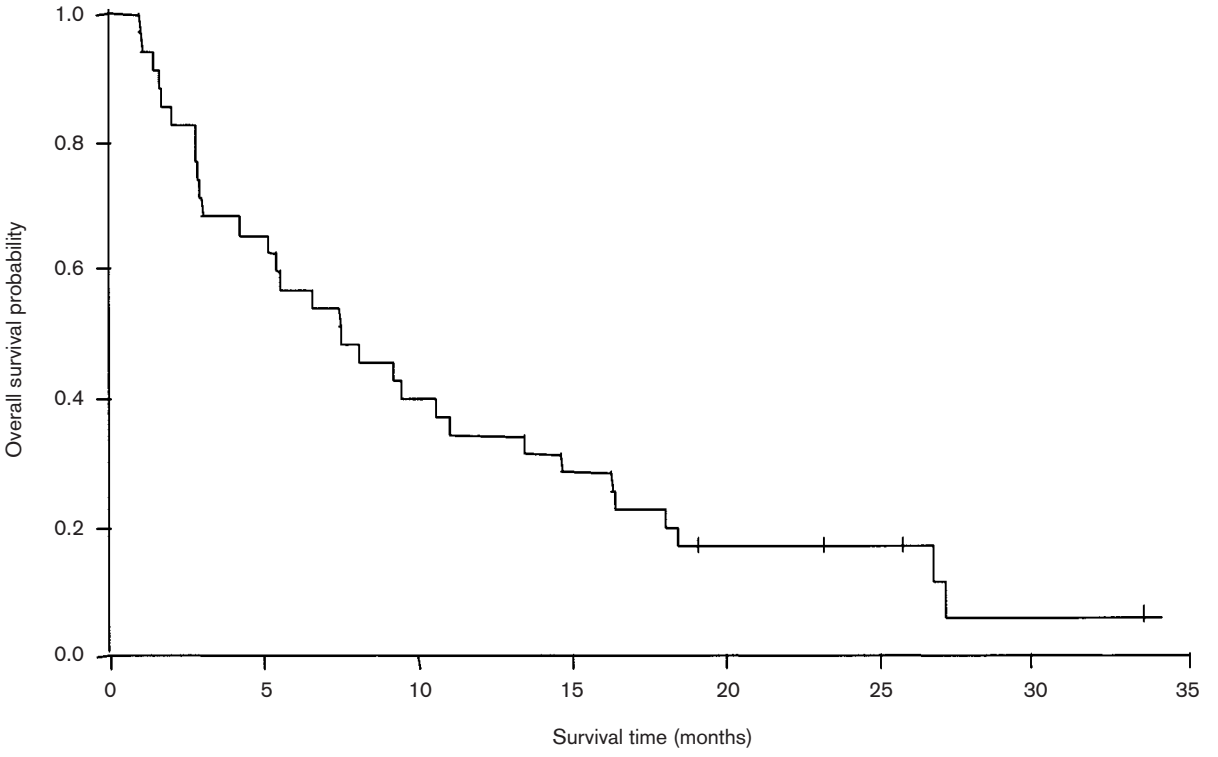

Figure 2. Survival time.

Table 5. Tumor response

Dose levels	No. of patients	No. (%) of patients			
		Partial response	Stable disease	Disease progression	Not evaluable
1	4	0	1 (2.9)	3 (8.6)	0
2	3	0	1 (2.9)	2 (5.7)	0
3	3	0	3 (8.6)	0	0
4	4	1 (2.9)	1 (2.9)	2 (5.7)	0
5	3	1 (2.9)	2 (5.7)	0	0
6	6	2 (5.7)	2 (5.7)	2 (5.7)	0
7	6	1 (2.9)	3 (8.6)	1 (2.9)	1 (2.9)
8	6	3 (8.6)	0	3 (8.6)	0
Total patients (%)	35	8 (22.9)	13 (37.1)	13 (37.1)	1 (2.9)

where grade 3 and 4 episodes were rarely observed and none lasted longer than 48 h.[19] The incidence of thrombocytopenia was comparatively low in our study, consistent with other reports,[20,21] although thrombocytopenia has been absent with some schedules.[19] Interestingly, it appears that paclitaxel is able to diminish the thrombocytopenia associated with carboplatin by exerting a platelet-protective effect.[13,21]

Neurotoxicity is usually regarded as a problem when paclitaxel is administered over a short infusion time and may be accentuated in combinations with platinum analogs.[18] However, in this study, grade 3 neurotoxicity occurred in only three (8.6%) patients at the highest dose level and no grade 4 symptoms were observed. An earlier dose-finding study found that grade 3 peripheral neuropathy occurred consistently after the second or third cycle of paclitaxel 225 and 235 mg/m^2 given as 3-h infusion.[19] A further study of paclitaxel 225 mg/m^2 as a 1-h infusion followed by carboplatin dosed to an AUC of 6, resulted in grade 3 neurotoxicity in 15% of patients, with 12% of patients discontinuing treatment.[18] The authors of this study

maintained that the problem of neurotoxicity associated with shorter infusions was outweighed by decreased myelosuppression and the ease of administration. Furthermore, they suggested that the development of neurotoxicity may be partially alleviated by reducing the paclitaxel dose from 225 mg/m^2 to 200 mg/m^2. Our results support this proposal as grade 3 or 4 neurotoxicity was not seen at dose levels below 225 mg/m^2. Indeed, a study of paclitaxel 175 mg/m^2 as a 3-h infusion combined with carboplatin dosed at an AUC of 7 only reported grade 1 or 2 neurotoxicity in 30 and 3% of patients, respectively.[20]

Among other non-hematological toxicities, the incidence of alopecia (51.4% of patients) was the most noticeable. Nausea and vomiting were well controlled by antiemetics and no grade 3 or 4 incidences were reported. Following prophylactic medication, only one patient in the present study had a hypersensitive reaction (transient hypotension).

With respect to efficacy, the overall response rate in our study was 23%. However, paclitaxel doses of under 175 mg/m^2 are considered suboptimal,[11] and when the response was considered at doses above 175 mg/m^2, the response rate rose to 32%. Not unexpectedly, although responders had higher AUC for carboplatin compared with nonresponders, they were more likely to experience hematological toxicity. The median duration of response was 460 days and the median survival time was 7.5 months. Other studies of combined paclitaxel and carboplatin have reported response rates of 27.3–63% and median survival times of 8.95–13.25 months.[9,17–20] These response rates appear to be independent of dosing schedule since similar responses have been reported with both 24-h infusions, and shorter, 1- and 3-h, infusions.[10,13]

Conclusion

This dose-finding study of paclitaxel given as a short 3-h infusion combined with carboplatin in advanced NSCLC established the recommended doses as paclitaxel 225 mg/m^2 followed by carboplatin 325 mg/m^2 every 3 weeks. Promising activity and acceptable toxicity supports the development of this combination as a feasible chemotherapeutic option in advanced NSCLC.

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