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Carboplatin plus Weekly Paclitaxel Combined with Bevacizumab as First-line Treatment for Non-small Cell Lung Cancer

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Abstract. *Aim: We aimed to evaluate the efficacy and safety of carboplatin plus weekly paclitaxel with bevacizumab in patients with advanced non-squamous non-small cell lung cancer (NSCLC). Patients and Methods: Patients with stage IIIB/IV or postoperative recurrent NSCLC (n=33) were treated with carboplatin (area under the curve of 6) on day 1; paclitaxel (80 mg/m^2) on days 1, 8, and 15; and bevacizumab (15 mg/kg) on day 1 repeated every 4 weeks, for four to six cycles; followed by maintenance bevacizumab (15 mg/kg) every 3 weeks. Results: The overall response rate was 76%. The median progression-free survival and overall survival were 8.4 months and 22.2 months, respectively. Grade 3-4 toxicities included neutropenia in 55% of patients, anemia in 18%, febrile neutropenia in 12%, and anorexia in 9%. No treatment-related deaths were observed. Conclusion: Carboplatin plus weekly paclitaxel with bevacizumab was effective and well tolerated by patients with advanced NSCLC.*

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Lung cancer is the leading cause of cancer-related mortality in most developed countries. Approximately 85% of patients with lung cancer have non-small cell lung cancer (NSCLC) histology (1). For patients with advanced NSCLC, platinum-based two-drug chemotherapy regimens have been accepted as standard treatment based on their survival benefit (2, 3). The combination of carboplatin plus paclitaxel is one of the most commonly used regimens.

Bevacizumab has been shown to benefit patients with a variety of cancer types, including NSCLC (4-6). Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor that inhibits tumor growth by blocking angiogenesis. A phase III trial (ECOG 4599), conducted primarily in the United States, demonstrated that the addition of bevacizumab to first-line carboplatin plus paclitaxel improved overall survival (OS) in patients with advanced non-squamous NSCLC (4). Therefore, carboplatin plus paclitaxel with bevacizumab has become one of the standard regimens for the treatment of advanced non-squamous NSCLC. A randomized phase II trial (JO19907) conducted among Japanese patients indicated that the addition of bevacizumab to carboplatin plus paclitaxel prolonged progression-free survival (PFS) (7). However, this combination also caused worsening of adverse events, including peripheral neuropathy (4, 7).

In the carboplatin plus paclitaxel regimen, weekly administration of paclitaxel reduces the rate of peripheral

neuropathy compared to the standard triweekly administration of paclitaxel, while maintaining comparable efficacy (8, 9). A phase III trial by Belani *et al*. comparing carboplatin plus weekly paclitaxel with carboplatin plus standard paclitaxel demonstrated that the incidence of grade 2/3 neuropathy was lower after the weekly paclitaxel regimen (8). A phase II trial of elderly Japanese patients also demonstrated the superiority of the weekly paclitaxel regimen regarding peripheral neuropathy (9). However, it is still uncertain whether carboplatin plus weekly paclitaxel in combination with bevacizumab shows clinical benefits regarding efficacy and the reduction of adverse events, including peripheral neuropathy, compared to carboplatin plus standard paclitaxel with bevacizumab.

Therefore, we conducted this phase II trial to evaluate the efficacy and safety of carboplatin plus weekly paclitaxel with bevacizumab in patients with advanced NSCLC. Our aim was to determine if this combination is a beneficial alternative regimen to carboplatin plus standard paclitaxel with bevacizumab.

Patients and Methods

The primary end-point of the study was to determine the overall response rate (ORR). Secondary endpoints included determination of the time to response (TTR), PFS, OS, and toxicity and safety.

Patient eligibility. Eligibility criteria included histologically or cytologically proven non-squamous NSCLC, stage IIIB (including only patients with no indication for curative radiotherapy), stage IV [according to the seventh edition of the Union for International Cancer Control TNM Classification of Malignant Tumors (10)] or postoperative recurrence, age 20-74 years, Eastern Cooperative Oncology Group performance status of 0 or 1, measurable lesions, an estimated life expectancy of at least 3 months, and adequate major organ function (neutrophil count ≥2,000/μl; platelet count ≥100,000/μl; hemoglobin concentration ≥9.0 g/dl; total serum bilirubin level ≤1.5 mg/dl; aspartate aminotransferase and alanine aminotransferase level ≤2.5× upper limit of normal; serum creatinine level ≤1.5 mg/dl; prothrombin time-international normalized ratio ≤1.5; and proteinuria ≤1+). Exclusion criteria included central nervous system metastases or spinal cord compression, hemoptysis (≥2.5 ml per event), tumor invasion to major blood vessels, a tumor with cavitation, interstitial pneumonia, uncontrolled hypertension, active infection, or any contraindication to carboplatin, paclitaxel, or bevacizumab. Written informed consent was obtained from all patients before enrollment. The protocol of this study was approved by the Ethics Committee, and was registered at University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) in Japan (UMIN number: UMIN000003566).

Study design. This study was a multicenter, open-label, phase II study of first-line carboplatin plus weekly paclitaxel with bevacizumab for patients with non-squamous NSCLC. Carboplatin was administered at a dose calculated to produce an area under the curve (AUC) of 6 min×mg/ml on day 1; paclitaxel was administered at a dose of 80 mg/m^2 on days 1, 8 and 15; and bevacizumab at a dose of 15 mg/kg on day 1 intravenously every 4 weeks, for four to six cycles, followed by maintenance bevacizumab (15 mg/kg) every 3 weeks until disease progression or intolerable toxicity occurred. The dosages of carboplatin and paclitaxel were administered as determined in our previous study (11). The induction cycle number was decided by the attending physicians while taking into consideration the treatment efficacy and adverse events.

The study was conducted in two steps. Step 1 was performed for six patients to evaluate the tolerability of the treatment regimen. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 (12). Transition to step 2 of the trial was possible if no more than two patients presented grade 4 hematological toxicity or grade 3 or more non-hematological toxicity during the first treatment cycle. Step 2 was performed for 33 patients (the six patients from step 1 and an additional 27 patients) in order to evaluate the efficacy and safety of the treatment regimen. Administration of paclitaxel on day 8 and/or 15 was skipped if grade 3 or more hematological toxicity or grade 2 or more non-hematological toxicity occurred. Administration of bevacizumab was skipped if grade 2 or 3 proteinuria or grade 2 hemorrhage occurred. When grade 4 proteinuria, grade 3 or more hemorrhage, grade 2 or more hemoptysis, grade 2 or more arterial thrombosis, or perforation of the digestive tract occurred, chemotherapy was discontinued. Therapy initiation was delayed when the neutrophil count was ≤1.500/μl or the platelet count was ≤100,000/μl, with no more than 3 weeks of delay. Dose reduction of carboplatin and paclitaxel was performed if grade 4 hematological toxicity, grade 3 or more non-hematological toxicities, or paclitaxel skips on both day 8 and day 15 were observed. When the induction treatment was performed for 3 or more cycles and the response was stable disease or better, transition to maintenance bevacizumab was permitted.

Efficacy and safety assessments. After baseline evaluation, tumor lesions were evaluated every 4 weeks during the induction treatment, and every 8 weeks thereafter during the maintenance treatment by computed tomography until evidence of disease progression. The tumor responses were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (13). Toxicities were evaluated according to NCI-CTCAE version 4.0.

Statistical analysis. To determine the sample size, Southwest Oncology Group (SWOG) One Arm Binomial software was used (14). In our previous phase I/II trial of carboplatin and weekly paclitaxel, the ORR was 50% (11). The null hypothesis was an ORR of 30%, with an alternative hypothesis of 55% at a significance level of 0.05 and statistical power of 0.8. This study required 33 patients, allowing for patient dropouts. The 95% confidence interval (CI) for the ORR was calculated using the Clopper–Pearson method. OS was defined as the time from the enrolment to the date of the last follow-up or death. PFS was defined as the time from the enrolment to the date of disease progression or death. Survival curves were estimated using the Kaplan–Meier method.

Results

Step 1 of the study was performed for six patients. None of these patients developed grade 4 hematological toxicities or grade 3/4 non-hematological toxicities; therefore, they were transferred to step 2.

Table I. *Patient characteristics*.

Characteristic	No. of patients (N=33)	%
Age, years		
Median (range)	64 (39-74)	
Gender		
Male	24	73
Female	9	27
ECOG PS		
0	19	58
1	14	42
Stage		
IIIB	4	12
IV	28	85
Relapse after surgery	1	3
Histology		
Adenocarcinoma	31	94
Other	2	6
EGFR gene mutation		
Wild-type	23	70
Mutated	7*	21
Not evaluated	3	9

ECOG, Eastern Cooperative Oncology Group; PS, performance status; EGFR, epidermal growth factor receptor. *One patient had also T790M mutation.

Table II. *Tumor response*.

Response	No. of patients	%
CR	0	
PR	25	
SD	4	
PD	3	
NE	1	
Total	33	
CR+PR	25	
Response rate		76
95% CI		58-89

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; CI, confidence interval.

Patient characteristics. From August 2010 to February 2014, a total of 33 patients were enrolled. All patients were treated and evaluated for efficacy and safety according to the study protocol. Baseline patient characteristics are summarized in Table I. The median age was 64 years (range=39-74 years), and 24 patients were male (73%). Thirty-one patients had adenocarcinoma (94%), and seven patients (21%) had epidermal growth factor receptor (*EGFR*) mutations, including one patient with the T790M mutation.

Treatment delivery. A total of 149 cycles of induction chemotherapy were administered (median=4; range=1-6). Transition to maintenance bevacizumab was conducted for 19 patients (58%), and a total of 121 cycles of maintenance bevacizumab were administered (median=5; range= 1-18). A total of 53 paclitaxel administrations (day 8, 17 times; day 15, 36 times) were skipped in 19 patients (58%), and the main cause of the skips was grade 3 or more neutropenia (37 times, 70%). One bevacizumab administration was skipped because of grade 2 proteinuria. The doses of carboplatin and paclitaxel were reduced in 11 patients (33%). The main reasons for dose reductions were febrile neutropenia (four cases), paclitaxel-skips on both day 8 and day 15 (three cases), and grade 4 neutropenia (two cases). The study drug compliance (the actual dose divided by the planned dose) for carboplatin, paclitaxel, and bevacizumab was 91%, 81%, and 95%, respectively. The main reasons for discontinuation of therapy were disease progression (22 patients, 67%) and adverse events (seven patients, 21%). Twenty-nine patients (88%) received second-line or higher chemotherapy.

Efficacy. The treatment response of 32 patients was evaluated. Partial response was observed in 25 patients, and the ORR was 76% (95% CI=58-89%) (Table II). The median TTR was 1.6 months (range=0.6-5.8 months), the median PFS was 8.4 months (95% CI=6.3-8.8 months), and the median OS was 22.2 months (95% CI=13.8-28.1 months) (Figure 1).

Toxicity. The adverse events observed in all 33 patients are listed in Table III. Hematological toxicities reaching grade 3/4 were neutropenia (18 patients, 55%), leukopenia (seven patients, 21%), anemia (six patients, 18%), thrombocytopenia (one patient, 3%), and febrile neutropenia (four patients, 12%). Non-hematological toxicities reaching grade 3/4 were anorexia (three, patients, 9%), diarrhea (one patient, 3%), and aminotransferase elevation (one patient, 3%). The most common hemorrhage was nasal bleeding, and this occurred in 14 patients (42%). Gingival bleeding occurred in two patients (6%), and hemorrhoid bleeding occurred in one (3%). All the cases of hemorrhage were grade 1. It is worth noting that only three patients (9%) had grade 2 neuropathy, and no patient had grade 3/4 neuropathy. One patient had grade 1 pneumothorax, and two had hyperkalemia (grade 2 and grade 3). No treatment-related deaths were observed.

Discussion

In this study, we made two important clinical observations. Carboplatin plus weekly paclitaxel with bevacizumab demonstrated a high ORR for the treatment of previously untreated non-squamous NSCLC. In addition, this regimen was well tolerated, and the frequency of peripheral neuropathy, a clinically-important adverse reaction, was low.

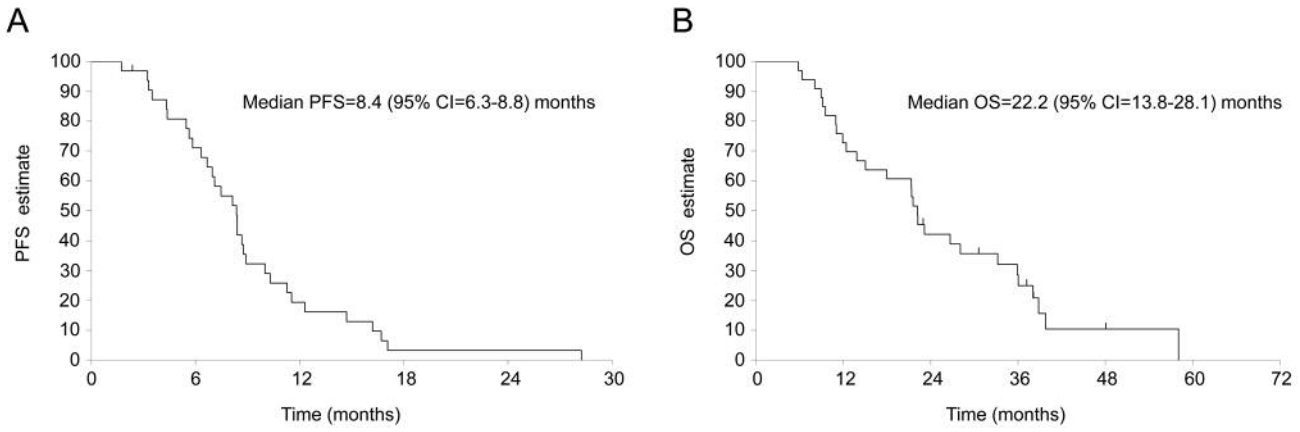

Figure 1. *Progression-free (PFS) (A) and overall (OS) (B) survival. CI: Confidence interval.*

Firstly, carboplatin plus weekly paclitaxel with bevacizumab resulted in a high ORR in the treatment of previously untreated non-squamous NSCLC. The ORR of 76% was superior to that of previous studies of carboplatin plus paclitaxel with bevacizumab (4, 7). In the carboplatin plus paclitaxel regimen, it was reported that the weekly administration of paclitaxel improved the ORR compared to the standard triweekly administration of paclitaxel (8). The weekly administration of paclitaxel in the carboplatin plus paclitaxel with bevacizumab regimen may result in a higher ORR than that with regimens using the standard triweekly administration of paclitaxel. Additionally, prior studies have suggested that weekly paclitaxel treatment has anti-angiogenic properties (15-17). Weekly paclitaxel may have a synergistic effect with bevacizumab. Meanwhile, the median PFS of 8.4 months and median OS of 22.2 months were comparable to those of a previous Japanese study (JO19907) (7). These results suggest that carboplatin plus weekly paclitaxel with bevacizumab may represent an alternative regimen to carboplatin plus standard paclitaxel in terms of efficacy.

Secondly, the toxicities of the regimen, including peripheral neuropathy, were well tolerated. Neutropenia was the most common grade 3/4 hematological toxicity (55%), but the frequency was relatively low. The non-hematological toxicities were mostly mild and manageable, including peripheral neuropathy. Previous reports have demonstrated that weekly administration of paclitaxel reduces the incidence of neutropenia, peripheral neuropathy, and myalgia/arthralgia (8, 9). These findings support our results. In our study, the administrations of paclitaxel on day 8 and/or day 15 were skipped in 19 patients (58%). The weekly paclitaxel regimen is easily skipped in mid-cycle when moderate to severe adverse events occur. This property may be related to the decreased toxicity of the weekly paclitaxel regimen. Regarding adverse events of bevacizumab, we should pay attention to hemorrhage, including hemoptysis, a life-threatening toxicity. In our study, 14 patients had nasal bleeding and three patients had

Table III. *Summary of adverse events.*

	Grade (NCI-CTC)					Grade 3/4 (%)
	0	1	2	3	4	
Hematological toxicity						
Leukopenia	5	6	15	7	0	21
Neutropenia	3	3	9	15	3	55
Anemia	0	14	13	6	0	18
Thrombocytopenia	9	19	4	1	0	3
Febrile neutropenia	29	-	-	4	0	12
Non-hematological events						
Anorexia	13	15	2	3	0	9
Nausea	16	13	4	0	0	0
Vomiting	25	6	2	0	0	0
Diarrhea	26	4	2	1	0	3
Constipation	16	15	2	0	0	0
Fatigue	16	13	4	0	0	0
Infection	31	0	2	0	0	0
Alopecia	9	13	11	-	-	-
Neuropathy	11	19	3	0	0	0
Hypertension	30	2	1	0	0	0
Bleeding						
Nasal bleeding	19	14	0	0	0	0
Other	30	3	0	0	0	0
Proteinuria	26	2	5	0	0	0
AST/ALT	16	14	2	1	0	3
Total bilirubin	24	7	2	0	0	0
Creatinine	28	4	1	0	0	0

NCI-CTC, National Cancer Institute common toxicity criteria; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

other types of bleeding, but all episodes of hemorrhage were mild. Hemoptysis did not occur in this study. The exclusion criteria of this study included patients with a history of hemoptysis, tumor invasion to major blood vessels, and a cavitated tumor as risk factors for pulmonary hemorrhage (4, 5, 7). Appropriate selection of patients might have reduced the risk of hemoptysis.

To our knowledge, only one prospective study examining carboplatin plus weekly paclitaxel with bevacizumab has been reported (18). That study reported an ORR of 67.4% (95% CI=53.4-81.4%), a median PFS of 7.6 months (95% CI=5.5-9.5 months), and a median OS of 17.7 months (95% CI=11.6-28.6 months). Our results confirmed the findings of this previous study and showed the excellent efficacy of carboplatin plus weekly paclitaxel with bevacizumab for the treatment of patients with advanced NSCLC. However, there are several differences between our study and the previous study. Firstly, our study (as well as the JO19907 study) excluded patients aged 75 years or more. Secondly, the dose of paclitaxel in our study was 80 mg/m^2; in the previous study, the dose of paclitaxel was lower (70 mg/m^2). Our study showed that patients under 75 years old can safely be treated with paclitaxel at a dose of 80 mg/m^2. Finally, the present study provides mature data for both PFS and OS; the previous study presented mature data for PFS and immature data for OS.

This study has several limitations. Firstly, this study was a single-arm trial, and a direct comparison with tri-weekly carboplatin plus paclitaxel with bevacizumab was not carried out. However, the eligibility criteria of this study were modeled based on the JO19907 study; therefore, it is possible to make an indirect comparison with the results of the previous study. Secondly, our sample size was too small to assess the PFS and OS. However, our results regarding these parameters were comparable to those of the JO19907 study. To confirm the results, a randomized study with sufficient sample size is needed.

In conclusion, carboplatin plus weekly paclitaxel with bevacizumab was effective and well tolerated by patients with advanced non-squamous NSCLC. A randomized study comparing this regimen with carboplatin plus standard paclitaxel with bevacizumab is warranted. This regimen may be a better alternative to the current standard regimen.

Conflicts of Interest

None declared.

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