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ORIGINAL ARTICLE

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A multicenter phase II study of carboplatin and paclitaxel with a biweekly schedule in patients with advanced non-small-cell lung cancer: Kyushu thoracic oncology group trial

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Abstract *Purpose*: This multicenter phase II study was conducted to investigate the efficacy and safety of carboplatin in combination with paclitaxel administered according to a biweekly schedule as a first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC). *Patients and methods*: Eligibility criteria included histologically or cytologically confirmed NSCLC (stage IIIb or IV), no prior treatment, and measurable or evaluable disease. Paclitaxel (140 mg/m^2) was administered intravenously on day 1, in combination with carboplatin at an area under the concentration time curve (AUC) of 3, every 2 weeks. *Results*: Seventy-four patients (45 men) with a median age of 62 years (range 40–74) and a median ECOG performance status of 1 (range 0–2) were enrolled. The response rate was 35.1% [95% confidence interval (CI): 24.4–47.1%], with 26 partial responses. The median survival was 357 days, and the median time to progression was 218 days. Toxicity was generally mild; National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grades 3 and 4 neutropenia was observeded in 50.0% of the patients, and grades 3 and 4 nausea/vomiting in 4.1%. *Conclusions*: Biweekly carboplatin combined with paclitaxel demonstrated anti-tumor activity in advanced NSCLC, with response and survival rates similar to those of carboplatin combined with paclitaxel administered every 3 weeks but with a more favorable toxicity profile, and the present data indicate that the regimen is suitable for use on an outpatient basis.

Keywords Phase II study · Carboplatin · Paclitaxel · Biweekly schedule · Non-small-cell lung cancer

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Introduction

Platinum-agents are considered the mainstay of first-line combination regimens for the treatment of advanced non-small-cell lung cancer (NSCLC). Platinum-based doublets including new agents such as paclitaxel, docetaxel, vinorelbine, gemcitabine, and irinotecan have shown activity against NSCLC, but none of these platinum-based regimens offered a significant advantage over the others [16, 21]. Based on a survey carried out in the US [22], a combination chemotherapy using

carboplatin and paclitaxel is the most favored option for medical oncologists and the most widely used regimen among all. This is mainly because carboplatin is neither nephrotoxic, neurotoxic, nor ototoxic and it provokes much less emesis than cisplatin. Moreover, this combination has an advantage of low incidence of thrombocytopenia.

In several previous studies using the combination therapy of carboplatin and paclitaxel, paclitaxel was given by intravenous infusion for 1, 3, or 24-hours at doses ranging between 135 and 225 mg/m^2 every 3 weeks, and carboplatin injected at a targeted area under the concentration time curve (AUC) ranging between 5 and 7.5 (mainly six) mg/mL/min [1, 4, 6–10, 13, 17, 20]. The combination therapy of carboplatin and paclitaxel has been shown to possess anti-tumor activity in patients with advanced NSCLC and to be a well-tolerated regimen. However, it was reported that some patients required unanticipated hospitalizations due to intolerable adverse events [4, 6–9, 17].

In our previous phase I study [11], the regimen was modified to a biweekly schedule to facilitate administration to outpatients, and the recommended dose of paclitaxel for a phase II study was 140 mg/m^2 on day 1 with carboplatin at an AUC of 3, every 2 weeks. In order to find a highly effective and safe regimen for NSCLC, we evaluated the potential of a biweekly schedule for this regimen for patients with advanced NSCLC.

Patients and methods

Eligibility

Patients with unresectable stage IIIb without any indication for radiotherapy or IV NSCLC, no prior treatment, an ECOG performance status of 0–2, and a life expectancy greater than 12 weeks, were enrolled for the study. Patients aged between 18 and 75 years were required to have measurable disease (target lesions that can be accurately measured in at least one dimension as ≥20 mm by conventional CT scan), and adequate bone marrow, hepatic, and renal functions, defined as a white blood cell count ≥4,000 and ≤ 12,000 per μl, hemoglobin ≥9.5 g/μl, platelet count ≥100,000 per μl, bilirubin ≤ 1.5 mg/dl, aspartate aminotransferase ≤ 2.0 times the upper limit of normal, serum creatinine ≤ 1.5 mg/dl, and PaO_2≥60 Torr. Patients were excluded when they had a significant cardiac disease, active infections, symptoms of brain metastases, diarrhea, pulmonary fibrosis, massive pleural effusion, a preexisting sensory or motor neuropathy, a history of drug allergy, a past or current history of other malignancy, or were pregnant. Finally, the study protocol was approved by the ethics committee of the participating institutions, and written informed consent was obtained from the patients before the initiation of treatment.

Treatment protocol

All the patients who fulfilled the eligibility criteria and underwent staging assessment received the chemotherapy according to the following dose schedule: paclitaxel 140 mg/m^2 dissolved in 500 ml of 0.9% saline was intravenously administered over 90 min followed by carboplatin (AUC 3), which was infused i.v. over 60 min. The dose of carboplatin was calculated using Calvert's formula [mg = targeted AUC × (GFR + 25)] [5]. Glomerular filtration rate (GFR) was estimated from the creatinine clearance as calculated using Jelliffe's formula [12]. Treatment cycles were repeated every 2 weeks for a planned maximum of ten cycles. All patients were premedicated with dexamethasone (15.2 mg, i.v.), ranitidine (50 mg, i.v.), and diphenhydramine (50 mg). A 5HT3-receptor antagonist was administered before the chemotherapeutic treatment. Granulocyte colony-stimulating factor (G-CSF, 2 μg/kg) was subcutaneously administered to patients who developed grade 4 neutropenia, but it was not routinely used during subsequent courses. The dose of paclitaxel was reduced by 20 mg/m^2 when grade 4 myelosuppression lasting 4 days or grade 3 or greater non-hematological toxicity occurred during the previous cycle. There was no other premedication or supportive therapy for this regimen. A treatment delay of no more than 2 weeks was allowed.

Treatment evaluation

Pretreatment evaluation included medical history, physical examination with assessment of the performance status score, chest X-ray, chest computed tomography (CT), 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 for the study. Physical examination together with the evaluation of the performance status score, chest X-ray, 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 NCI-CTC Version 2.0 [18]. Although formal quality of life assessments were not included in this study, disease or treatment-related symptoms and performance status were recorded for all patients.

Patients were considered to be evaluable for response if they had received at least four 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 ≥30% reduction in the sum of the longest diameter for all target lesions for at least 4 weeks; progressive disease (PD) was defined as a ≥20% increase in the sum of the longest diameter for all target lesions,

reappearance of any lesions that had disappeared, or appearance of a new lesion; stable disease (SD) was defined as any situation that did not qualify as response or progression [23].

Statistics

Response rates were calculated as relative rates with their 95% confidence interval (CI). The Kaplan–Meier method was used to analyze median survival and median time to progression. Survival time was determined from the start of treatment until the date of death. Time to progression was calculated from the start of treatment to the first documented disease progression. The required sample size was determined with a binominal distribution. Population size was established for phase II studies with α error of 5% and β error of 20% and for an expected response rate of 40%. Thus at least 71 patients had to be enrolled into the study.

Results

Patient characteristics

Eighty patients were enrolled for this study between September 2001 and July 2003. Six patients were not assessable just before the first treatment (two for massive pleural effusion, two for refusal, one for cerebral hemorrhage, and one for progressive anemia), leaving 74 patients evaluable for toxicity, response and survival. Their characteristics are shown in Table 1.

Toxicity

The adverse effects of this regimen were generally well-tolerated (Table 2). The major one was myelosuppression. Thirty-seven patients (50%) experienced grades 3 and 4 neutropenia while 14 patients (19%) experienced grade 4 neutropenia to whom G-CSF was administered. Two patients experienced grade 3 anemia. There were no patients with grades 3 and 4 thrombocytopenia. With respect to non-hematologic toxicity, one patient experienced grade 3 neuropathy, but recovered within 3 months. Most patients were administered a 5HT3-receptor antagonist to prevent nausea/vomiting before chemotherapy. However, neither extra administration of the 5HT3-receptor antagonist nor anti-emetic therapy was necessary in any patient, only three patients experienced grades 3 and 4 nausea/vomiting. One patient experienced a grade 4 allergic reaction (anaphylactic shock), but recovered within 14 days. Other grades 3 and 4 non-hematologic adverse effects were uncommon. There were no treatment-related deaths.

Table 1 Patient characteristics

Total number of patients	74
Sex	
Male	45
Female	29
Age	
Median	62
Range	40–74
Performance status (ECOG)	
0	34
1	35
2	5
Histology	
Adenocarcinoma	56
Squamous cell carcinoma	11
Large cell carcinoma	7
Stage	
IIIb	11
IV	63

ECOG Eastern cooperative oncology group

Treatment delivery

In total, 374 cycles of chemotherapy were administered with a median of 5.5 cycles (range 1–10). About 13 patients received only one or two cycles of therapy due to rash, myalgia, brain metastasis and refusal by patient, and 37 patients were treated for six or more cycles. Treatment was delayed in 39 patients (88 cycles) due to neutropenia, and dose reduction was required in eight patients (22 cycles). The mean relative dose intensity for paclitaxel was 0.853.

Response and survival

Seventeen patients (22.9%) did not receive at least four cycles of chemotherapy and were considered non-evaluable (NE) for response (ten for rash or allergy, three for deterioration of complication, two for refusal, and two for true non-target lesions). Of the 74 patients, 26 (35.1%) achieved a PR [95% CI: 24.4–47.1%], 21 (28.4%) showed SD, and in 11 (14.9%) the disease progressed during treatment.

The last patient was enrolled in this study at July 2003, and we performed a final prognostic investigation of all eligible patients at November 2005. The median follow-up time was 365 days (range, 15–1,399 days). The overall median survival was 357 days. The 1- and 2-year survival rates were 48.6 and 33.0%, respectively (Fig. 1). The median time to progression of all patients was 218 days.

Discussion

Large randomized studies have demonstrated the equivalence of regimens containing a new agent and cisplatin or carboplatin [16, 17, 21]. Among them, the triweekly carboplatin/paclitaxel is the most widely used regimen. However, according to the previous studies of this regimen, the most frequent grade 4 toxicity was neutropenia,

Table 2 Toxity ($n = 74$)

Adverse effects	Grade				Incidence of grades 3 and 4 (%)
	1	2	3	4	
Leukopenia	24	24	15	0	20.3
Neutropenia	6	18	23	14	50.0
Thrombocytopenia	14	3	0	0	0.0
Anemia	33	23	2	0	2.7
Neuropathy	29	4	1	0	1.4
Asthralgia/Myalgia	27	9	1	0	1.4
Nausea/Vomiting	21	10	3	0	4.1
Rash	11	2	0	0	0.0
Allergy	1	2	0	1	1.4
Fever	2	0	2	0	2.7
Fatigue	30	8	3	0	4.1
Alopecia	33	21	–	–	–

which was dose-related [15]; besides, 7–13% of the patients required unanticipated hospitalization due to neutropenic fever, and 30–60% of the patients suffered from grade 1 or greater neuropathy [4, 6–10, 13, 17]. The use of nearly half the dose of carboplatin/paclitaxel is a relatively novel approach whose main aim is to diminish full dose carboplatin/paclitaxel-related toxicity and to facilitate administration to outpatients.

Little efficacy data are available on the nearly half dose carboplatin/paclitaxel combination with a biweekly schedule. However, in the present study, we observed a 35.1% response rate and a 357-day median survival time with 48.6% 1-year survival rate. This response rate fell into the range found in previous studies on carboplatin/paclitaxel administered every 3 or 4 weeks [10, 11, 16, 17], and these response and survival rates are similar to those found in the Japanese four-arm cooperative study (FACS) [16], including cisplatin combinations with irinotecan, gemcitabin, and vinorelbine as well as the conventional triweekly carboplatin/paclitaxel combination. In the carboplatin/paclitaxel arm in FACS, 87.8% of the patients experienced grades 3 and 4 neutropenia, and 23% of the patients experienced grades 2–4 neuropathy. In the carboplatin/paclitaxel arm in the ECOG four-arm study [21], grades 3 and 4 neutropenia and grades 3 and 4 neuropathy occurred in 63 and 10% of the patients, respectively. In the present study, hematological toxicity was moderate. Thirty-seven (50%) of the 74 patients experienced grades 3 and 4 neutropenia, but there were no patients with neutropenic fever. Nonhematological toxicity was also mild. Particularly, there were no cases of severe peripheral neuropathy. Only one patient experienced grade 3 neuropathy, which was not cumulative. Other one patient experienced grade 4 allergic reaction (anaphylactic shock). This patient was treated with steroid therapy and required an artificial respiration, but recovered within 14 days. Treatment was discontinued in 17 patients within four cycles and were considered to be NE for response. Among them, there were six patients at one institute in whom treatment was discontinued within two cycles due to rash or allergy during chemotherapy. According to the inspection by the study group, it became clear that paclitaxel had been infused a during a period of times shorter than that specified in the study protocol (over 90 min) in these patients. No patients in this institute experienced rash or allergy after the infusion time was adjusted to comply with the protocol.

Belani et al. carried out a randomized phase II trial with three weekly carboplatin/paclitaxel schedules: arm 1, paclitaxel 100 mg/m^2 weekly for 3 of 4 weeks with carboplatin (AUC = 6) on day 1; arm 2, paclitaxel

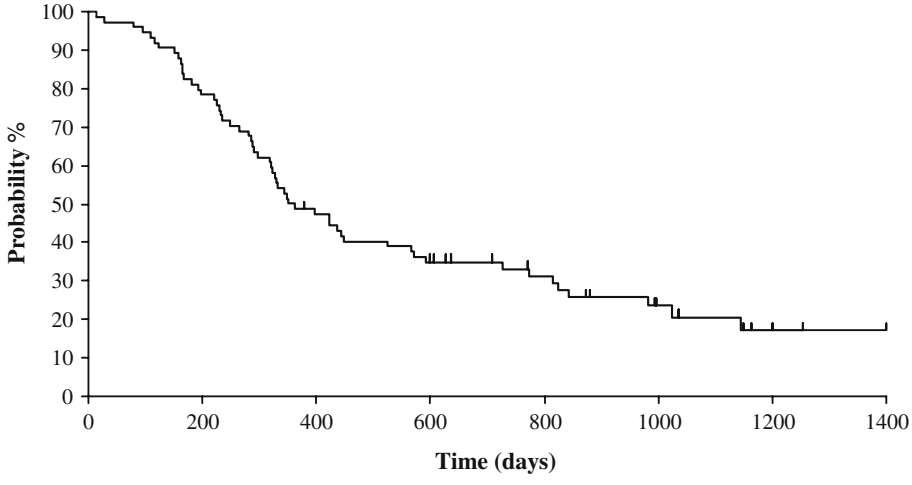

Fig. 1 Kaplan–Meier survival curve of all patients ($n = 74$)

100 mg/m^2 and carboplatin (AUC = 2) weekly for 3 of 4 weeks; arm 3, paclitaxel 150 mg/m^2 cycle 1 and 100 mg/m^2 cycle 2 and carboplatin (AUC = 2) weekly for 6 of 8 weeks [2]. With respect to survival, arm 1 was significantly better than arm 2 and marginally better than arm 3. It was concluded that arm 1 was associated with the best therapeutic index. The authors suggested that the true dose intensity of carboplatin on arm 2 might have been lower than that of arm 1 because the weekly doses of both carboplatin and paclitaxel had been omitted on arm 2 due to myelosuppression. Moreover, Belani et al. recently reported a phase III randomized trial with weekly schedule carboplatin/paclitaxel regimen (the above-mentioned arm 1) and standard triweekly carboplatin (AUC = 6)/paclitaxel 225 mg/m^2 regimen [19]. They concluded the efficacy of the weekly regimen appeared to be higher in terms of response rate, survival with reduction in neuropathy as compared to the standard triweekly regimen. In the present study, the response rate and survival were equivalent to those obtained with the conventional triweekly carboplatin/paclitaxel regimen, with a more favorable toxicity profile. Although treatment delay for several days was required in about 23% of the cycles, the omission of both drugs was not required in any patient. No omissions and high-dose intensity may be the advantages of a biweekly schedule as compared with a weekly schedule of both agents.

In conclusion, carboplatin combined with paclitaxel using a biweekly schedule is an effective and well-tolerated regimen for patients with advanced NSCLC. One of the most significant findings in our study was the lower toxicity as compared with conventional triweekly carboplatin/paclitaxel regimen, and this regimen is also suitable for outpatients. A multicenter randomized phase II study between this biweekly schedule and weekly carboplatin/paclitaxel schedule [paclitaxel weekly for 3 of 4 weeks with carboplatin (AUC = 6) on day 1] in patients with advanced NSCLC, is now ongoing.

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