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Evaluation of Natriuretic Peptide in Non-small Cell Lung Cancer Patients Treated with Bevacizumab Together with Carboplatin–Paclitaxel: A Prospective Study

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Abstract. *Aim: To identify predictive markers for efficacy of combination bevacizumab and carboplatin-paclitaxel treatment in patients with advanced non-squamous non-small cell lung cancer (NSCLC). Patients and Methods: Twenty patients received carboplatin (area under the concentration-time curve (AUC) 6 mg/ml×min) and paclitaxel (200 mg/m^2) with bevacizumab (15 mg/kg) on day 1 of a 21-day cycle. After four cycles of induction therapy, patients received bevacizumab maintenance therapy until disease progression or unacceptable toxicity occurred. Plasma and serum samples (baseline, day 8 and before cycle 2) were analyzed for natriuretic peptide content. Results: Plasma brain natriuretic peptide (BNP) levels were significantly decreased at day 8 (20.1±4.0 pg/ml vs. 9.1±1.8 pg/ml, p=0.0002). Patients whose plasma BNP level was reduced to <50% of the baseline at day 8 had a longer progression-free survival (PFS) than those with a less decrease (9.73 versus 2.63 months, p=0.00013). In multivariate Cox analysis, decrease of plasma BNP concentration was associated with a longer PFS (p=0.0022). Conclusion: Decrease of plasma BNP concentration correlated with PFS after a treatment of combination bevacizumab plus carboplatin-paclitaxel.*

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Lung cancer is the most common cause of cancer-related death worldwide (1). Improved understanding of activating mutations in the epidermal growth factor receptor (*EGFR*) gene and translocations involving the anaplastic lymphoma kinase (*ALK*) gene has resulted in the development of agents that have improved the survival of patients with non-small cell lung cancer (NSCLC) harboring these driver oncogenes (2, 3). Recently, pembrolizumab, a humanized monoclonal antibody against programmed death 1, has improved the survival of patients with programmed death ligand 1 expression on at least 50% of tumor cells in the first-line setting (4). However, in most patients with NSCLC without identifiable driver oncogenes, platinum-based chemotherapy regimens have remained standard first-line therapy.

Bevacizumab is a recombinant monoclonal antibody targeting vascular endothelial growth factor (VEGF). Two phase III trials have demonstrated that the addition of bevacizumab to paclitaxel plus carboplatin for non-squamous NSCLC yields a significant survival benefit compared to paclitaxel and carboplatin alone (5, 6). Current clinical guidelines recommend bevacizumab with paclitaxel plus carboplatin induction followed by bevacizumab continuation maintenance as a standard first-line treatment for patients with advanced non-squamous NSCLC (7, 8).

Because there are no reliable predictors or markers for treatment response to bevacizumab, one aim of the present study was to identify such biomarkers. Previously, two phase III trials (CALGB 90206 and ECOG 4599) showed that patients who developed hypertension on bevacizumab treatment had a significantly improved survival relative to those who did not (9, 10). The mechanism underlying the high blood pressure associated with bevacizumab treatment is thought to be inhibition of VEGF that causes a decrease in the production of endothelial nitric oxide synthase (eNOS) (11). The natriuretic peptide family includes atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), inducing activation of eNOS and resulting in lowered blood pressure (12). Therefore, we hypothesized that blood natriuretic peptide levels might be decreased by bevacizumab treatment. In this trial, we evaluated the natriuretic peptide levels in plasma and serum as circulating factors to explore potential predictive biomarkers of treatment response and resistance to this regimen.

Patients and Methods

Objectives and study design. This open-label, single-arm, multicenter pilot study was conducted at 3 sites in Japan. The primary objective was median progression-free survival (PFS). Secondary objectives were the objective response rate (ORR) during induction chemotherapy, overall survival (OS) and toxicity. PFS was defined as the time from study registration to disease progression or death. OS was defined as the time from study registration until death from any cause. Data on patients not known to have died or have progressed were censored at the date of last assessment. Natriuretic peptide levels in plasma and serum were measured at baseline, 8 days after the first cycle of chemotherapy and the day before the second cycle of chemotherapy began.

The study protocol was approved by each Institutional Ethics Committee and adhered to the principles outlined in the Guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all patients before commencement of the study. This study is registered with the University Hospital Medical Information Network in Japan (UMIN) Clinical Trials Registry, number UMIN000005328.

Patient selection. Patients were enrolled when they met all the following entry criteria: (i) histologically- or cytologically-confirmed non-squamous NSCLC; (ii) chemotherapy-naive stage IIIB/IV or postoperative recurrence; (iii) age ≥20 years; (iv) Karnofsky performance status (KPS) 70-100; (v) measurable or evaluable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (13); (vi) adequate hematological (neutrophil count ≥2,000/μl, platelets ≥100,000/μl and hemoglobin ≥9.0 g/dl), renal (serum creatinine ≤1.5 mg/dl, proteinuria ≤1+), liver (serum total bilirubin ≤1.5 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN)) and hemostatic (activated partial thromboplastin time ≤ULN, international normalized ratio of prothrombin time ≤1.5) function; (vii) estimated life expectancy >3 months; (viii) written informed consent available.

On the other hand, exclusion criteria were: (i) central nervous system metastases; (ii) history of gross hemoptysis (>2.5 ml); (iii) history of coagulation disorders or therapeutic anticoagulation; (iv) medically uncontrolled hypertension; (v) pregnancy, lactation, suspicion of being pregnant; (vi) clinically significant cardiovascular disease; (vii) radiation therapy outside the chest field within 2 weeks before enrollment; (viii) clinically significant complications or unstable medical conditions; (iv) other active neoplasia.

Study treatment. Patients received carboplatin (area under the concentration-time curve 6 mg/ml×min) and paclitaxel (200 mg/m^2) with bevacizumab (15 mg/kg) on day 1 and then tri-weekly. After four cycles of induction therapy, patients with no evidence of disease progression received bevacizumab maintenance therapy until disease progression or unacceptable toxicity occurred.

Subsequent treatment cycles were withheld until the following criteria were met: neutrophil count ≥1,500/mm^3, platelet count ≥100,000/mm^3, AST/ALT ≤3 times, proteinuria ≤1+ or ≤grade 1, other non-hematological toxicity ≤grade 2 and physician's recommendation. If toxicity did not resolve within 43 days, the patient was excluded from further study participation.

Assessments. Required baseline assessments included chest and abdominal computed tomography (CT), cranial CT or magnetic resonance imaging (MRI), as well as bone scintigraphy or positron emission tomography (PET), within four weeks before enrollment. Within 2 weeks prior to study entry, all patients underwent chest radiography, complete blood cell count and measurement of blood chemistry values. Within one week prior to study entry, all patients underwent physical examination, body weight measurement and performance status assessment. Medical history was recorded.

Overall response was evaluated according to RECIST version 1.1 every two cycles (13). Toxicity was graded by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Blood sampling and assay for natriuretic peptides. Natriuretic peptide levels in plasma and serum were measured at baseline, 8 days after the first cycle of chemotherapy and the day before the second cycle of chemotherapy began. Plasma or serum was separated from the blood samples and frozen at –80˚C until assayed. Plasma ANP and BNP concentrations were measured using the AIA-PACK chemiluminescence immunoassay (TOSOH Corporation, Tokyo, Japan). Serum concentrations of the N-terminal part of pro-brain natriuretic peptide (NT-proBNP) and N-terminal part of pro-C-type natriuretic peptide (NT-proCNP) were determined by chemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN, USA) and ELISA (Biomedica, Vienna, Austria), respectively.

Statistical analysis. The main efficacy analysis was conducted on the full analysis set from which ineligible patients were omitted. Kaplan-Meier (K-M) plots were used for PFS and OS analyses; the median and 95% confidence interval (CI) were determined. Statistical significance was defined as $p<0.05$. All biomarker levels and their changes were described using quartiles; the changes in biomarkers were defined using ratios and assessed with the one-sample, two-sided, exact Wilcoxon test. Missing measurements of biomarkers were excluded from the analysis. To compare groups, the Pearson's χ^2 test was used for categorical data. In multivariate Cox analysis, decrease of plasma ANP concentration, decrease of plasma BNP

Table I. *Patients' characteristics (n=20).*

Characteristic	No. of patients
Age in years	
Median (range)	67.5 (53-77)
Gender	
Male	14
Female	6
KPS	
90-100	18
70-80	2
Smoking status	
Former/current smoker	14
Never-smoker	6
Clinical stage	
IIIB	2
IV	18
Histology	
Adenocarcinoma	19
Pleomorphic carcinoma	1
EGFR mutation status	
(–) or unknown	12
Ex 19 del	5
L858R	2
G719A	1

EGFR, Epidermal growth factor receptor; KPS, Karnofsky performance status.

Table II. *Hematologic and laboratory toxicity (n=20).*

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)
Hematological					
Leukopenia	2	4	11	3	14 (70)
Neutropenia	1	2	4	13	17 (85)
Anemia	9	5	4	0	4 (20)
Thrombocytopenia	4	3	3	1	4 (20)
Non-Hematological					
Febrile neutropenia			3	2	5 (25)
Total bilirubin	4	2	0	0	0 (0)
AST increased	9	2	0	0	0 (0)
ALT increased	11	1	0	0	0 (0)
Creatinine increased	6	0	0	0	0 (0)
Nausea	3	4	1		1 (5)
Vomiting	1	2	1	0	1 (5)
Anorexia	6	2	4	0	4 (20)
Fatigue	4	3	1		1 (5)
Neuropathy	7	7	3	0	3 (15)
Diarrhea	4	0	0	0	0 (0)
Constipation	9	2	1	0	1 (5)
Rash	3	4	0	0	0 (0)
Pneumonitis	0	0	1	0	1 (5)
Mucositis oral	4	3	0	0	0 (0)
Epistaxis	2	0	0	0	0 (0)
Hemorrhoidal hemorrhage	0	2	0	0	0 (0)
Hypertension	4	10	6	0	6 (30)
Proteinuria	2	3	0	0	0 (0)

AST, Aspartate aminotransferase; ALT, alanine aminotransferase; CTC version AE 4.0.

concentration and smoking history were selected because their significance was $p<0.10$ in univariate analysis. All analyses were performed with JMP software, version 10 (SAS Institute Inc., Cary, NC, USA). The cut-off date was November 30, 2015.

Results

Between March 2011 and December 2013, a total of 20 patients were enrolled in this trial. Their characteristics are shown in Table I. The cohort comprised 14 men and 6 women with a median age of 67.5 years (range=53-77). Nineteen patients had adenocarcinoma and one had pleomorphic carcinoma histology. A history of smoking was recorded for 14 patients, while 6 had never smoked. The majority of patients (n=18) had good KPS (90 or 100). Two patients had stage IIIB disease and 18 had stage IV disease. Eight patients (40%) harbored activating epidermal growth factor receptor (*EGFR*) mutations (exon 18, 19 or 21).

Of the 20 patients, 11 achieved a partial response (PR), 7 had stable disease (SD) and one had progressive disease (PD). This resulted in an overall response rate (RR) of 55% (95% CI=34.2-74.1%) and a disease control rate of 90% (95% CI=69.8-97.2%). Response could not be evaluated in one patient due to sudden death after one treatment cycle.

The median PFS of all patients was 5.7 months (95% CI=3.1-13.8) (Figure 1). The median OS of all patients was 28.9 months (95% CI=13.2-not applicable (NA)) (Figure 1). In 12 patients with wild-type *EGFR*, the median PFS and OS were 4.18 months (95% CI=2.63-NA) and 12.8 months (95% CI=7.87-NA), respectively, while in the other eight patients harboring *EGFR* mutations, the median PFS and OS were 7.63 months (95% CI=5.83-NA) and 53.0 months (95% CI=NA-NA), respectively (Figure 1).

Hematological and non-hematological toxicities are summarized in Table II. Of grade 3 and greater hematological toxicities, neutropenia, decreased hemoglobin and thrombocytopenia were observed in 17 (85%), 4 (20%) and 4 patients (20%), respectively. Of the non-hematological toxicities, febrile neutropenia was observed in 5 patients (25%). Other grade 3 or greater toxicities included hypertension seen in 6 patients (30%), neuropathy in 3 (15%), anorexia in 4 (20%) and the following in one patient each: nausea, vomiting, fatigue, constipation, pneumonitis and sudden death (5% each). In two patients, bevacizumab maintenance therapy was stopped because grade 2 proteinuria did not resolve within 43 days.

Average ANP and BNP levels in plasma were significantly decreased on day 8 (18.7±3.4 pg/ml and 9.1±1.8 pg/ml,

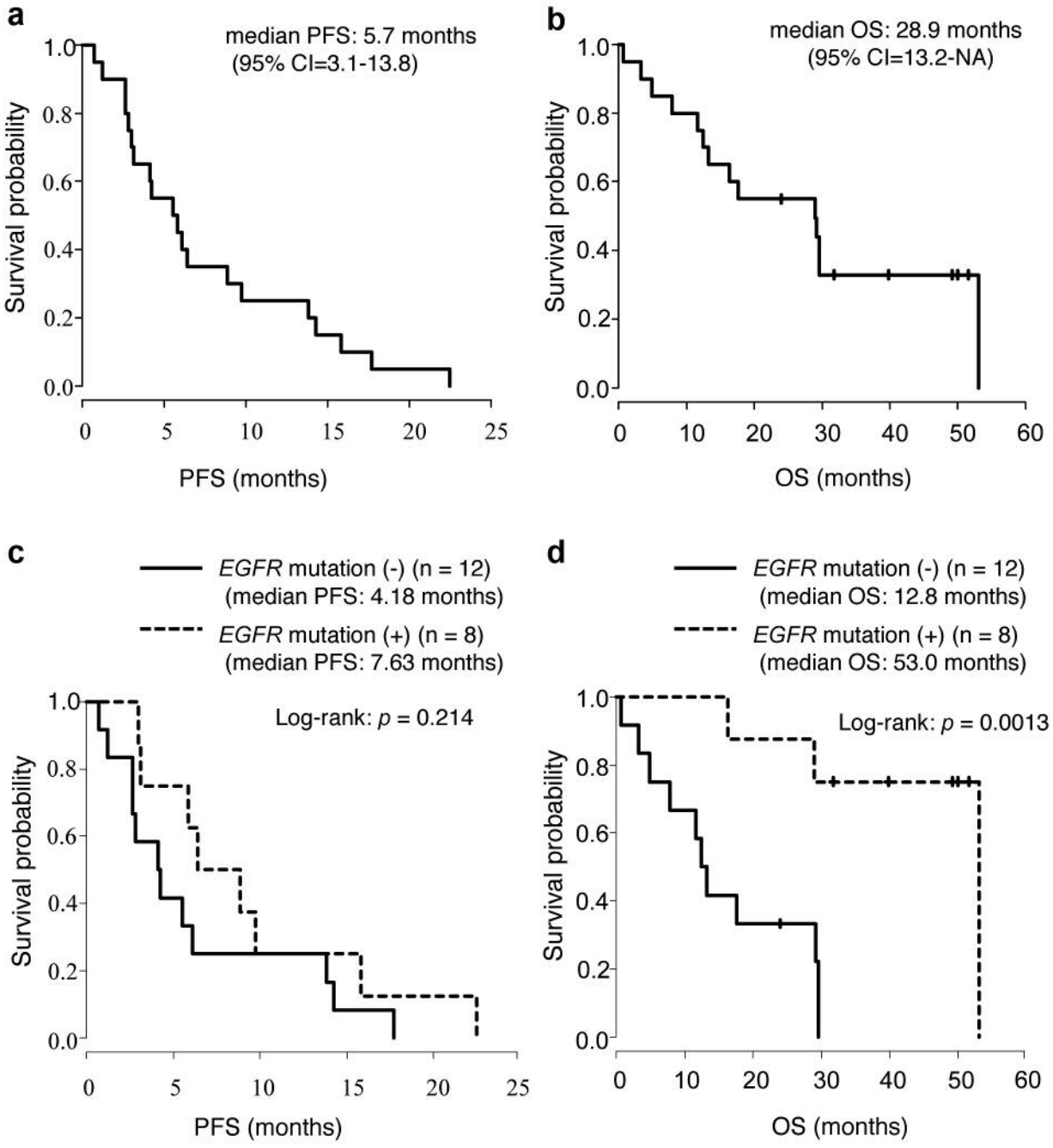

Figure 1. *Kaplan–Meier curves from the enrollment time. (a) and (c) Progression-free survival (PFS). (b) and (d) Overall survival (OS). CI, Confidence interval; NA, not applicable; EGFR, epidermal growth factor receptor.*

respectively) relative to baseline (30.4±4.5 pg/ml and 20.1±4.0 pg/ml, p=0.004 and 0.0002, respectively) (Figure 2). The average NT-proBNP levels in serum were 72.7±27.1 pg/ml at baseline, 54.3±22.7 pg/ml on day 8 of the first cycle of chemotherapy and 88.6±30.4 pg/ml on the day before the second cycle. Values for NT-proCNP levels in serum were 4.5±1.0 pg/ml, 4.0±0.9 pg/ml, 3.9±0.9 pg/ml. The only significant difference noted here is in NT-proBNP levels between day 8 and the day before the second cycle (p=0.03, Figure 2). Patients whose plasma ANP and BNP levels on day 8 were reduced to less than half of their baseline pre-treatment values had a longer PFS, compared to the other

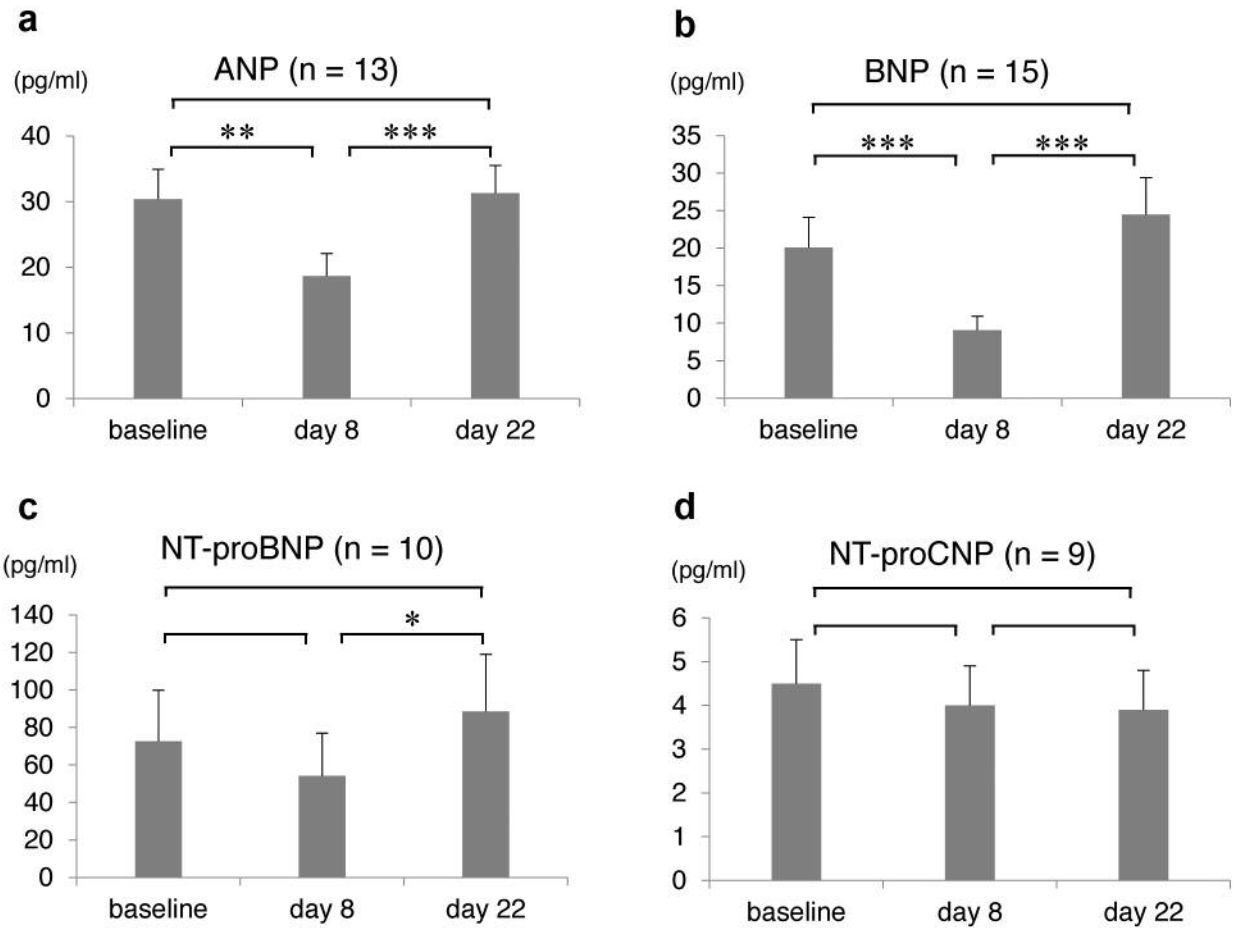

Figure 2. *Natriuretic peptide family member levels in plasma and serum. (a) Plasma atrial natriuretic peptide (ANP) levels (n=13), (b) plasma brain natriuretic peptide (BNP) levels (n=15), (c) Serum N-terminal part of pro-brain natriuretic peptide (NT-proBNP) levels (n=10), (d) serum N-terminal part of pro-c-type natriuretic peptide (NT-proCNP) levels (n=9) in each group at baseline, 8 days after the first cycle of chemotherapy (day 8) and the day before the second cycle of chemotherapy (day 22). Data are expressed as the mean±standard error (SE). Statistical significance was determined with the Wilcoxon test. *p≤0.05, **p≤0.01, ***p≤0.001.*

patients (15.8 *vs*. 4.18 months, p=0.047 and 9.73 *vs*. 2.63 months, p=0.00013, respectively) (Figure 3).

Patients in whom plasma BNP levels on day 8 showed less than half of the value on day 1 had a higher tendency to experience grade 3 hypertension (p=0.017, χ^2 test). On the other hand, no association was found between plasma ANP levels and occurrence of grade 3 hypertension (p=0.70, χ^2 test).

Univariate analysis revealed correlations between PFS and both decreased plasma ANP concentration and decreased plasma BNP levels (Table III). In multivariate analysis, including decrease of plasma ANP concentration, decrease of plasma BNP and smoking history, decreased plasma BNP remained the only statistically significant factor (Table III).

Discussion

Several biomarkers have been reported as predictive for the efficacy of chemotherapy together with bevacizumab (14). Hedge *et al*. showed that pretreatment levels of total circulating VEGF were prognostic for the efficacy of treatment with bevacizumab in patients with colorectal cancer, lung cancer and renal cell carcinoma (15). Ronzoni *et al*. showed that circulating endothelial cells and endothelial progenitor cells were predictive markers of clinical outcome on treatment with bevacizumab in patients with advanced colorectal cancer (16). However, the clinical usefulness of such biomarkers has yet to be proven.

In the present study, we measured natriuretic peptide family member levels in plasma and serum at baseline, 8

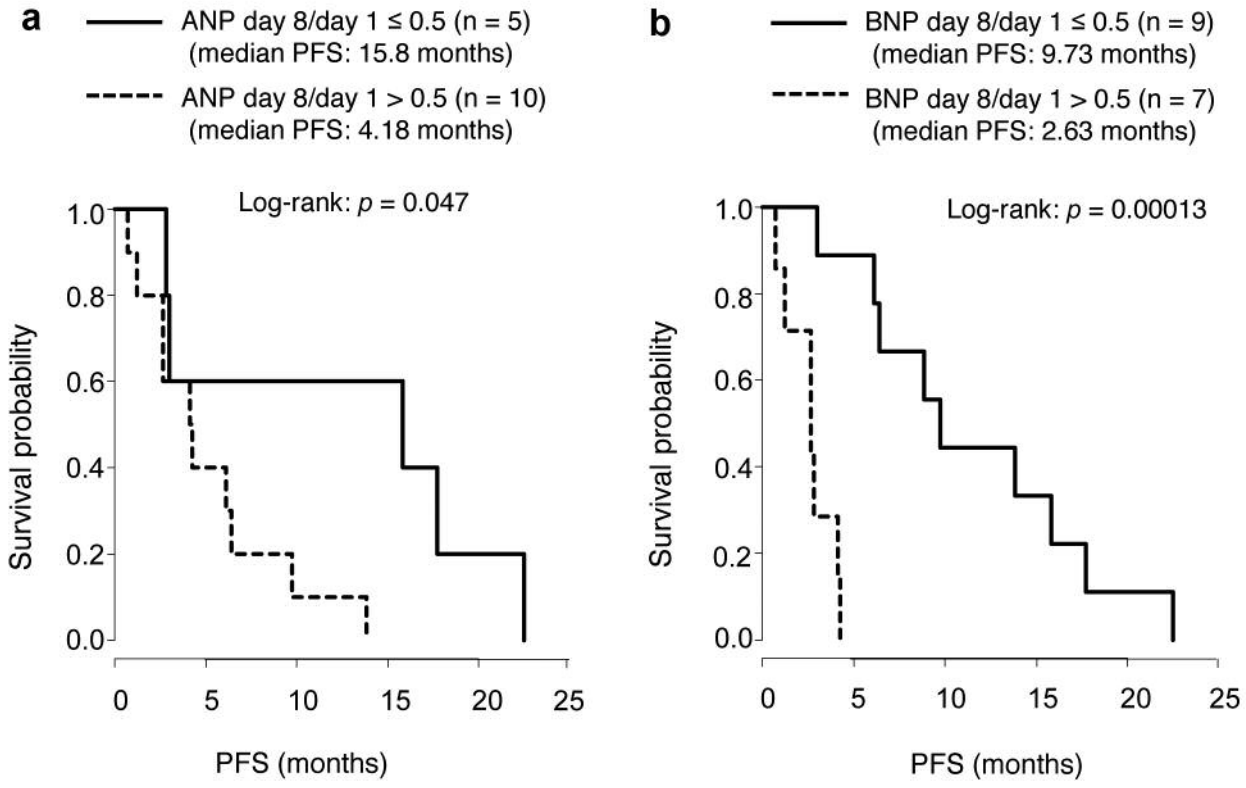

Figure 3. *Kaplan–Meier (K-M) curves by subgroup. Patients whose plasma atrial natriuretic peptide (ANP) (a) and brain natriuretic peptide (BNP) (b) levels on day 8 were reduced to less than half of the baseline values are denoted as "day 8/day 1≤0.5 group". The other patients are designated as "day 8/day 1>0.5 group". K-M curves show progression-free survival (PFS).*

Table III. *Results of univariate and multivariate Cox analyses for progression-free survival (n=15).*

	Univariate			Multivariate		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (>70 years)	1.24	0.40-3.62	0.70			
Gender (female)	0.46	0.12-1.40	0.18			
Decrease of ANP (yes)	0.23	0.035-0.92	0.037*	0.42	0.059-1.85	0.27
Decrease of BNP (yes)	0.052	0.0028-0.31	0.0005*	0.070	0.0036-0.42	0.0022*
Hypertension (grade 3)	0.53	0.15-1.63	0.28			
Smoking history (never)	0.35	0.078-1.16	0.088	0.43	0.093-1.49	0.19

"Decrease of ANP or BNP" was defined as plasma atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP) level at day 8 reduced to less than half of the baseline values. HR, Hazard ratio; CI, confidence interval. *Statistical significance.

days after the first cycle of chemotherapy and on the day before the second cycle of chemotherapy. ANP and BNP levels in plasma were decreased on day 8 relative to baseline, supporting our hypothesis that inhibition of VEGF reduces the production of natriuretic peptides and, subsequently, inactivates eNOS, resulting in increased blood pressure. On the other hand, there was no significant difference between baseline and the day before the second cycle of chemotherapy, probably due to the 20-day half-life of bevacizumab in the circulation (17). NT-proBNP is an N-

terminal inactive protein that is cleaved from BNP (18). There is considered to be a correlation of the NT-proBNP level in the serum with BNP in the plasma. In this study, the NT-proBNP level in serum on day 8 was decreased compared with the baseline level. To the best of our knowledge, this is the first evidence of decreased plasma ANP and BNP levels induced by bevacizumab treatment. The underlying mechanism of this effect remains unknown.

This study compared PFS of NSCLC patients treated with carboplatin and paclitaxel plus bevacizumab, using clinical markers. In multivariate Cox analysis, we found that patients with BNP levels that were reduced to less than half of the baseline level on day 8 had a longer PFS than other patients. Several factors are known to influence plasma BNP levels, which negatively correlate with body mass index (19), and are relatively high in patients with renal failure and markedly high in patients with heart failure (20). Therefore, we used a ratio relative to the baseline value rather than the absolute value at each time point for the evaluation of plasma BNP levels.

Limitations of this study contributing to lower statistical significance include the low number of enrolled patients. In addition, we did not evaluate natriuretic peptide family levels after the day before the second cycle of chemotherapy. Further investigations are necessary to clarify whether the changes of plasma BNP levels on bevacizumab-based treatment are truly predictive of clinical benefit.

In conclusion, we found that plasma BNP level could be a predictive marker for PFS in patients treated with bevacizumab plus carboplatin-paclitaxel. Further clinical trials with a greater number of patients are warranted to confirm our results.

Conflicts of Interest

Takashi Kijima has received lecture fees from Chugai Pharmaceutical Company. The other Authors indicated no potential conflicts of interest.

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