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ORIGINAL ARTICLE

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Phase I and pharmacokinetic study of carboplatin and paclitaxel with a biweekly schedule in patients with advanced non-small-cell lung cancer

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Abstract *Purpose*: A phase I study was conducted to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of carboplatin in combination with paclitaxel using a biweekly schedule in patients with advanced non-small-cell lung cancer (NSCLC). *Patients and methods*: The pharmacokinetics of paclitaxel were determined preliminarily in some patients. The criteria for eligibility for study entry included histologically and/or cytologically confirmed NSCLC (stage IIIb or IV), no prior treatment, and measurable disease. Paclitaxel was given in combination with a fixed dose of carboplatin at an area under the concentration-time curve (AUC) of 3 mg/ml·min, every 2 weeks. The starting dose of paclitaxel was 100 mg/m^2, and the dose was increased in increments of 20 mg/m^2. Three to six patients were allocated to each dose level. *Results*: A total of 19 patients (11 male and 8 female) with a median age of 61 years (range 43–74 years) and a median ECOG performance status of 0 (range 0–1) were enrolled. The MTD of paclitaxel proved to be 160 mg/m^2, and the DLT was neutropenia, which improved well following treatment with G-CSF. Gastrointestinal toxicity was well tolerated. Of 17 patients who received four cycles or more, 7 (41%; 95% confidence interval 18.4–67.1%) responded to this combination therapy. The pharmacokinetics of paclitaxel did not differ from published data. *Conclusions*: The recommended dose for phase II study is paclitaxel 140 mg/m^2 with a carboplatin AUC of 3 mg/ml·min. This biweekly regimen is highly effective and acceptable, and the present data indicate that the regimen may be suitable for use on an outpatient basis.

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Introduction

Several chemotherapeutic agents have been demonstrated to be effective in patients with non-small-cell lung cancer (NSCLC). According to the guidelines established by the American Society of Clinical Oncology (ASCO), platinum-based chemotherapies are recommended for the treatment of metastatic NSCLC [1]. Based on a survey carried out in the US [22], combination chemotherapy using carboplatin and paclitaxel is the most favored option for medical oncologists and the most widely used regimen. This is mainly because carboplatin shows no nephrotoxicity, neurotoxicity or ototoxicity, and provokes much less emesis than cisplatin. Moreover, this combination has the advantage of a low incidence of thrombocytopenia.

In several previous studies using the combination of carboplatin and paclitaxel, paclitaxel was given by intravenous (i.v.) infusion for 1, 3 or 24 h at doses ranging between 135 and 225 mg/m^2 every 3 weeks, with carboplatin injected at a target area under the concentration time curve (AUC) ranging between 5 and 7.5 mg/ml·min (mainly 6 mg/ml·min) [2, 4, 6, 7, 8, 10, 11, 14, 19, 20]. The combination of carboplatin and paclitaxel has been shown to possess antitumor activity in patients with advanced NSCLC and to be a well-tolerated regimen. However, it has been reported that some patients require unanticipated hospitalization due to intolerable adverse events [4, 6, 7, 8, 10, 19].

Based on these considerations, we conducted a phase I study of the combination of carboplatin and paclitaxel with a biweekly schedule in outpatients with advanced and untreated NSCLC to determine the maximum tolerated dose (MTD) of paclitaxel. Additionally, the pharmacokinetics of paclitaxel were investigated in some patients.

Patients and methods

Eligibility

Patients with stage IIIb and IV NSCLC, no prior treatment, an ECOG performance status of 0 to 2, and a life expectancy greater than 12 weeks, were enrolled in the study (Table 1). The patients were aged between 18 and 75 years, had measurable or evaluable disease, and were required to have adequate bone marrow, hepatic, and renal functions, defined as a white blood cell count of ≥4,000/μl, hemoglobin ≥9.5 g/μl, a platelet count of ≥100,000/μl, bilirubin ≤ 1.5 mg/dl, aspartate aminotransferase not more than twice the upper limit of normal, and serum creatinine ≤ 1.5 mg/dl. Patients were excluded if they had significant cardiac disease, active infection, symptoms of brain metastases, diarrhea, pulmonary fibrosis, massive pleural effusion, a past or current history of other malignancy, or were pregnant. Finally, the study protocol was approved by the ethics committee of Kurume University School of Medicine, and written informed consent was obtained from the patients before initiation of treatment.

Treatment plan

Paclitaxel was administered in combination with a fixed dose of carboplatin (AUC 3 mg/ml·min) on day 1. The dose of carboplatin was calculated using the Calvert formula: dose (mg) = target AUC×(GFR + 25) [5]. The GFR (glomerular filtration rate, in milliliters per minute) was estimated from the creatinine clearance calculated the formula of Jelliffe [13]. As shown in Table 2, the dose of paclitaxel was increased in increments of 20 mg/m^2 from 100 to 160 mg/m^2. There was no dose escalation in individual patients. Paclitaxel dissolved in 500 ml 0.9% saline was administered i.v. over 90 min followed by carboplatin infused i.v. over 60 min. Treatment cycles were repeated every 2 weeks for a planned maximum of eight cycles, unless the patient had progressive disease or developed intolerable toxicity. Patients with stable disease (SD) or who demonstrated a response to therapy were continued on therapy. All patients were premedicated with dexamethasone (15.2 mg i.v.), ranitidine (50 mg i.v.), and diphenhydramine (50 mg). A 5-HT3 receptor antagonist was administered before chemotherapeutic treatment. Granulocyte colony-stimulating factor (G-CSF, 2 μg/kg) was administered subcutaneously to patients who developed grade 4 neutropenia, but it was not routinely used during subsequent cycles. When a patient experienced grade 4 neutropenia lasting 4 days or more despite G-CSF treatment, the dose was reduced. Paclitaxel was reduced by 20 mg/m^2 at a time. Patients who experienced grade 2 or more allergic reactions to paclitaxel were removed from the study.

Dose-limiting toxicity (DLT) was evaluated during the first four cycles of treatment at each dose level. DLT was defined as grade 4 leukopenia or neutropenia lasting 4 days or more despite G-CSF treatment, grade 4 thrombocytopenia, and grade 3 or greater non-hematological toxicities. When the treatment had to be postponed for more than 8 days from the scheduled date for reasons such as leukopenia, this was also defined as a DLT. Anemia, alopecia, nausea and vomiting were excluded from the adverse effects to be considered in the evaluation of intolerance. If none of the three patients who had been originally allocated to a dosage level experienced DLT, the dose of paclitaxel was increased to the next level. If one of the three patients experienced DLT at that level, three additional patients were enrolled for the further evaluation of toxicity. If two of three patients experienced DLT at that level, that dose was defined as the MTD.

Pretreatment evaluation included medical history, physical examination with assessment of performance status, chest radiography, computed tomography (CT) scan of the chest, bronchoscopy, brain magnetic resonance imaging (MRI) or CT, abdominal CT, bone scintigraphy, complete blood cell count, biochemical analysis of serum, urinalysis, ECG and pulmonary function test. All pretreatment imaging procedures were performed within 2 weeks of enrollment. Physical examination together with the evaluation of performance status, chest radiography, serum chemistry analysis and urinalysis were performed at least once a week. A complete blood cell count was obtained at least twice a week. The indicator lesion was measured by CT scan every two cycles. Toxicity was evaluated according to the WHO criteria [24]. Although formal quality of life assessment was not included in this study, disease or treatment-related symptoms and performance status were recorded in all patients.

Patients were considered to be evaluable for response if they had received at least four full cycles of the protocol. Complete response (CR) was defined as the complete disappearance of all known disease for at least 4 weeks. Partial response (PR) was defined as a ≥50% reduction in the sum of the length-width products of measurable lesions for at least 4 weeks. Progressive disease (PD) was defined as a ≥25% increase in the sum of the products of all indicator lesions, reappearance of any lesion that had disappeared, or appearance of any lesion. Stable disease (SD) was defined as any situation that did not qualify as response or progression.

Pharmacokinetics

Heparinized blood samples for the pharmacokinetic study were obtained before and at the end of the infusion, and at 0.5, 1, 3, 6, 12, 24 and 48 h after completion of the infusion on day 1 during the first cycle. Plasma was separated, and samples were stored below −20°C until analysis. Plasma concentrations of paclitaxel

Table 1 Patient characteristics (values are number of patients, except age in years)

No. of patients	
Total	19
Male	11
Female	8
Age (years)	
Median	61
Range	43–74
Performance status (ECOG)	
0	12
1	7
Histology	
Adenocarcinoma	16
Squamous cell carcinoma	3
Stage	
IIIb	2
IV	17

Table 2 Dose levels and DLTs

Level	No. of patients	Paclitaxel (mg/m^2)	Carboplatin AUC	DLT (first four cycles)
1	3	100	3	–
2	7	120	3	Grade 3 hepatic toxicity (one patient)
3	6	140	3	Grade 4 neutropenia lasting 4 days (one patient)
4	3	160	3	Grade 4 neutropenia lasting 4 days (two patients)

were determined by high-performance liquid chromatography (HPLC) according to the method of Grem et al. [9] with modification developed by Sumikin Bio-Science (Sagamihara City, Kanagawa, Japan). The pharmacokinetic parameters of paclitaxel were determined by the non-compartmental method.

Results

Patient characteristics

From March 2000 to April 2001, 19 patients participated in this study. The characteristics of the patients are shown in Table 1. Consequently, no patient with a performance status of 2 was enrolled, although all patients were eligible for the study.

Dose escalation

The schedule for dose increases and the observed DLTs are presented in Table 2. One of three patients at dose level 2 experienced a hypersensitive reaction (grade 3 rash). As the rash occurred during the infusion of paclitaxel in the first cycle, paclitaxel infusion was discontinued and this patient was removed from the study. However, it was considered that this toxicity might not have been due to the increased dose of paclitaxel. Another patient was then added for the treatment with paclitaxel at this level. At dose level 4, two of three patients experienced DLT, suggesting this level to be the MTD. Therefore, dose level 3 was recommended as an optimal dose of this regimen for the phase II study.

Toxicity

Hematological toxicities are summarized in Table 3. A complete blood cell count was performed three times a week in all patients. A major adverse event was neutropenia, and eight patients experienced grade 4 neutropenia between day 10 and day 13, but no patients experienced neutropenic fever. Although five of eight patients with grade 4 neutropenia recovered within 4 days using G-CSF, two of those five patients required a treatment delay of 4 and 5 days. Accordingly, these events were not DLT. However, one patient at level 3 and two patients at level 4 experienced grade 4 neutropenia lasting 4 days despite G-CSF treatment, which was considered to be DLT. One of them required a treatment delay 10 days into the next schedule. Thus, it appeared that this adverse event of neutropenia might be a dose-related phenomenon. However, anemia and thrombocytopenia were very mild.

Non-hematological toxicities are summarized in Table 4. There were no patients with grade 3/4 nausea and vomiting. Only one patient at level 2 (paclitaxel dose 120 mg/m^2) experienced grade 2 neuropathy after four cycles, which was not cumulative. No other patients experienced neuropathy during or after the study. A grade 3 elevated transaminase activity was observed in one patient at level 2, and the patient was withdrawn from the study after two cycles. This toxicity was considered to be a DLT. One patient experienced a grade 3 hypersensitive reaction (rash). Other non-hematological toxicities were very mild. There were no treatment-related deaths.

Treatment delivery

A total of 105 cycles of chemotherapy were administered with a median of 6 cycles (range 1–8). One patient received only one cycle of therapy due to grade 3 rash, another received two cycles of therapy due to grade 3 liver dysfunction, and 17 patients were treated for four or more cycles. Three cycles required treatment delay on

Table 3 Hematologic toxicity per patient during the first four cycles

Level	No. of patients	Leukopenia			Neutropenia			Thrombocytopenia		
		grade			grade			grade		
		2	3	4	2	3	4	2	3	4
1	3	1	1	0	1	2	0	0	0	0
2	7	5	1	0	1	2	3	0	0	0
3	6	4	2	0	1	2	3	0	0	0
4	3	1	2	0	0	1	2	0	0	0

Table 4 Non-hematologic toxicity per patient during all cycles

Level	No. of patients	Nausea/vomiting (grade)			AST/ALT (grade)			Neurotoxicity (grade)			Allergy (grade)		
		2	3	4	2	3	4	2	3	4	2	3	4
1	3	0	0	0	0	0	0	0	0	0	0	0	0
2	7	1	0	0	0	1	0	1	0	0	0	1	0
3	6	0	0	0	0	0	0	0	0	0	0	0	0
4	3	0	0	0	0	0	0	0	0	0	0	0	0

day 1 because of unresolved neutropenia (4, 5, and 10 days).

Response

Of 17 patients with measurable diseases who received at least four cycles of chemotherapy and were evaluable for response, 7 (41.2%) achieved a PR (95% CI 18.4–67.1%), 9 (52.9%) showed stable disease (SD), and one showed progression of disease during treatment.

Pharmacokinetics

The pharmacokinetics of paclitaxel were investigated using the blood samples from only 14 patients because of refusal by 5 patients. The pharmacokinetic parameters of paclitaxel are listed in Table 5. Marked interpatient variation was observed at each dose level. Although Cmax and AUC of dose level 1 tended to be low, there were no significant differences in these parameters among dose levels 2, 3 and 4. Plasma concentration-time curves for the four doses of paclitaxel are shown in Fig. 1.

Discussion

The present study was conducted to determine the feasibility of administering paclitaxel in a biweekly schedule combined with a fixed dose of carboplatin to patients with advanced NSCLC. The MTD of paclitaxel was determined to be 160 mg/m^2. It has been shown in several other studies that combination therapy with carboplatin and paclitaxel is efficacious and well tolerated. Recently, an ECOG randomized clinical trial comparing three ''cisplatin-plus-a-new agent (paclitaxel, gemcitabine, docetaxel)'' regimens with a carboplatin/paclitaxel regimen showed no significant differences either in the response rate or in the survival rate among the four arms [21]. However, the carboplatin/paclitaxel regimen was associated with less toxicity and was tolerated better than the other ''cisplatin-plus-a-new agent'' regimens. A SWOG randomized trial showed similar results [18]. These groups consistently concluded that the carboplatin/paclitaxel regimen should be the reference arm in future studies. In Western countries, the regimen with paclitaxel 200–225 mg/m^2 infused over 3 h and carboplatin at an AUC of 6 mg/ml·min has been the most extensively evaluated and it is an approved schedule for clinical use. According to previous phase I or II studies of this regimen, the most frequent grade 4 toxicity was neutropenia which is dose-related [17]. Furthermore, about 7–13% patients require unanticipated hospitalization due to neutropenic fever and grade 1 or greater neuropathy which occurs in 30–60% of the patients [4, 6, 7, 8, 10, 11, 14, 19].

In the present phase I study, the regimen was modified to a biweekly schedule to facilitate outpatient administration. Hematological toxicity was moderate. Of 19 patients, 8 (42%) experienced grade 4 neutropenia. However, the duration of grade 4 neutropenia was 2 to 4 days, and there were no patients with neutropenic fe-

Table 5 Mean (range) pharmacokinetic parameters of paclitaxel: first cycle (*Cmax* maximum plasma concentration, $T_{1/2}$ half-life, *Vdss* volume of distribution at steady state, *CL* total clearance, *AUC* area under the concentration time curve)

Level	No. of patients	Dose (mg/m^2)	Cmax (ng/ml)	$T_{1/2}$ (h)	Vdss (l/kg)	CL (l/h/kg)	AUC (ng·h/ml)
1	2	100	1460 (1140–1780)	16.9 (15.7–18.0)	0.25 (0.19–0.30)	0.021 (0.016–0.025)	5194 (4043–6345)
2	5	120	3598 (2300–4940)	14.8 (12.0–18.1)	0.12 (0.09–0.15)	0.013 (0.010–0.018)	9948 (6576–12522)
3	5	140	3550 (2790–5360)	18.6 (15.9–22.3)	0.17 (0.12–0.21)	0.017 (0.011–0.026)	8912 (7604–13057)
4	2	160	3965 (2440–5490)	19.4 (17.5–21.2)	0.20 (0.11–0.29)	0.019 (0.012–0.025)	9233 (5488–12978)

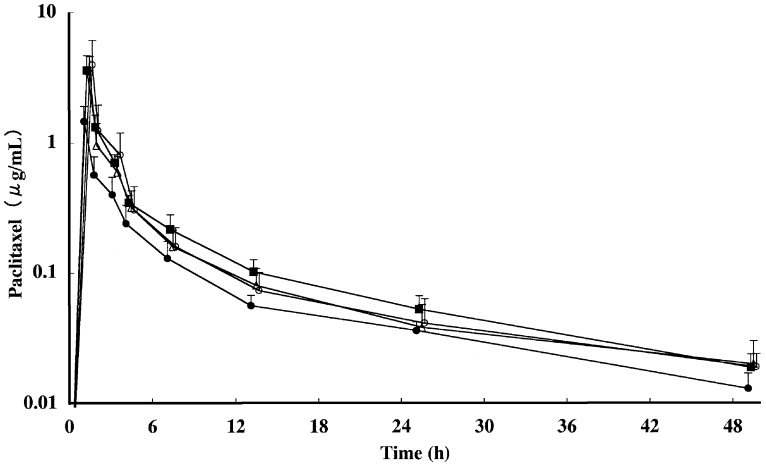

Fig. 1 Paclitaxel plasma concentration-time curves in patients treated at four different dose levels: 100 mg/m^2 (●), 120 mg/m^2 (■), 140 mg/m^2 (△), and 160 mg/m^2 (○). Data points are the means ± SD from two (●), five (■), five (△), and two (○) patients

ver. Moreover, this toxicity was not cumulative and was easily manageable. In three patients, the treatment had to be postponed due to neutropenia, but the prophylactic use of G-CSF is not recommended because it is not suitable for outpatients. Grade 1 thrombocytopenia was observed in one patient, and there were no patients with grade 3 or greater anemia. In a study of topotecan, a biweekly schedule produced milder hematological toxicity than a 3-weekly schedule [15]. The result of our present study was also similar to that of the topotecan study. Non-hematological toxicity was also mild. In particular, there were no cases of severe peripheral neuropathy. Only one patient experienced grade 2 neuropathy, which was not cumulative. This non-severe hematological toxicity, and the low-incidence non-cumulative neuropathy may have been due to the lower dose per cycle used in the present schedule. Liver toxicity occurred after the second cycle in one patient, but this toxicity disappeared within a few days.

The Cmax and AUC of paclitaxel did not differ from the values reported when paclitaxel is given as a 3-h infusion [16, 23]. Although interpatient variation was observed at each dose level, the mean Cmax and AUC of dose level 1 were lower than those of other dose levels. In several studies the relationship between the time during which the plasma paclitaxel concentration exceeds 0.05 or 0.1 μM (about 0.043 or 0.085 μg/ml) and the resulting degree of relative neutropenia has been shown to be well described by a sigmoid-Emax model [3, 12]. In the present study, although it was recognized that there was a similar tendency, the time the concentration of paclitaxel exceeded 0.05 and 0.1 μM at dose level 1 was shorter than that observed at other dose levels. Thus, grade 4 neutropenia might not have occurred in patients at level 1.

In conclusion, the MTD of paclitaxel was 160 mg/m^2 and the DLT was neutropenia. The recommended dose for phase II study is 140 mg/m^2 in a biweekly schedule combined with carboplatin at an AUC of 3 mg/ml·min. This combination therapy administered according to a biweekly schedule shows a favorable toxicity profile and is suitable for outpatients. A multicenter phase II study of this regimen in advanced NSCLC is ongoing.

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