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ORIGINAL ARTICLE

Efficacy and Tolerability of the Bevacizumab/carboplatin/paclitaxel Combination Therapy as First-line or Non-first-line Therapy for Non-small-cell Lung Cancer

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ABSTRACT —— ***Objective.*** Bevacizumab／carboplatin／paclitaxel (BEV-CP) combination therapy extends the progression-free survival (PFS) of chemotherapy-naive patients with non-small-cell lung cancer. However, the efficacy and tolerability of BEV-CP therapy in patients with a history of chemotherapy have not been investigated. In the present study, patients receiving BEV-CP therapy at the Nagara Medical Center were divided into 2 groups. ***Methods.*** The first-line therapy (FLT) group consisted of 18 patients who had never received chemotherapy before treatment with BEV-CP, and the non-FLT group included 13 patients who had received other chemotherapy regimens before BEV-CP therapy. The efficacy and tolerability of BEV-CP therapy in the FLT and non-FLT groups were analyzed retrospectively. ***Results.*** The response rate (RR) was 72.2% in the FLT group and 61.5% in the non-FLT group, whereas the disease control rate (DCR) was 83.3% in the FLT group and 92.3% in the non-FLT group. However, neither RR nor DCR was statistically significant between the FLT and non-FLT groups ($p = 0.40$ and 0.43, respectively). The median PFS time was 240 days in the FLT group and 258 days in the non-FLT group, which was not statistically significant ($p = 0.84$). The rate of discontinuation of BEV-CP therapy because of adverse effects was 22.2% in the FLT group and 7.7% in the non-FLT group. The discontinuation rate was lower in the non-FLT group than in the FLT group, but the difference was not statistically significant ($p = 0.28$). ***Conclusion.*** The efficacy and tolerability of BEV-CP therapy as non-FLT and FLT were comparable.

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KEY WORDS —— Non-small-cell lung cancer, Bevacizumab, Second-line therapy, Carboplatin／paclitaxel combination therapy

INTRODUCTION

Bevacizumab (BEV) is an anti-vascular endothelial growth factor monoclonal antibody. BEV was originally approved for use in colon and rectal cancers and, later, for the treatment of non-small-cell lung cancer (NSCLC) except for squamous cell carcinoma, in combination with carboplatin (CBDCA) and paclitaxel (PTX),[1] or gemcitabine and cisplatin.[2] The implementation of maintenance therapy, based on the administration of BEV after the completion of combination therapy, was reported to extend progression-free survival (PFS) compared with combination therapy without BEV.[1] As a result, BEV was approved for use in NSCLC. However, these clinical trials were conducted in chemotherapy-naive patients and data on the efficacy and the tolerability of BEV administered as second-line therapy are extremely limited.

In the Nagara Medical Center, when NSCLC patients

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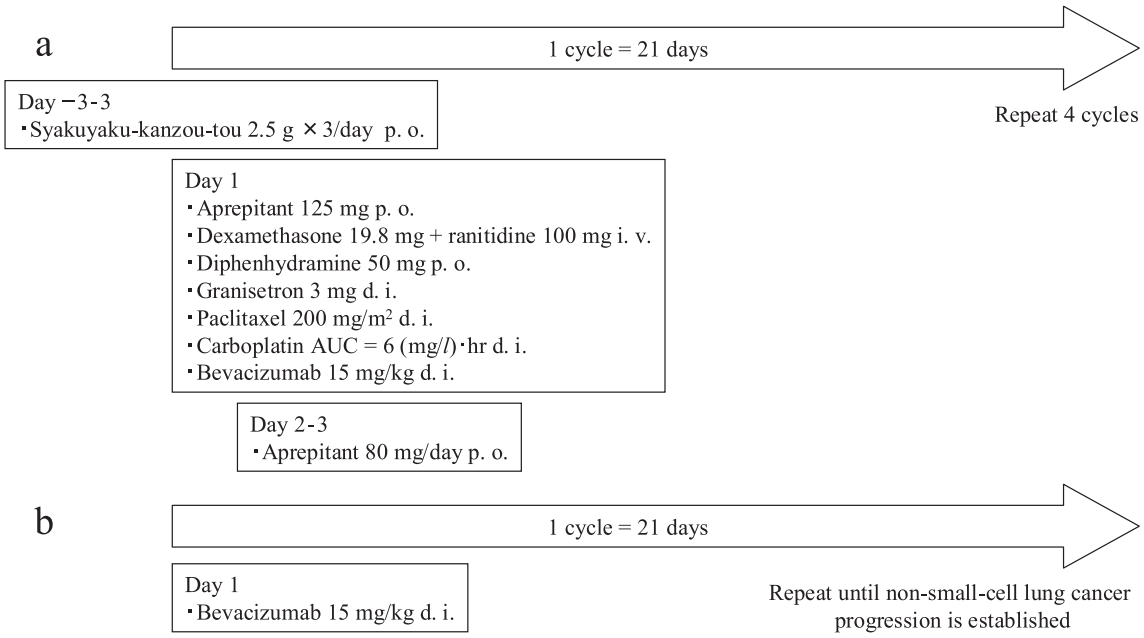


Figure 1. Schedule of bevacizumab/carboplatin/paclitaxel combination therapy and maintenance therapy using bevacizumab. **a.** Schedule of bevacizumab/carboplatin/paclitaxel combination therapy. **b.** Schedule of maintenance therapy using bevacizumab. Syakuyaku-kanzou-tou is administered to palliate myalgia caused by paclitaxel. AUC means area under the blood time-concentration curve. p. o. means per os. i. v. means intravenous injection. d. i. means drip infusion.

did not respond to chemotherapy, NSCLC patients were assessed for brain metastasis and tumor sites to determine the indications for BEV. If the risk of hemorrhage[3] was determined to be low and BEV administration was considered a possibility, the attending physicians discussed the usefulness and the possible adverse effects of the combination therapy with BEV with the eligible patients. If a patient agreed to the treatment with BEV, the physician initiated a BEV regimen while carefully monitoring its efficacy and adverse effects. Based on evidence of the effectiveness of the combination therapy with BEV, CBDCA, and PTX (BEV-CP therapy), this combination was the most frequently used treatment regimen in our center.

The patients included in the present study were divided into 2 groups based on whether or not they had received prior chemotherapy, and the efficacy and the tolerability of BEV-CP therapy were compared between the 2 groups.

PATIENTS AND METHODS

1. Patients

The NSCLC patients who started and completed the BEV-CP therapy at Nagara Medical Center from January 2010 to August 2011 were included in the study. The patients were divided into 2 groups: the first-line therapy (FLT) group consisted of chemotherapy-naive patients, and the non-FLT group consisted of patients who had been treated with other chemotherapy regimens before starting the BEV-CP therapy. The patients' clinical records were retrospectively reviewed to assess patient background, BEV, CBDCA, and PTX doses, the efficacy and adverse effects of BEV-CP therapy.

The present study was conducted according to the ethical guidelines for clinical trials and was approved by the ethics committee of our center (approval no. 10-6).

2. Therapy schedule

The schedules of the BEV-CP therapy and maintenance BEV therapy after combination regimen are shown in Figure 1. Combination therapy with 4 cycles of platinum doublet for advanced NSCLC was recommended by the 2003 Japan Lung Cancer Society (JLCS) guidelines.[4] Therefore, we gave of BEV-CP therapy and maintenance therapy was administered after 4 cycles of BEV-CP therapy until disease progression or unacceptable toxicity.

Table 1. Patient Background

	First-line therapy group	Non-first-line therapy group	p value
n	18	13	
Age (years)*1	64.7 ± 9.7	67.2 ± 11.6	0.53*4
Male/Female	13/5	9/4	0.58*5
Histlogical classification (adeno/large cell/adeno or large cell)	15/0/3	12/1/0	0.63*6
Clinical stage (stage ⅡB/ⅢA/ⅢB/IV)	1/3/3/11	0/1/1/11	0.25*6
ECOG performance status (0/1/2)	7/10/1	3/8/2	0.33*6
State of EGFR gene mutation (mutated/not mutated/unknown)	3/12/3	2/6/5	0.37*6
Patient with a history of hypertension (exist/never)	7/11	5/8	0.64*5
Body weight (kg)*1	58.5 ± 10.8	57.5 ± 9.3	0.79*4
Body surface area (m^2)*1	1.57 ± 0.18	1.56 ± 0.15	0.80*4
Creatinine clearance (ml/min)*1	98.4 ± 23.3	75.6 ± 26.4	0.02*4
Number of regimens received (1/2/≥3)*2	-	4/4/5	
Elapsed number of days between the last day of previous treatment and the beginning of BEV-CP therapy*1	-	212.8 ± 186.3	
○ Bevacizumab/carboplatin/paclitaxel combination therapy			
Number of cycles*1	3.4 ± 1.2	3.8 ± 0.4	0.63*6
Relative dose intensity			
・Bevacizumab*1	0.96 ± 0.08	0.87 ± 0.16	0.06*6
・Carboplatin*1	0.91 ± 0.14	0.78 ± 0.17	0.04*6
・Paclitaxel*1	0.86 ± 0.12	0.77 ± 0.15	0.15*6
Average relative dose intensity	0.91 ± 0.11	0.80 ± 0.15	0.01*6
○ Maintenance therapy			
Number of cycles*1	4.9 ± 4.5	5.1 ± 5.7	0.78*6
Relative dose intensity			
・Bevacizumab*1,3	0.97 ± 0.05	0.92 ± 0.12	0.15*6
Status of therapy (ongoing/finished)	3/15	4/9	0.31*5

ECOG: Eastern Cooperative Oncology Group, BEV-CP therapy: Bevacizumab/carboplatin/paclitaxel combination therapy.

*1: Mean ± S.D. *2: Adjuvant chemotherapy and epidermal growth factor receptor tyrosine kinase inhibitor were counted as 1 regimen. *3: Not calculated in patients who did not receive maintenance therapy (4 patients in both groups). *4: Student *t* test. *5: Fisher exact probability test. *6: Mann-Whitney *U* test.

3. Efficacy

Tumor size was measured on computed tomographic images obtained after 2 and 4 cycles of the BEV-CP therapy, and the effects were determined using the Response Evaluation Criteria in Solid Tumors Version 1.1. The response rate (RR; complete response + partial response) and the disease control rate (DCR; complete response + partial response + stable disease) were compared between the FLT and non-FLT groups. Furthermore, PFS was calculated from the start of treatment to disease progression, and the PFS times were compared between the 2 groups.

4. Adverse effects

The occurrence of adverse effects due to BEV-CP therapy and the maintenance therapy were determined in the FLT and non-FLT groups. The occurrence rate of all grades of adverse effects and those higher than grade 3 were compared between the FLT and non-FLT groups, using the Common Terminology Criteria for Adverse Events Version 4.0. In addition, the rates of BEV-CP therapy discontinuation due to adverse effects were compared between the FLT and non-FLT groups.

5. Statistical analysis

The Fisher exact probability test, the Mann-Whitney *U* test and the Student *t* test were used to compare the patient backgrounds between the FLT and non-FLT groups. The effectiveness, occurrence rate of adverse effects, and rate of BEV-CP therapy discontinuation due to adverse effects were analyzed using the Fisher exact probability test. Kaplan-Meier graphs were generated for PFS, and the log-rank test was used to compare the PFS time between the 2 groups. All statistical calcula-

Table 2-a. Drugs Administered to the Non-first-line Therapy Group Before the Administration of Bevacizumab/carboplatin/paclitaxel Combination Therapy (Case No. 1-6).

Case no.	Previously treated regimen	Dose	Cycles	Cytoreductive effect	Response rate (%)	Reason for completion of therapy	Days from completion of therapy to starting BEV-CP therapy
1	Carboplatin/Paclitaxel*	Carboplatin: AUC = 5.7 (mg/*l*) · hr Paclitaxel: 159.6 mg/m^2	2 cycles	PR	100	Completion of designed cycles	378
2	Carboplatin/Paclitaxel	Carboplatin: AUC = 6.0 (mg/*l*) · hr Paclitaxel: 198.8 mg/m^2	4 cycles	PR	50.0	Completion of designed cycles	322
	Pemetrexed	500 mg/m^2	4 cycles	SD		Completion of designed cycles	137
3	Carboplatin/Paclitaxel	Carboplatin: AUC = 6.0 (mg/*l*) · hr Paclitaxel: 210.5 mg/m^2	4 cycles	PR	16.7	Completion of designed cycles	1112
	Carboplatin/Paclitaxel	Carboplatin: AUC = 6.0 (mg/*l*) · hr Paclitaxel: 175.4 mg/m^2	4 cycles	SD		Completion of designed cycles	790
	Docetaxel	70.2 mg/m^2	4 cycles	PD		Disease progression	574
	Carboplatin/Gemcitabine	Carboplatin: AUC = 2.0 (mg/*l*) · hr Gemcitabine: 983.0 mg/m^2	2 cycles	PD		Disease progression	455
	Cisplatin/S-1	Cisplatin: 56.2 mg/m^2 S-1: 120 mg/body	4 cycles	PD		Disease progression	315
	Pemetrexed	499.2 ± 5.2 mg/m^2	4 cycles	SD		Completion of designed cycles	70
4	Carboplatin/Paclitaxel*	Carboplatin: AUC = 4.7 (mg/*l*) · hr Paclitaxel: 140.5 mg/m^2	2 cycles	PR	100	Completion of designed cycles	176
5	Carboplatin/Paclitaxel	Carboplatin: AUC = 5.9 (mg/*l*) · hr Paclitaxel: 172.4 mg/m^2	4 cycles	PR	100	Completion of designed cycles	356
	Gefitinib	250 mg/body	281 days	PR		Disease progression	8
6	Carboplatin/Paclitaxel	Carboplatin: AUC = 6.1 (mg/*l*) · hr Paclitaxel: 200.0 mg/m^2	4 cycles	PR	100	Completion of designed cycles	256

*This therapy was conducted followed by 2 cycles of weekly carboplatin/paclitaxel concurrent radiation therapy.

S-1, combination capsule that contains tegafur, gimeracil, and oteracil potassium. Dose of S-1 indicated tegafur dose.

AUC, area under the blood time-concentration curve; BEV-CP, combination therapy with bevacizumab/carboplatin/paclitaxel; PR, partial response; SD, stable disease; PD, progressive disease.

tions were performed using Statcel 2 software, and the level of significance was set as $p < 0.05$.

RESULTS

1. Patient backgrounds

The backgrounds of the patients in the FLT and non-FLT groups are shown in Table 1. There were 18 patients in the FLT group and 13 in the non-FLT group. Three patients in the FLT group and 4 patients in the non-FLT group completed the course of the BEV-CP therapy and had begun or were about to start maintenance therapy as of September 1, 2011. The creatinine clearance in the non-FLT group was significantly lower than that in the FLT group ($p = 0.02$). The relative dose intensity (RDI) of each drug and the average-RDI for BEV-CP therapy in the non-FLT group were lower than those in the FLT group, and the RDI of CBDCA and the average-RDI were statistically significant ($p = 0.04$ and 0.01, respectively).

The previous chemotherapy regimens in the non-FLT group are shown in Table 2. CBDCA and PTX combination therapy was the most frequently administered regimen and was reported in 12 (92.3%) of the 13 patients.

Table 2-b. Drugs Administered to the Non-first-line Therapy Group Before the Administration of Bevacizumab/carboplatin/paclitaxel Combination Therapy (Case No. 7-9).

Case no.	Previously treated regimen	Dose	Cycles	Cytoreductive effect	Response rate (%)	Reason for completion of therapy	Days from completion of therapy to starting BEV-CP therapy
7	Cisplatin/Docetaxel	Cisplatin: 79.9 mg/m^2 Docetaxel: 59.7 mg/m^2	6 cycles	PR	100	Completion of designed cycles	636
	Gefitinib	250 mg/body	609 days	PR		Disease progression	6
8	Carboplatin/Paclitaxel* (induction therapy)	Carboplatin: AUC = 5.0 (mg/*l*) · hr Paclitaxel: 174.7 mg/m^2	2 cycles	SD	0	Completion of designed cycles	1310
	Carboplatin/Paclitaxel	Carboplatin: AUC = 5.9 (mg/*l*) · hr Paclitaxel: 200.0 mg/m^2	2 cycles	SD		Inadequate effect	1128
	Gemcitabine/Vinorelbine	Gemcitabine: 980.4 mg/m^2 Vinorelbine: 26.1 mg/m^2	2 cycles	PD		Disease progression	1050
	Gefitinib	250 mg/body	646 days	SD		Disease progression	652
	Docetaxel	65.4 mg/m^2	4 cycles	SD		Completion of designed cycles	422
	Pemetrexed	500.0 mg/m^2	2 cycles	PD		Disease progression	342
	Erlotinib	150 mg/body	50 days	SD		Adverse reaction	265
	Cisplatin/S-1	Cisplatin: 58.8 mg/m^2 S-1: 120 mg/body	4 cycles	SD		Completion of designed cycles	78
9	Carboplatin/Paclitaxel	Carboplatin: AUC = 5.6 (mg/*l*) · hr Paclitaxel: 175.1 mg/m^2	4 cycles	PR	25.0	Completion of designed cycles	1056
	Carboplatin/Gemcitabine	Carboplatin: AUC = 1.8 (mg/*l*) · hr Gemcitabine: 987.3 mg/m^2	3 cycles	PD		Disease progression	657
	Pemetrexed	500.0 mg/m^2	2 cycles	SD		Inadequate effect	608
	Docetaxel	74.7 mg/m^2	4 cycles	SD		Completion of designed cycles	210

*One cycle of weekly carboplatin/paclitaxel concurrent radiation therapy was conducted between cycles of this therapy.

S-1, combination capsule that contains tegafur, gimeracil, and oteracil potassium. Dose of S-1 indicated tegafur dose.

AUC, area under the blood time-concentration curve; BEV-CP, combination therapy with bevacizumab/carboplatin/paclitaxel; PR, partial response; SD, stable disease; PD, progressive disease.

2. Efficacy

The effectiveness of the BEV-CP therapy is shown in Figure 2. No patients showed complete response in either the FLT or non-FLT groups. The RR was 72.2% in the FLT group and 61.5% in the non-FLT group. The RR of the non-FLT group was lower than that of the FLT group, although the difference did not reach statistical significance ($p = 0.40$). The DCR in the non-FLT group was higher (92.3%) than that in the FLT group (83.3%), although the difference did not reach statistical significance ($p = 0.43$). The effectiveness of the BEV-CP therapy in the non-FLT group was similar to that of CBDCA and PTX previously administered combination therapy.

The Kaplan-Meier PFS curve for each group is shown in Figure 3. The median PFS time was 240 days in the FLT group and 258 days in the non-FLT group, which was not statistically significant ($p = 0.84$).

3. Adverse effects

The hematologic toxicity and abnormal laboratory data collected during the course of the BEV-CP therapy are shown in Table 3, and other adverse effects are shown in Table 4. The rate of occurrence of increased gamma-glutamyl transpeptidase of all grades in the non-FLT group was significantly lower than that in the FLT group, but the rate of occurrence of the other adverse effects was not statistically significant between the 2 groups. The 4 BEV-CP patients in whom therapy was discontinued in the FLT group because of adverse effects were treated with other chemotherapy regimens.

Table 2-c. Drugs Administered to the Non-first-line Therapy Group Before the Administration of Bevacizumab/carboplatin/paclitaxel Combination Therapy (Case No. 10-13).

Case no.	Previously treated regimen	Dose	Cycles	Cytoreductive effect	Response rate (%)	Reason for completion of therapy	Days from completion of therapy to starting BEV-CP therapy
10	Carboplatin/Paclitaxel (adjuvant therapy)	Carboplatin: AUC = 6.1 (mg/*l*) · hr Paclitaxel: 169.5 mg/m^2	2 cycles	-	0	Completion of designed cycles	1736
	Carboplatin/Paclitaxel	Carboplatin: AUC = 5.9 (mg/*l*) · hr Paclitaxel: 189.7 mg/m^2	4 cycles	SD		Completion of designed cycles	343
11	Carboplatin/Paclitaxel	Carboplatin: AUC = 5.7 (mg/*l*) · hr Paclitaxel: 192.3 mg/m^2	4 cycles	SD	0	Completion of designed cycles	561
12	Carboplatin/Paclitaxel (adjuvant therapy)	Carboplatin: AUC = 6.0 (mg/*l*) · hr Paclitaxel: 173.6 mg/m^2	2 cycles	-	25.0	Completion of designed cycles	2414
	Gemcitabine/Vinorelbine	Gemcitabine: 979.0 mg/m^2 Vinorelbine: 24.5 mg/m^2	3 cycles	PR		Completion of designed cycles	2017
	Carboplatin/Paclitaxel	Carboplatin: AUC = 5.9 (mg/*l*) · hr Paclitaxel: 172.4 mg/m^2	4 cycles	SD		Completion of designed cycles	477
	Pemetrexed	500.0 mg/m^2	4 cycles	SD		Completion of designed cycles	177
	Docetaxel	60.7 mg/m^2	4 cycles	SD		Completion of designed cycles	71
13	Carboplatin/Paclitaxel*[1]	Carboplatin: AUC = 5.6 (mg/*l*) · hr Paclitaxel: 175.2 mg/m^2	2 cycles	PR	25.0	Completion of designed cycles	1100
	Docetaxel	59.4 mg/m^2	3 cycles	SD		Inadequate effect	622
	Carboplatin/Gemcitabine	Carboplatin: AUC = 2.4 (mg/*l*) · hr Gemcitabine: 979.0 mg/m^2	1 cycle	-*[2]		Adverse reaction	482
	Cisplatin/S-1	Cisplatin: 59.4 mg/m^2 S-1: 100 mg/body	4 cycles	SD		Completion of designed cycles	309

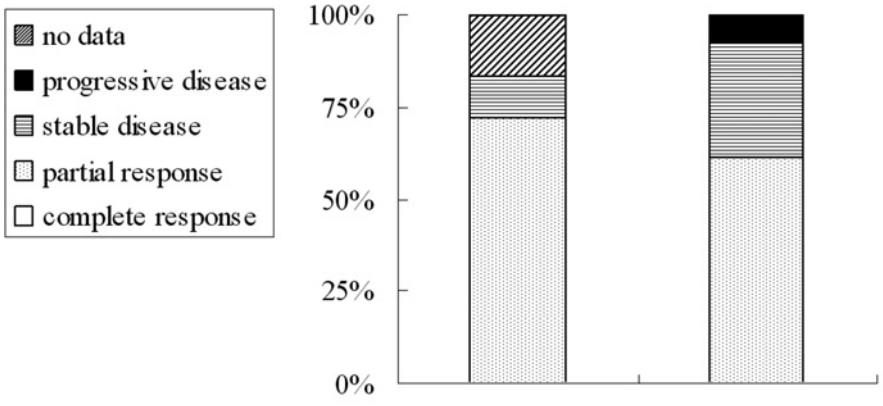
*[1]This therapy was conducted followed by 2 cycles of weekly carboplatin/paclitaxel concurrent radiation therapy. *[2]Treatment was discontinued before efficacy was assessed.

S-1, combination capsule that contains tegafur, gimeracil, and oteracil potassium. Dose of S-1 indicated tegafur dose.

AUC, area under the blood time-concentration curve; BEV-CP, combination therapy with bevacizumab/carboplatin/paclitaxel; PR, partial response; SD, stable disease; PD, progressive disease.

BEV-CP therapy was discontinued after 1 cycle in 3 of the 4 patients and after 2 cycles in the remaining patient. The reasons for discontinuation were colon perforation; thromboembolic events; severe eruption; deterioration of general condition because of severe anorexia and diarrhea, and fatigue, nausea, and hyponatremia, each of which developed in 1 of the 4 patients. BEV-CP therapy was discontinued in 1 patient in the non-FLT group owing to severe peripheral neuropathy. This patient received 3 cycles of BEV-CP therapy, and the cytoreductive effect was a partial response; therefore, the patient was placed on maintenance therapy. One patient in the non-FLT group developed transient ischemic attacks. This patient received 4 cycles of BEV-CP therapy but was not placed on maintenance therapy. The discontinuation rate was lower in the non-FLT group (7.7%) than in the FLT group (22.2%), but the difference did not reach statistical significance ($p = 0.28$).

The adverse effects reported during maintenance therapy are shown in Table 5. In the FLT group, 14 of the 18 patients received maintenance therapy. Four patients who discontinued the BEV-CP therapy because of adverse effects did not receive maintenance therapy. In the non-FLT group, 9 of the 13 patients received maintenance therapy. In the non-FLT group, 1 patient discontinued BEV-CP therapy because of disease progression, 1 developed transient ischemic attacks in response to the therapy, and 2 patients who completed 4 cycles of BEV-CP therapy had not started maintenance therapy as of September 1, 2011. The adverse effects of the main-



	First-line therapy group	Non-first-line therapy group	p value
response rate (RR)	72.2%	61.5%	0.40
disease control rate (DCR)	83.3%	92.3%	0.43

Fisher exact probability test

Figure 2. The cytoreductive effect with bevacizumab/carboplatin/paclitaxel combination therapy. The response rate (RR) was calculated by dividing the number of patients whose cytoreductive effect was better than a partial response by the total number of patients in each group. The disease control rate (DCR) was calculated by dividing the number of patients who achieved an improved cytoreductive effect due to stable disease by the total number of patients in each group.

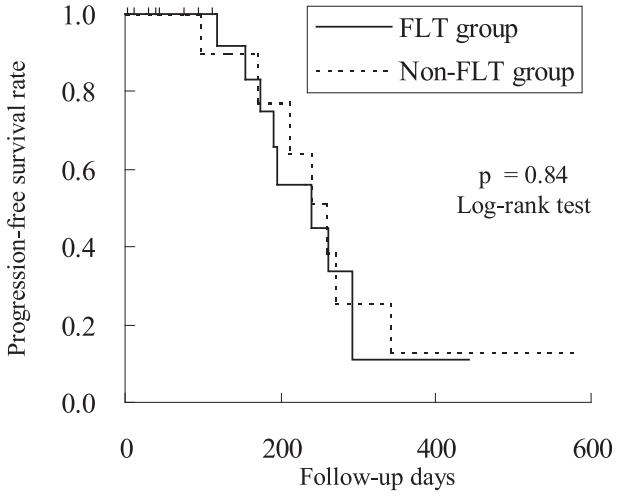


Figure 3. The progression-free survival rate in first-line therapy and non-first-line therapy patients. Vertical bar on graph shows censored cases. FLT means first-line therapy.

tenance therapy were few, and the occurrence rates of such adverse effects were not statistically significant between the 2 groups.

DISCUSSION

In the present study, the patient population was divided into 2 groups based on whether or not they had been treated with chemotherapy before the administration of the BEV-CP therapy, and the efficacy and the tolerability of BEV-CP therapy in the 2 groups were compared. The RR, DCR, and PFS results did not show statistically significant differences between the 2 groups, indicating that the effect of BEV-CP therapy are similar effective in patients previously treated with other chemotherapy regimens.

The rate of discontinuation of BEV-CP therapy due to adverse effects in the non-FLT group was lower than that in the FLT group, but this difference did not reach statistical significance. In addition, the rates of occurrence of adverse effects during the BEV-CP therapy were not statistically significant between the 2 groups, except for the increase in gamma-glutamyl transpeptidase. In particular, the rate of occurrence of hypertension, proteinuria, digestive tract perforation, thromboembolic events, and transient ischemic attacks, which are characteristic adverse effects of BEV, did not show

Table 3. Hematological Toxicity and Abnormal Laboratory Data That Developed with Bevacizumab/carboplatin/paclitaxel Combination Therapy

	First-line therapy group (n = 18)		Non-first-line therapy group (n = 13)		p value	
	all grades	≥grade 3	all grades	≥grade 3	all grades	≥grade 3
WBC decreased	16 (89)	12 (67)	13 (100)	7 (54)	0.33	0.36
Neutrophil count decreased	17 (94)	15 (83)	13 (100)	13 (100)	0.58	0.18
Anemia	16 (89)	2 (11)	13 (100)	3 (23)	0.33	0.34
Platelet count decreased	15 (83)	5 (28)	12 (92)	2 (15)	0.43	0.36
AST increased	3 (17)	0	2 (15)	0	0.66	-
ALT increased	4 (22)	0	2 (15)	0	0.50	-
GGT increased	11 (61)	0	3 (23)	0	0.04	-
Creatinine increased	3 (17)	0	1 (8)	0	0.43	-
Hyponatremia	12 (67)	2 (11)	6 (46)	3 (23)	0.22	0.34
Hypokalemia	8 (44)	2 (11)	3 (23)	0	0.20	0.33
Hyperkalemia	3 (17)	0	3 (23)	0	0.50	-
INR increased	4 (22)	0	2 (15)	0	0.50	-

Fisher exact probability test.

The data are shown by the number of patients (%).

WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, INR: international normalized ratio.

statistically significant differences between the 2 groups. These results indicate the tolerability of BEV-CP for patients who have received prior chemotherapy.

The RDI of BEV, CBDCA, PTX, and the average-RDI in the non-FLT group were lower than those in the FLT group. In particular, the RDI of CBDCA and the average-RDI were significantly lower in the non-FLT group. In the non-FLT group, the mean (SD) first dose of CBDCA was lower (0.90 (0.11) vs. 0.96 (0.06); p = 0.38, Mann-Whitney *U* test), the rate of reduction of the dose of PTX during the BEV-CP therapy was higher (53.8% vs. 22.2%; p = 0.08, Fisher exact probability test), and the mean (SD) number of days between cycles of the BEV-CP therapy was longer (26.2 (8.0) vs. 23.2 (5.6); p = 0.12, Mann-Whitney *U* test) in comparison with the FLT group. The dose-limiting toxicity of CBDCA and PTX was based on bone marrow suppression.[5] In the non-FLT group, the dose of CBDCA and PTX was often reduced because of bone marrow suppression and the administration interval was often extended because the recovery from bone marrow suppression was delayed. This may explain the lower RDI of each drug and the average-RDI in the non-FLT group. When patients who had previously received CBDCA and PTX combination therapy were treated with BEV-CP, it was necessary to carefully determine the dose of CBDCA and PTX and to control the administration intervals by considering the adverse effects developed in previous chemotherapy and by monitoring patients' condition. On the other hand, it was interesting that lowering the average-RDI in the non-FLT group did not lead to a reduction in efficacy in the present study.

The efficacy of BEV for colon cancer patients who have received prior chemotherapy has been reported.[6] However, combination therapy with BEV for advanced NSCLC has been recommended only as first-line chemotherapy according to the JLCS guidelines ver. 2010[1,2] (The Japan Lung Cancer Society. "Clinical Guideline for Lung Cancer ver. 2010.": <http://www.haigan.gr.jp/>, cited 20 April 2012). The use of docetaxel,[7-9] pemetrexed,[10-13] and erlotinib[14,15] was recommended in the JLCS guidelines ver. 2010 as second-line therapy for patients treated with cytotoxic agents as FLT. Takeda et al. reported that a platinum doublet was selected in 20-30% of patients as second-line therapy, and in 10-15% of patients as third-line therapy by physicians in clinical practice (Presented at The 51st Annual Meeting of the Japanese Lung Cancer Society, International Conference Center Hiroshima, Hiroshima, on 3 November, 2010). However, the NSCLC patients without a mutated epidermal growth factor receptor gene had a less favorable prognosis. If the performance status of patient permits and it is thought that the patient could tolerate the adverse effects of platinum doublet when disease pro-

Table 4. Side Effects That Developed with Bevacizumab/carboplatin/paclitaxel Combination Therapy, Excluding Hematological Toxicity and Abnormal Laboratory Data

	First-line therapy group (n = 18)		Non-first-line therapy group (n = 13)		p value	
	all grades	≥grade 3	all grades	≥grade 3	all grades	≥grade 3
Hypertension	14 (78)	6 (33)	11 (85)	5 (38)	0.50	0.75
Proteinuria	5 (28)	0	1 (8)	0	0.18	-
Epistaxia	10 (56)	0	8 (62)	0	0.52	-
Hemorrhoidal hemorrhage	0	0	1 (8)	0	0.42	-
Hematuria	1 (6)	0	0	0	0.58	-
Febrile neutropenia	3 (17)	2 (11)	0	0	0.18	0.33
Nausea	9 (50)	2 (11)	6 (46)	1 (8)	0.56	0.62
Vomiting	1 (6)	1 (6)	0	0	0.58	0.58
Anorexia	13 (72)	4 (22)	11 (85)	6 (46)	0.70	0.15
Dysgeusia	0	-	3 (23)	-	0.06	-
Constipation	14 (78)	0	8 (62)	0	0.28	-
Diarrhea	5 (28)	1 (6)	8 (62)	1 (8)	0.07	0.67
Malaise	13 (72)	-	11 (85)	-	0.70	-
Peripheral neuropathy	16 (89)	0	13 (100)	2 (15)	0.33	0.17
Myalgia	14 (78)	0	10 (77)	0	0.64	-
Arthralgia	10 (56)	0	9 (69)	0	0.35	-
Alopecia	14 (78)	-	9 (69)	-	0.45	-
Mucositis oral	2 (11)	0	4 (31)	1 (8)	0.18	0.42
Cheilitis	0	0	1 (8)	1 (8)	0.42	0.42
Skin disorders	0	0	1 (8)	0	0.42	-
Rash maculopapular	7 (39)	4 (22)	4 (31)	1 (8)	0.47	0.28
Pruritus	5 (28)	2 (11)	5 (38)	0	0.40	0.33
Hiccups	1 (6)	0	3 (23)	0	0.19	-
Edema limbs	3 (17)	0	4 (31)	0	0.31	-
Transient ischemic attacks	0	-	1 (8)	-	0.42	-
Colon perforation	1 (6)	1 (6)	0	0	0.58	0.58
Thromboembolic events	1 (6)	1 (6)	0	0	0.58	0.58

Fisher exact probability test.
The data are shown by the number of patients (%).

Table 5. Side Effects Developed with Maintenance Therapy Using Bevacizumab

	First-line therapy group (n = 14)		Non-first-line therapy group (n = 9)		p value	
	all grades	≥grade 3	all grades	≥grade 3	all grades	≥grade 3
Anemia	1 (7)	0	0	0	0.61	-
ALT increased	1 (7)	0	0	0	0.61	-
GGT increased	0	0	1 (11)	0	0.39	-
Creatinine increased	1 (7)	0	2 (22)	0	0.33	-
Hyponatremia	1 (7)	1 (7)	0	0	0.61	0.61
Hypokalemia	1 (7)	0	2 (22)	0	0.33	-
INR increased	1 (7)	0	0	0	0.61	-
Hypertension	0	0	1 (11)	0	0.39	-
Proteinuria	1 (7)	0	1 (11)	0	0.64	-
Epistaxia	1 (7)	0	0	0	0.61	-
Mucositis oral	1 (7)	0	0	0	0.61	-

Fisher exact probability test.
The data are shown by the number of patients (%).
ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, INR: international normalized ratio.

gression is confirmed, we think that re-treatment by platinum doublet might be one of the treatment options. In addition, if patient do not have a history of hemoptysis and tumor sites are not near large vessels, there is possibility that BEV could be administered in combination. The combination therapy with BEV is expected to prolong PFS, based on clinical trials as first-line therapy. While our study was intended for a few patients, our findings suggest that efficacy of BEV-CP therapy administered to patients as second-line therapy was similar to that of first-line therapy. In addition, tolerability of BEV-CP therapy administered as second-line therapy was also similar to that of first-line therapy by controlling the dose of CBDCA and PTX and administration intervals depending on patients' condition. In future, implementation of prospective clinical trials to estimate efficacy and tolerability of combination therapy with BEV administered as non-FLT is necessary.

本論文内容に関連する著者の利益相反：なし

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