Safety of Bevacizumab-containing chemotherapy in Non-small-cell Lung Cancer Patients with Brain metastases

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Abstract
Introduction: Patients with brain metastases have commonly been denied bevacizumab treatment because of the suspected risk of central nervous system (CNS) hemorrhage. Although safety information on bevacizumab treatment of non-small-cell lung cancer (NSCLC) with CNS metastases has been accumulated, its use is still controversial. We conducted the present retrospective study to investigate bevacizumab safety in patients with NSCLC and brain metastases.

Methods: Clinical data of NSCLC patients treated with chemotherapy regimens containing bevacizumab in a single institution from Feb. 2010 to Nov. 2011 were assembled retrospectively from medical records. Hematologic toxicity, non-hematologic toxicity, progression-free survival (PFS), and overall survival (OS) were analyzed.

Results: Fifty two patients were included in this analysis of whom 10 had brain metastases. Incidence of grade ≥3 major bleeding events such as CNS hemorrhage and pulmonary hemorrhage were not observed in either group. Neither were there any differences in toxicity profiles between groups. The median OS and PFS of all patients were 13.1 months (95% confidence interval (CI), 10.7 - not reached) and 9.1 months (95% CI, 4.1 - 11.1 months), respectively. No significant differences in median OS or PFS were observed between the two groups.

Conclusion: These data suggest that bevacizumab treatment may be safe for NSCLC with brain metastases and deserves further study.

Key Words: bevacizumab, non-small-cell lung cancer, brain metastases

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Introduction

Bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is approved for diverse cancers such as recurrent glioblastoma, metastatic breast cancer, colorectal cancer and non-small-cell lung cancer (NSCLC). In the treatment of NSCLC, addition of bevacizumab in combination with a standard regimen of carboplatin plus paclitaxel was shown to significantly improve overall survival (OS) and progression-free survival (PFS) (1). In Japan, bevacizumab was approved for NSCLC by the Ministry of Health, Labour and Welfare in 2009.

Until recently, patients with central nervous system (CNS) metastases have been routinely excluded from receiving treatments containing bevacizumab. This was because of a fatal CNS hemorrhage in a single case with hepatocellular carcinoma during a Phase I trial of bevacizumab in 1997 (2). The perceived risk of intracranial hemorrhage currently precludes its use in patients with brain metastases, which are cited in Japanese guidelines as a contra-indication for its use. Although more recent data in fact indicate bevacizumab is safe in NSCLC patients with CNS metastases (3-5), application of this drug in such patients is controversial. Therefore, here we retrospectively assessed the safety of bevacizumab in NSCLC patients with and without CNS metastases.

Patients and Methods

Patients
Advanced NSCLC patients who had received bevacizumab-containing chemotherapies at Fukujuji Hospital were retrospectively investigated by reviewing their medical records from between February 2010 and November 2011. Chemotherapies, which had been approved by an institutional committee responsible for chemotherapy regimens, were selected by the attending physicians.
Patients who had brain metastases but no symptoms therefrom were eligible for bevacizumab-containing chemotherapy at least 2 weeks after completion of radiotherapy for brain metastases.

Clinicopathologic data and follow-up information were obtained from the medical records. Patient characteristics (gender, Eastern Cooperative Oncology Group (ECOG) performance status, smoking status, stage, presence of epidermal growth factor receptor (EGFR) gene mutations, and line of therapy) were assessed before the first cycle of the bevacizumab-containing chemotherapy.

Treatment and Management of Side Effects

Patients received bevacizumab at a dose of 15 mg/kg every 21 days until disease progression, unacceptable toxicity, or death. Patients also received platinum-based doublet chemotherapy (cisplatin or carboplatin, in combination with paclitaxel, docetaxel, or pemetrexed) for up to six cycles. Patients who received bevacizumab with platinum plus pemetrexed were then given pemetrexed with bevacizumab or pemetrexed alone as a maintenance regime until disease progression.

During treatment, dose reduction and/or delay were managed by the attending physician on the basis of hematologic or non-hematologic toxicities. The physician also decided on the use of granulocyte colony-stimulating factor and/or blood transfusions according to standard guidelines.

Toxicity, Progression-Free Survival (PFS) and Overall Survival (OS)

Toxicity grading was performed according to the National Cancer Institute's Common Toxicity Criteria for Adverse Events, version 4.0 grading system. Differences between patients with or without brain metastasis were investigated using Chi-square tests, and a p-value <0.05 was considered statistically significant.

PFS was calculated from the start of the treatment until disease progression or until the last follow-up visit. OS was calculated from the start of the treatment until death or until the last follow-up visit. Kaplan-Meier and Wilcoxon testing were used for data analysis. Hazard ratios were calculated using the Cox proportional hazards model. Statistical analysis was performed using JMP 9.0.2 software (SAS institute, Japan, Ltd.), and a p-value <0.05 was considered statistically significant.

RESULTS

Patients

The medical records of 52 patients receiving bevacizumab-containing chemotherapies were reviewed retrospectively. Ten of these patients had brain metastases. Baseline characteristics were similar between the two groups except for gender and smoking status.

Table 1. Baseline characteristics of the patients. P values were analyzed by Chi square testing. Data on epidermal growth factor receptor (EGFR) status were not available for 20 patients (4 of which were in the brain metastases group).

|                              | total n=52 | Brain metasta. + n=10 | - n=42 | p-value |
|------------------------------|------------|------------------------|--------|---------|
| Number of cases              |            |                        |        |         |
| Median age (range)           | 66(39-74)  | 66(53-71)              | 65.5(39-74) |         |
| Gender                       |            |                        |        |         |
| Male/Female                  | 28/24      | 2/8                    | 26/16  | 0.0169  |
| Smoking status               |            |                        |        |         |
| current or have smoked/never | 33/19      | 3/7                    | 30/12  | 0.0145  |
| Stage                        |            |                        |        |         |
| III/IV/A/B/C/recurrence      | 3/2/36/11  | 1/0/8/2                | 3/2/28/9 |         |
| PS 0/1/2                     | 27/23/2    | 4/6/0                  | 23/17/2 |         |
| EGFR gene mutation           |            |                        |        |         |
| positive/negative/unknown    | 13/19/20   | 4/2/4                  | 9/17/6 |         |
| Line of therapy              |            |                        |        |         |
| 1st/2nd                      | 24/28      | 5/5                    | 19/23  |         |

Table 2. Grade ≥3 toxicity profiles. P values were analyzed by Chi square testing.

|                              | Total n=52 | Brain metastasis + n=10 | - n=42 | p-value |
|------------------------------|------------|------------------------|--------|---------|
| Hematologic toxicities       |            |                        |        |         |
| Neutropenia                  | 30 (57.7%) | 5 (50%)                | 25 (59.5%) | 0.5855 |
| Thrombocytopenia             | 22 (42.3%) | 4 (40%)                | 18 (42.9%) | 0.8692 |
| Anemia                       | 1 (1.9%)   | 0                      | 1 (2.3%) | 0.5111 |
| Non-hematologic toxicities   |            |                        |        |         |
| Bleeding events              | -          | -                      | -      |         |
| New or exacerbated           | 2          | 1                      | 1      | 0.3170 |
| Hypertension                 | -          | -                      | -      |         |
| Arterial thromboembolic events| -         | -                      | -      |         |
| Others                       | 13         | 3                      | 10     | 0.7499 |

(Table 1). Of these 52 patients, 20 received platinum plus pemetrexed together with bevacizumab as first-line treatment; 3 received platinum plus docetaxel with bevacizumab and one platinum plus paclitaxel and bevacizumab. Of the 28 patients treated with bevacizumab-containing chemotherapies as the second-line or later treatment, 18 received platinum and pemetrexed and the other 10 platinum and paclitaxel. In the whole cohort, 17 patients received maintenance therapies: pemetrexed plus bevacizumab (n=15); single-agent pemetrexed (n=1) and gefitinib (n=1). The median number of cycles of bevacizumab administered was 4 in the group with brain metastases, and 4.5 in the group free of brain metastases.

Toxicity

Table 2 summarizes the major grade 3 to 5 toxicities seen. Only one patient had grade 1 epistaxis, but there was no grade 1 to 5 CNS or pulmonary hemorrhage. Death during the treatment period occurred in one pa-
tient in the brain metastases-free group because of a grade 5 lung infection. With respect to grade 3 to 5 hematologic and non-hematologic toxicities, there was no significant difference between the two groups.

**PFS and OS**

The whole patient cohort in this study had a median PFS of 9.1 months (95% CI, 4.1 - 11.1 months) and a median OS of 13.1 months (95% confidence interval (CI), 10.7 - not reached) (Fig. 1A, B). The median PFS of the patients with brain metastases was 12 months versus 7.2 months for those without (p=0.71) (Fig. 2A). The median OS was 13.0 months for patients with brain metastases versus 16.5 months for those without (p=0.52) (Fig. 2B). Thus, there were no significant differences between groups either for OS or PFS. In addition, no significant differences in PFS and OS according to EGFR mutation status were observed, probably due to the limited number of patients investigated. Smoking status was a factor associated with PFS and OS, as determined by multivariate analysis (Table 3). Gender and smoking status were associated with OS, as determined by univariate analysis. Multivariate analysis revealed that smoking status remained as a significant factor affecting OS (Table 4). However, these results may be of limited reliability due to the small study population.

**Discussion**

Bevacizumab is the first targeted agent to result in improved survival in combination with chemotherapy in the first line setting for patients with NSCLC\(^1\). The presence of brain metastases and squamous cell histology have been the most common reasons for denying bevacizumab treatment. The main justification for the former was a single episode of severe CNS hemorrhage in a hepatocellular carcinoma patient with intracranial metastasis observed in the phase I trial of single-agent bevacizumab\(^2\). However, accumulating experience from treating patients with primary or metastatic brain tumors revealed that intracranial hemorrhage was rare. Therefore, patients with previously-treated or inactive brain metastases were allowed to participate in clinical trials, such as the PASSPORT\(^3\) and ATLAS trials. Thus, we evaluated...
Table 3. Progression-free survival according to clinical characteristics.  
For univariate analysis, p value by Wilcoxon test; for multivariate analysis, p value by Cox regression.  
ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal Growth Factor Receptor; HR: hazard ratio.

| Factor                        | Median PFS (mo) | Univariate Analysis | Multivariate Analysis |
|-------------------------------|-----------------|---------------------|-----------------------|
|                               |                 | HR                  | P        | HR              | P        |
| Brain metastasis yes (n=10)  | 12              | 0.65                | 0.71     | 0.60            | 0.315    |
| no (n=42)                     | 7.2             |                     |          |                 |          |
| Gender                        |                 |                     |          |                 |          |
| Male (n=28)                   | 9.1             | 0.68                | 0.56     | 1.34            | 0.685    |
| Female (n=24)                 | 6               |                     |          |                 |          |
| Age                           |                 |                     |          |                 |          |
| ≥70 yr (n=14)                 | 7.2             | 1.30                | 0.67     | 1.17            | 0.700    |
| <70 yr (n=38)                 | 9.1             |                     |          |                 |          |
| Smoking status no (n=19)      | 5.3             | 2.23                | 0.15     | 3.74            | 0.046    |
| yes (n=33)                    | 9.1             |                     |          |                 |          |
| Performance status (ECOG) 0  | 9.1             | 0.62                | 0.34     | 0.95            | 0.906    |
| ≥1 (n=25)                     | 11.1            |                     |          |                 |          |
| EGFR mutation                 |                 | 0.46                | 0.34     | 0.48            | 0.174    |
| Positive (n=13)               | 12              |                     |          |                 |          |
| negative (n=19)               | 7.2             |                     |          |                 |          |

a: Kaplan-Meier analysis by Wilcoxon test.; b: Cox regression.

Table 4. Overall survival according to clinical characteristics.  
For univariate analysis, p value by Wilcoxon test; for multivariate analysis, p value by Cox regression.  
ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal Growth Factor Receptor; HR: hazard ratio.

| Factor                        | Median OS (mo) | Univariate Analysis | Multivariate Analysis |
|-------------------------------|----------------|---------------------|-----------------------|
|                               |                | HR                  | P        | HR              | P        |
| Brain metastasis yes (n=10)  | 16.5           | 0.86                | 0.52     | 0.62            | 0.425    |
| no (n=42)                     | 13.1           |                     |          |                 |          |
| Gender                        |                | 0.65                | 0.60     | 16.84           | 0.020    |
| Male (n=28)                   | 11             |                     |          |                 |          |
| Female (n=24)                 |                | 0.85                | 0.54     | 0.36            | 0.065    |
| Age                           |                | 16.5                | 0.54     | 0.36            | 0.065    |
| ≥70 yr (n=14)                 | 12.8           | 3.34                | 0.03     | 90.71           | 0.0001   |
| <70 yr (n=38)                 |                |                     |          |                 |          |
| Smoking status no (n=19)      | 10.8           | 1.15                | 0.36     | 0.40            | 0.096    |
| yes (n=33)                    |                |                     |          |                 |          |
| Performance status (ECOG) 0  |                | 13.1                | 0.88     | 0.78            | 0.31     |
| ≥1 (n=25)                     | 10.8           | 12.8                | 0.88     | 0.78            | 0.31     |
| EGFR mutation                 |                | 1.15                | 0.36     | 0.40            | 0.096    |
| Positive (n=13)               | 13.1           |                     |          |                 |          |
| negative (n=19)               | 10.8           |                     |          |                 |          |

a: Kaplan-Meier analysis by Wilcoxon test.; b: Cox regression.
the safety and tolerability of bevacizumab for advanced NSCLC patients with brain metastases in clinical practice.

Besse et al. carried out a retrospective analysis of multiple datasets of patients with systemic cancer treated with bevacizumab and reported a low rate of intracranial hemorrhage. Similarly, Khasraw et al. reported that ICH in various cancer patients treated with bevacizumab was rare in their retrospective analyses, and did not seem different from the ICH rate in a similar population not treated with bevacizumab. In an open-label trial for treatment of non-squamous NSCLC including patients with treated brain metastases, there were no reported episodes of grade ≥2 CNS hemorrhage. Kevin et al. reported that the use of bevacizumab even in patients with active brain metastases seemed to be safe. Consistent with these previous reports, in our study, there was only one grade 1 epistaxis and no case of grade ≥3 bleeding events such as intracranial hemorrhage, pulmonary hemorrhage etc.

Some reports imply that severe hemorrhage events associated with anti-angiogenic therapy may be attributed not only to endothelial cell dysfunction but also the weakening of major vessel walls induced by tumor erosion, necrosis, and cavitation, and that vascular damage leading to hemorrhage may be an unintended consequence of the enhanced cytotoxicity against tumors with vascular wall infiltration. However, the precise mechanisms underlying these bleeding events following VEGF inhibition are still unclear. It remains necessary to exercise caution when using bevacizumab for NSCLC with brain metastases until further safety data are available.

This present study has several limitations. First, it is a retrospective analysis in a single institution with inherent potential for bias. Second, a limited number of patients was investigated. Third, decisions on dose reduction during therapy or maintenance therapy were made by the attending physicians. Therefore, toxicity profiles in the two groups should be interpreted with caution.

In conclusion, our study suggests that bevacizumab administration to NSCLC patients with brain metastases may be safe in Japanese patients in clinical practice. The results from this study need to be confirmed in large-scale prospective studies.

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