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Feasibility of cisplatin/pemetrexed with 15 mg/kg bevacizumab for the treatment of patients with advanced non-squamous non-small cell lung cancer

FUMIHIKO HIRAI[1], TAKASHI SETO[1], EIKO INAMASU[1], MOTOTSUGU SHIMOKAWA[2], GOUJI TOYOKAWA[1], TSUKIHISA YOSHIDA[1], KANAME NOSAKI[1], TOMOYOSHI TAKENAKA[1], MASAFUMI YAMAGUCHI[1], MITSUHIRO TAKENOYAMA[1] and YUKITO ICHINOSE[1,2]

[1]Department of Thoracic Oncology; [2]Clinical Research Institute, National Kyushu Cancer Center, Fukuoka, Fukuoka 811-1395, Japan

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Abstract. The aim of the present study was to retrospectively evaluate the feasibility of cisplatin/pemetrexed/bevacizumab (CPB) therapy at a bevacizumab (BEV) dose of 15 mg/kg as a first-line chemotherapeutic strategy for patients with advanced non-squamous non-small cell lung cancer (NSCLC). A total of 31 consecutive patients with non-squamous NSCLC were treated with first-line chemotherapy of CPB at a BEV dose of 15 mg/kg at the National Kyushu Cancer Center (Fukuoka, Japan) between November 2009 and December 2011. Clinical characteristics, response rate (RR), progression-free survival (PFS) time, overall survival (OS) time and adverse events were retrospectively analyzed. The 31 patients exhibited a male:female ratio of 21:10 and a median age of 60 years (range, 38-76 years). In total, 5 patients were of clinical stage III and 26 patients were of stage IV, 15 had a performance status of 0 and 16 had a performance status of 1, and 29 patients were diagnosed with adenocarcinoma and 2 were diagnosed with adenosquamous carcinoma. The *EGFR* mutation status was positive (exon 19 deletion), wild-type and unknown in 3, 21 and 7 patients, respectively. A total of 28 patients (90.3%) received a minimum of four courses of CPB therapy. Hematological toxicities classified as grade III or higher included neutropenia (29.0%), anemia (3.2%) and thrombocytopenia (3.2%), however, no severe non-hematological toxicities were observed. Additionally, 22 patients (71.0%) exhibited a partial response and 9 (29.0%) exhibited stable disease, resulting in a RR of 71.0% [95% confidence interval (CI), 41-74]. The median PFS and OS times were 8.4 months (95% CI, 7.9-9.0) and 28.5 months (95% CI, 26.4-30.6), respectively. Therefore, CPB therapy at a BEV dose of 15 mg/kg appears to be a feasible treatment strategy for patients with advanced non-squamous NSCLC.

Correspondence to: Dr Takashi Seto, Department of Thoracic Oncology, National Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka, Fukuoka 811-1395, Japan
E-mail: tseto@nk-cc.go.jp

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Introduction

At present, the standard first-line chemotherapy for patients with advanced non-small cell lung cancer (NSCLC) is platinum doublet chemotherapy using a third-generation anticancer agent (1,2). Pemetrexed (PEM) is a novel metabolic antagonist capable of inhibiting multiple enzymes involved in folate metabolism that has been clinically introduced as an effective therapeutic agent in the treatment of NSCLC (3-5). Previously, the results of two phase III studies indicated the efficacy of PEM as a first-line therapy for advanced NSCLC (6,7). In the JMDB study, cisplatin (CDDP) plus PEM therapy was not determined to be inferior to CDDP plus gemcitabine (GEM) therapy in terms of the overall survival (OS), and the incidence of severe adverse events was significantly lower following CDDP plus PEM therapy (6). Furthermore, in a subgroup analysis according to histological type, the OS of patients with non-squamous NSCLC was significantly longer in the CDDP plus PEM therapy group compared with the CDDP plus GEM group. In addition, the effectiveness of PEM for the treatment of non-squamous NSCLC was supported by two of the phase III studies (JMEI and JMEN) (8,9). Thus, at present, CDDP plus PEM therapy is used as a standard primary therapeutic strategy for patients with advanced non-squamous NSCLC.

Vascular endothelial growth factor (VEGF) is important in tumor neovascularization (10,11), with a previous study reporting that increased VEGF expression levels are associated with prognosis in NSCLC (12). Bevacizumab (BEV) is a humanized monoclonal antibody to VEGF and its clinical efficacy in the treatment of various types of cancer has been previously reported (13-17).

A randomized phase II study conducted in the United States investigated the time to progression in patients with

NSCLC. The study demonstrated a significant extension of the time to progression following carboplatin (CBDCA) and paclitaxel (CP) with BEV therapy compared with CP therapy alone, however, severe lung bleeding occurred in a large number of the patients exhibiting squamous cell carcinoma (18). Subsequently, the Eastern Cooperative Oncology Group (ECOG) conducted a phase III study (E4599) comparing CP therapy with CP plus BEV therapy in patients with advanced non-squamous NSCLC (13). In study E4599, the addition of BEV to platinum doublet chemotherapy resulted in an extension in the primary endpoint of OS [hazard ratio (HR), 0.79; 95% confidential interval (CI), 0.67-0.92]. In the subsequent Avastin® in Lung (AVAiL) study, which was primarily conducted in Europe, the effects of adding 7.5 mg/kg BEV to CDDP plus GEM therapy was evaluated, revealing a significant extension in the primary endpoint of progression-free survival (PFS) (19). In accordance with these results, the addition of BEV to platinum doublet chemotherapy has become a standard treatment strategy for patients with advanced NSCLC, excluding cases of squamous cell carcinoma.

In Japan, the randomized phase II JO19907 study was conducted to clarify the efficacy of adding BEV to CP therapy for Japanese patients. This study demonstrated a significant extension of the PFS time following the administration of CP plus BEV (dose, 15 mg/kg) therapy compared with CP therapy alone (HR, 0.61; 95% CI, 0.42-0.89) (20). Therefore, the BEV combined with platinum therapy is now considered to be a standard chemotherapeutic regimen for the treatment of advanced non-squamous NSCLC in Japan.

Furthermore, the phase III AVAPERL study reported a comparison between maintenance therapy of uncombined BEV, and combined BEV plus PEM following initial treatment with CDDP, PEM and BEV (CPB) chemotherapy. This study reported that the PFS time was significantly extended following maintenance therapy with BEV plus PEM and that the patients exhibited a high tolerability to this therapeutic regime (21). However, the dose of BEV used in the AVAPERL study was 7.5 mg/kg (a commonly used dose in Europe). This differs from the dose of 15 mg/kg used in the E4599 study (13), which identified an extension in the OS period following the addition of BEV to platinum doublet chemotherapy. Furthermore, in the United States and Japan, 15 mg/kg is the approved and most frequently used BEV dose (13,20).

The aim of the present study was to evaluate the safety of CPB therapy with a BEV dose of 15 mg/kg. In addition, the current study aimed to analyze the percentage of patients for whom CPB therapy is applicable as the primary chemotherapeutic strategy for advanced non-squamous NSCLC.

Patients and methods

Patients. A total of 31 consecutive patients with non-squamous NSCLC were treated with CPB therapy (BEV dose, 15 mg/kg) as the first-line chemotherapeutic strategy at the National Kyushu Cancer Center (Fukuoka, Japan) between November 2009 and December 2011. CPB therapy was applied for patients who satisfied all the following criteria: i) An age of ≥20 years; ii) pathologically or cytologically diagnosed as exhibiting non-squamous NSCLC (including cases of adenosquamous NSCLC with a significant adenocarcinoma component); iii) disease for which CDDP treatment was considered to be applicable; iv) clinical stage III or IV disease (including stage IIIA, non-applicable for radical radiotherapy); v) evaluable lesions (cases with no measurable lesions were acceptable); vi) no severe disorders of the major organs (bone marrow, heart, lungs, liver and kidneys); and vii) laboratory analysis data at the commencement of treatment indicating a neutrophil count of ≥2,000/mm^3 (normal range, 1,500-5,950/mm^3), a hemoglobin level of ≥9.0 g/dl (normal range, 13.5-17.0 g/dl), a platelet count of ≥10.0x10^4/mm^3 (normal range, 12.0-35.0x10^4/mm^3), a prothrombin time-international normalized ratio of ≤1.5 (normal ratio, 1.0), an aspartate aminotransferase (AST) level of ≤100 IU/l (normal range, 13-33 IU/l), an alanine aminotransferase (ALT) level of ≤100 IU/l (normal range, 8-42 IU/l), a total bilirubin level of ≤1.5 mg/dl (normal range, 0.3-1.2 mg/dl), a serum creatinine level of ≤1.2 mg/dl (normal range, 0.6-1.1 mg/dl), a creatine clearance rate (calculated with the Cockcroft-Gault equation) of ≥45 ml/min [normal range, 90-120 ml/min (male); 80-110 ml/min (female)], a urinary protein level of ≤1+ (normal level, 0) and an SpO_2 level of ≥90% (normal range, 90-100%). CPB therapy was not applied for patients with brain metastases, a history of hemoptysis (≥2.5 cm^3 blood per bleeding episode from the respiratory tract) or the possibility of tumor invasion of the large blood vessels based on diagnostic imaging. This study was approved by the ethics committee of the National Kyushu Cancer Center. Patients were provided with sufficient information regarding the treatment strategy prior to entry into the current study. Treatment was administered to all patients following the receipt of written consent.

Treatment strategy and study design. A total of 4-6 courses of CPB therapy were administered at intervals of 3 weeks, with initial doses of 75 mg/m^2 CDDP plus 500 mg/m^2 PEM plus 15 mg/kg BEV administered on day 1. To reduce the incidence of adverse events caused by PEM, patients were administered folic acid and vitamin B12 supplements beginning 7 days prior to the commencement of therapy. After 4-6 courses of CPB therapy, patients free of progressive disease received maintenance therapy with 15 mg/kg BEV alone or combined with 500 mg/m^2 PEM. The condition of the individual patient was considered upon selection of one of the two maintenance regimes. Maintenance therapy was continued at intervals of 3 weeks until disease progression was noted.

Prior to commencing therapy with CPB, diagnostic imaging with computed tomography (CT) scanning was performed to yield baseline information. Diagnostic imaging, including CT scanning, was repeated every sixth week from the commencement of treatment until disease progression was noted. Adverse events were evaluated in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (22). Additionally, responses to the treatment strategies were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (23).

Statistical analysis. Survival curve calculations were performed using the Kaplan-Meier method. PFS time was defined as the time from the start of treatment to disease

Table I. Patient characteristics[a].

Characteristic	No. of patients (n=31)
Gender	
Male	21
Female	10
ECOG performance status	
0	15
1	16
Histology	
Adenocarcinoma	29
Adenosquamous	2
Stage	
IIIA[b]	2
IIIB	3
IV	26
EGFR mutation status	
Positive (exon 19 deletion)	3
Wild-type	21
Unknown	7

[a]Patients had a median age of 60 years (range, 38-76 years). [b]Unresectable and non-applicable for radiotherapy. ECOG, Eastern Cooperative Oncology Group.

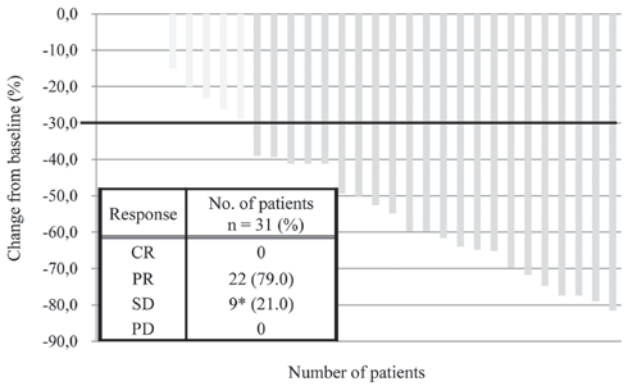

Figure 1. Waterfall plot of the best responses of patients exhibiting advanced non-squamous non-small cell lung cancer with *EGFR* wild-type or unknown status who received cisplatin/pemetrexed/bevacizumab chemotherapy. Response rate, 71.0% (95% confidence interval, 41-74%). *Including 4 patients with SD who were not evaluated. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

progression or mortality. OS time was defined as the time from the start of treatment to mortality. Follow-up concluded on April 30, 2013, for patients still receiving treatment or commencing receipt of subsequent treatment strategies.

Results

Patient characteristics. Table I summarizes the background characteristics of the 31 patients that received CPB therapy in the present study. The cohort consisted of 21 male and 10 female individuals, with a median age of 60 years (range, 38-76 years). The ECOG performance status (PS) was 0 in 15 cases and 1 in 16 cases, and the histological type was adenocarcinoma in 29 cases and adenosquamous carcinoma in 2 cases. Furthermore, the clinical stage was IIIA, IIIB and IV in 2, 3 and 26 cases, respectively. Additionally, the *EGFR* mutation status was positive (exon 19 deletion) in 3 patients, wild-type in 22 patients and unknown in 6 patients.

Treatment strategy. The median follow-up time for the 31 patients who received CPB therapy was 1,057 days (range, 640-1288 days). A total of ≥4 courses of CPB therapy were administered to 28/31 patients (90.3%). Of the 3 patients who received fewer than 4 courses, 1 patient discontinued therapy after 1 course due to a reduction in the ECOG PS, and the remaining 2 patients discontinued therapy due to disease relapse after 3 courses. Maintenance therapy was administered to 24/31 patients (77.4%), consisting of BEV in 15 cases (62.5%), PEM in 6 cases (25.0%) and combined PEM plus BEV in 3 cases (12.5%). The median number of courses of BEV, PEM and PEM/BEV maintenance therapy was 5 (range, 1-21 courses), 3 (range, 1-9 courses) and 4 (range, 3-15 courses), respectively. The primary reasons for the selection of PEM maintenance therapy among the 6 cases were hypertension (2 cases), gastric ulcers (1 case), diverticulitis (1 case) and bloody sputum (1 case). The reasons for the non-applicability of maintenance therapy in 7 cases were disease progression (5 cases), patient decision (1 case) and surgery after the initial therapy (1 case).

Response and survival analysis. Treatment efficacy was evaluated by each attending physician in accordance with the RECIST criteria, version 1.1. Among the 31 patients who received CPB therapy, the best overall response was a partial response in 22 cases and stable disease in 9 cases. Furthermore, no cases of progressive disease or complete response were observed; therefore, the response rate was 71.0% (95% CI, 41-74%; Fig. 1). The median PFS and OS time were 8.4 months (95% CI, 7.9-9.0; Fig. 2A) and 28.5 months (95% CI, 26.4-30.6 months; Fig. 2B), respectively.

Safety analysis. Observed hematological toxicities of grade III or higher included neutropenia (9 cases; 29.0%), decreased hemoglobin levels (1 case; 3.2%) and thrombocytopenia (1 case; 3.2%). No adverse events classified as non-hematological toxicities or febrile neutropenia were observed, however, 4 cases of grade III hypertension (12.9%) and 1 case of colitis (3.2%; Table II) did occur. Grade II hemoptysis was observed in 1 case (3.2%) during the first course of treatment. This patient subsequently developed grade III anorexia and nausea during the first course of treatment; therefore, BEV was discontinued and the therapy was changed from CDDP to CBDCA from the second course of treatment onward in this patient. No treatment-associated mortality was observed.

Discussion

Two phase III studies (E4599 and AVAiL) demonstrated extension in the OS and PFS times (primary endpoints)

Table II. Toxicities and grades of patients with advanced non-squamous non small-cell lung cancer.

	Patients, % (n=31)				
Toxicity	G1	G2	G3	G4	G3/4
Neutropenia	0	6	29	0	29
Anemia	19	23	3	0	3
Thrombocytopenia	3	6	0	3	3
Febrile neutropenia	0	0	0	0	0
Hypertension	3	42	13	0	10
Bleeding					
Hemopytsis	0	3	0	0	3
Epistaxis	5	0	0	0	0
Pulmonary thromboembolism	0	0	0	3	0
Congestive heart disease	0	0	0	0	0
Proteinuria	10	0	0	0	0
Fatigue	13	10	3	0	3
Anorexia	58	16	6	0	6
Vomiting	6	6	0	0	0
Diarrhea	3	0	0	0	0
Constipation	19	3	0	0	0
Gastric ulcer	0	0	3	0	3
Colitis	0	0	3	0	3
Pneumonitis	0	0	0	0	0
Elevated AST	16	6	0	0	0
Elevated ALT	13	6	0	0	0
Elevated creatinine	32	3	0	0	0

G, grade; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

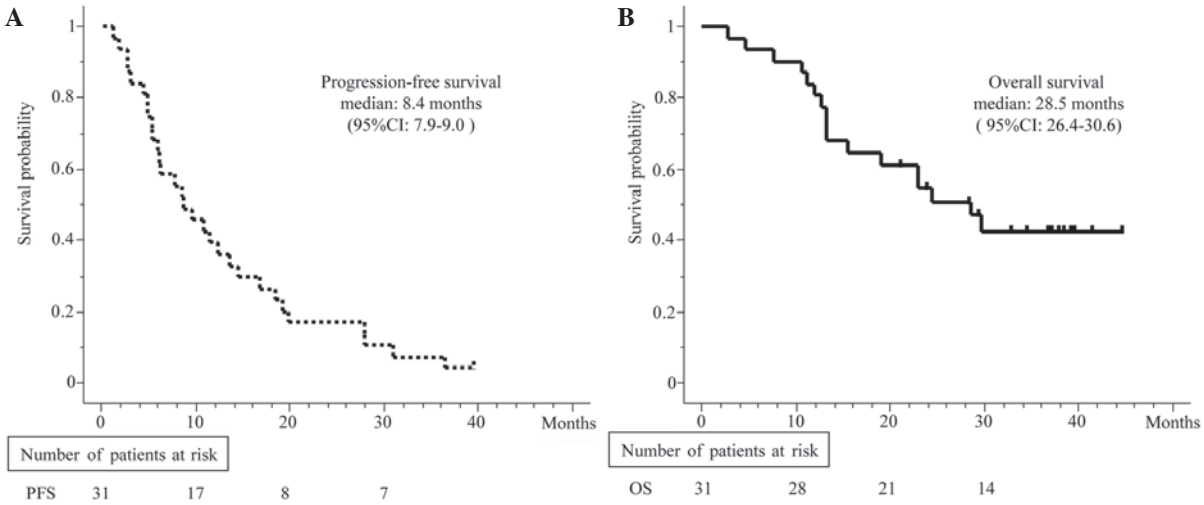

Figure 2. Survival curves of patients with advanced non-squamous non-small cell lung cancer showing (A) progression-free and (B) overall survival.

following treatment with BEV in combination with standard platinum doublet chemotherapy (13,19). Based on these findings, this therapeutic regime has become a standard for the treatment of patients with advanced NSCLC, excluding cases of squamous cell carcinoma. However, in all phase III studies conducted thus far, the effects of adding BEV to

platinum doublet chemotherapy have been evaluated only for platinum doublet CP or CDDP plus GEM (doublets that are commonly used at the start of such studies). To the best of our knowledge, no studies have been designed to evaluate the effect of adding BEV (dose, 15 mg/kg) to platinum doublet CDDP plus PEM therapy. Thus, the present retrospective study allowed clarification of the tolerability of combined CDDP, PEM and BEV (dose, 15 mg/kg) therapy in patients with non-squamous NSCLC.

In the current study, CPB therapy at a BEV dose of 15 mg/kg resulted in a median PFS time of 10.5 months and a median OS time of 27.2 months. Therefore, the outcome of this treatment strategy dose not appear to be inferior to the outcomes of alternative platinum doublet plus BEV (15 mg/kg) regimes reported in previous phase II studies (24,25). In addition, the outcome of the present study is comparable to the outcome of the JO19907 study, which yielded a median PFS time of 6.1 months (20), and the subgroup analysis of Asian subjects in the AVAiL study, which yielded median PFS times of 8.5 (15 mg/kg) and 8.2 months (7.5 mg/kg) (26). Furthermore, the response rate to CPB therapy in the present study was 71.0% (95% CI, 41-74%), a value not inferior to the response rate of 61% recorded in the CP plus BEV (15 mg/kg) therapeutic group of a previously conducted domestic randomized phase II trial (20).

In the present study, no previously unknown toxicities associated with BEV and no treatment-associated mortalities were noted. In a previous study (JO19907) (20), the CP plus BEV therapeutic group developed grade III or higher neutropenia, decreased hemoglobin levels and thrombocytopenia at incidences of 91, 12 and <5%, respectively. In addition, the incidence of febrile neutropenia was 8%. In contrast to the results of the JO19907 study, febrile neutropenia was not observed in the present study, and the incidence of hematological toxicities was typically lower in patients treated with combined CDDP plus PEM therapy.

The adverse events associated with BEV treatment were comparable between the present and aforementioned studies. In a subgroup analysis of data regarding Asian subjects obtained in the AVAiL study (27), the incidence of grade III or higher hypertension, bleeding and proteinuria in the 15 mg/kg BEV group was 9.1, 3.0 and 6.1%, respectively. Therefore, the indicators of BEV-specific toxicities observed in the present study were not markedly different from those identified in previous studies. Furthermore, in consideration of the inclusion and exclusion criteria adopted in previous clinical analyses of BEV, the present study excluded patients exhibiting: i) A history of hemoptysis, ii) void formation and iii) tumor invasion of large blood vessels. As a result, no subjects developed grade III or higher hemoptysis or pulmonary bleeding in the present study.

The most frequent reason for the non-applicability of CPB therapy was the presence of brain metastases. BEV is not contraindicated for patients with brain metastases in Western countries. By contrast, BEV was contraindicated for patients with brain metastasis following its approval under the National Health Insurance program in Japan (during the current study period). However, the relative contraindication of BEV for patients with brain metastasis was lifted in Japan in June 2012. Therefore, CPB therapy will be applied in more cases as it begins to be administered to patients with brain metastasis. Furthermore, a recent report demonstrated the effectiveness of CDDP plus PEM therapy in patients with brain metastasis (28). Thus, a prospective evaluation of CPB therapy in patients exhibiting brain metastasis with a poor prognosis is required.

In conclusion, the present single center retrospective study clarified the feasibility, including the efficacy and safety, of CDDP plus PEM combined with 15 mg/kg BEV as a primary therapeutic strategy for patients with advanced non-squamous NSCLC.

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