

Effect of erlotinib plus bevacizumab on brain metastases in patients with non-small cell lung cancer

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Background: The standard therapy for brain metastasis (BM) in non-small cell lung cancer (NSCLC) is radiation therapy (RT), although it is associated with complications such as leukoencephalopathy. In the current report, we retrospectively review data from eight patients who had NSCLC and harbored epidermal growth factor receptor (EGFR) mutations, and who were received erlotinib plus bevacizumab (E+B) as first-line therapy for BM.

Methods: Patients were given E+B as first therapy for BM until August 2017 at our institution. Patients receiving local therapy for BM, such as surgery or radiotherapy, were excluded. Patients were administered erlotinib orally (once daily at 150 mg/body) plus bevacizumab by intravenous infusion (15 mg/kg on day 1 of a 21- or 28-day cycle).

Results: Eight NSCLC patients who were diagnosed with BM received E+B, including 2 men and 6 women with a median age of 65 years (range, 46–84 years). Four patients had an L858R *EGFR* mutation, while the other four had an exon 19 deletion. Seven patients had a partial response to E+B treatment, and one had a complete response. The 2-year survival rate was 62.5%. Three patients who were pre-treated with gefitinib had an E+B treatment duration of less than 1 year. At the time of this analysis, four patients had BM-related neurologic symptoms and multiple BMs, and were still receiving E+B with no evidence of treatment failure after more than 1 year.

Conclusions: E+B can be used as first-line therapy for BM, even in patients with BM-related neurologic symptoms and multiple BMs.

Keywords: brain metastasis (BM); non-small cell lung cancer (NSCLC); erlotinib; bevacizumab

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Introduction

Lung cancer is the leading cause of cancer death worldwide. The recent development of the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) gefitinib and erlotinib has markedly improved the treatment of advanced non-small cell lung cancer (NSCLC) (1). Brain

metastasis (BM) occurs in approximately 20–40% of NSCLC patients (2,3), and is generally the site of metastasis most associated with a poor prognosis (4). Without treatment, the prognosis for NSCLC patients with BM is poor, with a median overall survival (OS) of 1–2 months (5).

BM in NSCLC is typically treated with radiation therapy (RT), including stereotactic radiosurgery (SRS) and whole-

brain radiotherapy (WBRT) (6). However, RT is associated with complications such as leukoencephalopathy, meaning that systemic treatment may be preferable (7). Despite this, chemotherapy for BM in NSCLC has traditionally been considered ineffective because of the difficulties in penetrating the blood–brain barrier (8). Moreover, patients with BM were initially excluded from clinical trials for bevacizumab after the occurrence of a fatal cerebral hemorrhage in a phase I study (9). On the other hand, the contraindication of bevacizumab for BM was removed from the EU Summary of Product Characteristics in 2009 after the submission of comprehensive safety data. The BRAIN study demonstrated the efficacy and safety of bevacizumab with first-line paclitaxel and carboplatin therapy in patients with NSCLC and asymptomatic untreated BM (10). At present, there is increasing interest in the systemic treatment of BM in NSCLC patients (6). In particular, good responses to treatment with molecular targeted drugs [such as EGFR-TKIs and anaplastic lymphoma kinase (ALK) inhibitors] have been reported for BM (11,12). Furthermore, it has been shown that the concentration of erlotinib in cerebrospinal fluid may be higher than that of other EGFR-TKIs (such as gefitinib), thus increasing its efficacy in the treatment of BM, especially leptomeningeal metastases (13).

Recently, Seto *et al.* suggested that combination therapy of erlotinib plus bevacizumab (E+B) was effective and safe in patients with *EGFR* mutation-positive NSCLC (14), a patient population that is at increased risk of developing BM (15). The successful management of NSCLC patients using E+B therefore represents an effective alternative to RT for BM. In the current report, we review 8 cases treated by E+B as first-line therapy for BM.

Methods

We retrospectively examined data from who had patients with NSCLC and BM, and harbored *EGFR* mutations, and, who were given E+B as first-line therapy for BM until August 2017 at our institution. Patients receiving local therapy for BM, such as surgery or radiotherapy, were excluded.

Patients were diagnosed with BM at the first medical examination, during postoperative observation after completion resection, or during systemic chemotherapy.

EGFR mutations were diagnosed in surgical specimens in recurrent patients, and by transbronchial biopsy specimen in advanced lung cancer patients. BM was diagnosed

by computed tomography (CT) or magnetic resonance imaging (MRI). Extracranial disease was examined by CT or positron emission tomography (PET) at the time of detection of BM. Patients were orally administered erlotinib (once daily at 150 mg/body) plus bevacizumab by intravenous infusion (15 mg/kg on day 1 of a 21- or 28-day cycle). For adverse events related to erlotinib, treatment was suspended until the adverse events resolved, and dose reduction of erlotinib followed. For adverse events related to bevacizumab, treatment was suspended and bevacizumab was retried after resolution of the adverse events. Tumor lesions were assessed radiologically every 1–3 months. Treatment was administered sequentially until disease progression or the occurrence of intolerable adverse events. Where E+B treatment was suspended, some patients then selected systemic chemotherapy (e.g., platinum-based doublet regimens) or local treatment for BM (e.g., SRS or WBRT), while others selected best supportive care. The objective tumor response was evaluated by CT or PET for extracranial disease and by CT or MRI for BM, according to the Response Evaluation Criteria in Solid Tumors guidelines (16).

Survival curves were calculated using the Kaplan-Meier method. Statview version 5.0 (Abacus Concepts, Inc., Berkeley, CA, USA) was used for all statistical analyses.

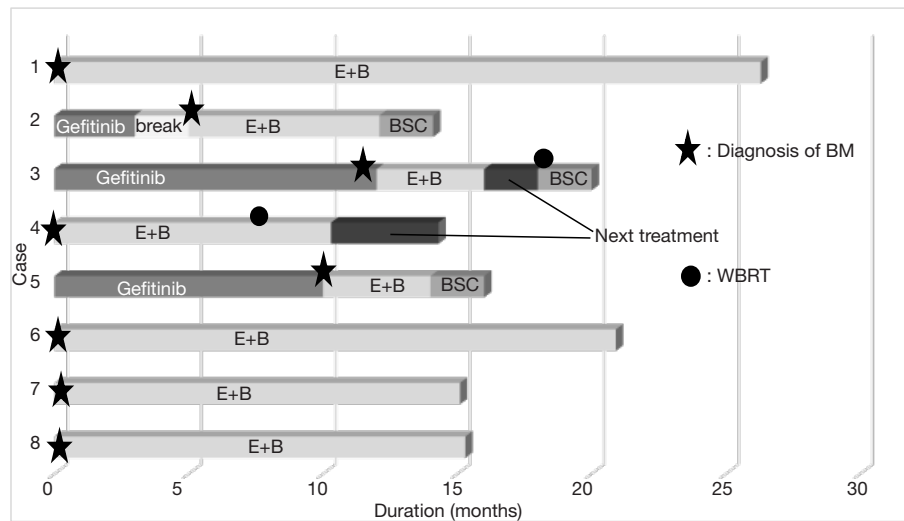
Results

Eight patients with NSCLC who were diagnosed with BM, including two men and six women with a median age of 65 years (range, 46–75 years), received E+B as initial treatment for BM. The patient characteristics are shown in *Table 1*. Six patients had an Eastern Cooperative Oncology Group performance status (PS) of 0/1, and 2 patients had a PS of 2 at the start of therapy. Four patients had an L858R *EGFR* mutation, while four had an exon 19 deletion. BMs were variable in number and size (*Table 1*) and caused symptoms (headache) in 2 patients. Extracerebral metastases were found in the lung in 6 patients, bone in 6 patients, adrenal glands in 1 patient, and lymph nodes in 4 patients. BM was diagnosed in 3 patients during postoperative observation after completion resection, in 2 patients during the first medical examination, and in 3 patients during systemic chemotherapy (including for recurrent disease after surgery). In terms of surgical history, 5 patients had recurrent disease after surgery, and 3 patients had been pretreated with gefitinib before being diagnosed with BM (*Figure 1*). Regarding the additional brain metastatic sites of

Table 1 Clinical and pathological characteristics of NSCLC patients diagnosed with BM who received erlotinib plus bevacizumab as initial treatment for BM

Case	Age (years)/sex	EGFR mutation	PS	Number of BMs	BM size (mm)	BM-related symptoms	Extracerebral portion	History of surgery	History of TKI
1	65/F	L858R	2	2	10	None	OSS	LUL	None
2	71/F	L858R	1	6	8	None	PUL, OSS, pleural	RLL	Gefitinib
3	65/F	Exon 19 deletion	1	6	13	None	LN, OSS	RLL	Gefitinib
4	46/M	Exon 19 deletion	1	≥10	17	Headache	PUL	LLL	None
5	65/M	L858R	0	≥10	9	None	PUL, OSS	None	Gefitinib
6	75/F	L858R	0	≥10	27	None	PUL, LN	None	None
7	60/F	Exon 19 deletion	2	7	17	Headache	PUL, OSS, ADR, LN	None	None
8	74/F	Exon 19 deletion	0	6	11	None	PUL, LN, OSS	RLL	None

NSCLC, non-small cell lung cancer; PS, performance status; BM, brain metastasis; TKI, tyrosine kinase inhibitor; OSS, ossa; PUL, pulmonary; LN, lymph node; ADR, adrenal; LUL, left upper lobectomy; RLL, right lower lobectomy; LLL, left lower lobectomy.

**Figure 1** Treatment course of erlotinib plus bevacizumab for each case. E+B, erlotinib plus bevacizumab; BSC, best supportive care; BM, brain metastasis.

the 3 patients previously treated with gefitinib, at the time of initiating treatment with erlotinib plus bevacizumab, case 2 was diagnosed with a new lesion (pulmonary and bone metastasis), case 3 was controlled expect for brain metastatic sites, and case 5 was diagnosed the recurrence of the primary lesion.

The outcomes of E+B treatment are summarized in

Table 2. In terms of the objective tumor response for BM, 7 patients had a partial response (PR) and 1 patient had a complete response. In terms of the objective tumor response for extracerebral metastases, 6 patients had a PR and 1 patient had a complete response. The 2-year survival rate following treatment with E+B was 62.5% (*Figure 2*). Each treatment course is shown in *Figure 1*. Three patients

Table 2 E+B treatment outcomes

Case	Response		Time until erlotinib dose reduction (days)	Duration of treatment (days)	Cause of cessation	BM		Extra		Local therapy for BM	Outcome	Next treatment	OS (days)
	BM	Extra				Progression	PFS (days)	Progression	PFS (days)				
1	CR	CR	350	789	Ongoing	None	789	None	789	None	Alive	None	789
2	PR	PR	75	215	Malaise	Failure	259	Failure	190	None	Deceased	None	322
3	PR	PR	68	152	Regrowth	Failure	263	Failure	201	WB	Deceased	Osimerfinib	368
4	PR	PR	277	481	Regrowth	Failure	255	Failure	447	WB	Alive	CBDCA + PEM + BEV	586
5	PR	SD	99	99	Personal	None	178	Failure	114	None	Deceased	None	178
6	PR	PR	28	628	Ongoing	None	628	None	628	None	Alive	None	628
7	PR	PR	25	453	Ongoing	None	453	None	453	None	Alive	None	453
8	PR	PR	46	460	Ongoing	None	460	None	460	None	Alive	None	460

E+B, erlotinib plus bevacizumab; BM, brain metastasis; PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; ADR, adrenal; WB, whole brain; CBDCA, carboplatin; PEM, pemetrexed; BEV, bevacizumab.

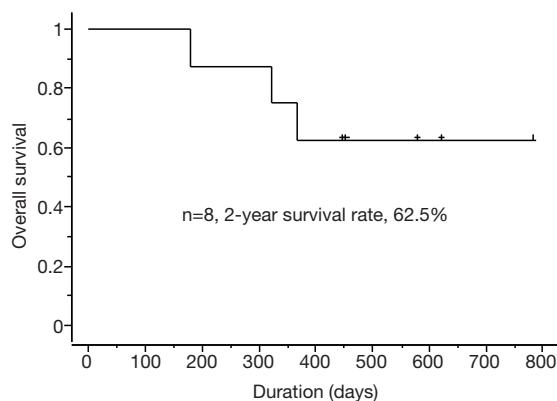


Figure 2 Kaplan-Meier curves for brain metastases in patients with non-small cell lung cancer receiving erlotinib plus bevacizumab.

who received prior treatment with gefitinib had an E+B treatment duration of less than 1 year. However, the 5 patients who received E+B as first-line treatment had treatment duration of 1 year or longer. All patients had suspended E+B treatment because of adverse events (cases 1–4 and 6–8) or for personal reasons (case 5), although 7 patients had restarted E+B with dose reduction of erlotinib (cases 1–4 and 6–8). One patient could not continue on E+B for personal reasons (case 5). Adverse events of erlotinib treatment included skin and subcutaneous tissue disorders (cases 1–4 and 6–8) and malaise (cases 1, 2, and 7), with other events such as gastrointestinal disorders not observed. Adverse events of bevacizumab were hypertension (case 1) and malaise (case 2), and no critical adverse events such as hemoptysis and proteinuria were observed. Among the 4 patients who discontinued E+B treatment, 2 patients had tumor regrowth (case 3 had regrowth and a new BM lesion, while a new lesion was detected in case 4), 1 patient had malaise (case 2), and 1 patient discontinued for personal reasons (case 5). The patient in case 4 was still alive and undergoing third-line treatment at the time of writing, with a systemic PR and BM controlled using WBRT. The cases 2 and 3 patients died from primary illness after therapy. Two patients (cases 3 and 4) received WBRT, the timing of which is described in Figure 1. Four patients were still receiving treatment without tumor regrowth at the time of writing (cases 1, 6, 7, and 8).

Three representative cases who received E+B treatment for more than 1 year are presented in Figure 3. In case 1, two BMs have virtually disappeared, along with a remarkable effect on bone metastasis (Figure 3A,B). In case 6, more than 10 BMs with edema of various sizes

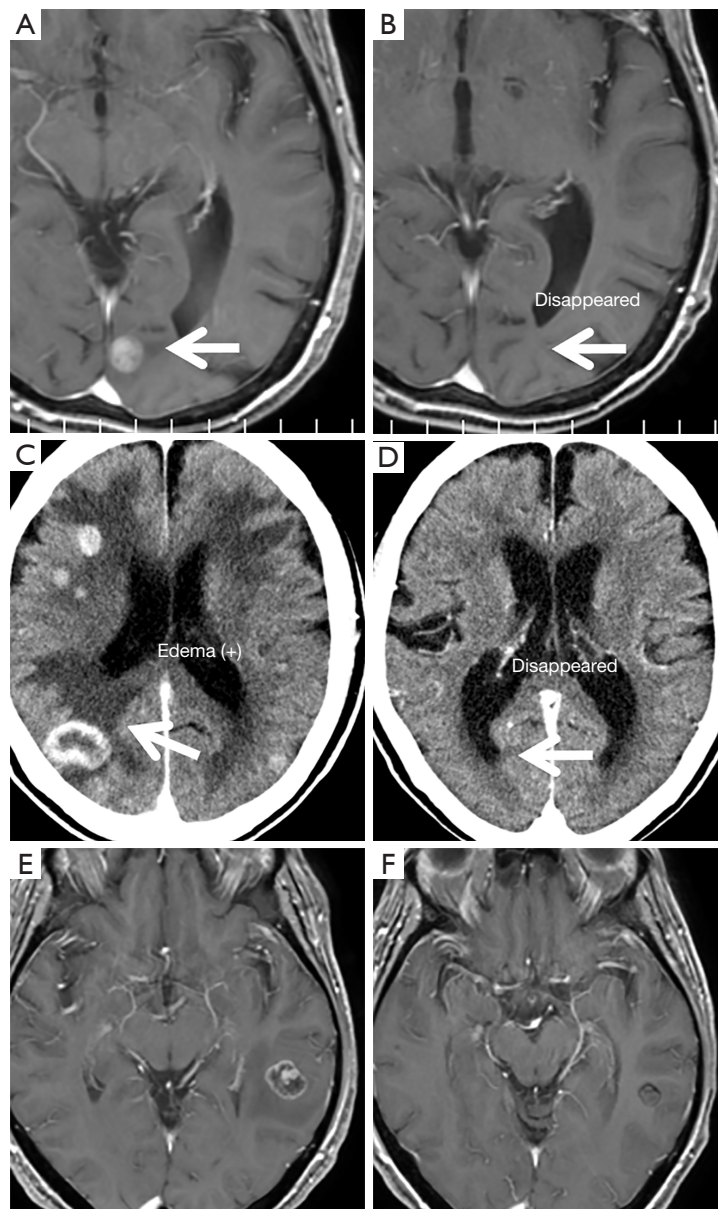


Figure 3 Radiological findings before and after E+B treatment. (A,B) Brain MRI of case 1 prior to E+B treatment (A) and 18 months after E+B treatment (B). A complete response was observed, with the disappearance of a 10-mm BM (white arrows). (C,D) Brain CT of case 6 prior to E+B treatment (C) and 11 months after E+B treatment (D). More than 10 BMs with edemas of various sizes virtually disappeared (white arrows). (E,F) Brain MRI of case 7 prior to E+B treatment (E) and 15 months after E+B treatment (F). The main BM with edema was good PR and the BM-related symptom of headache improved. E+B, erlotinib plus bevacizumab; BM, brain metastasis; MRI, magnetic resonance imaging; PR, partial response.

almost disappeared, along with a remarkable reduction of the main tumor and mediastinal lymph nodes (*Figure 3C,D*). In case 7, seven BMs of various sizes were good PR, and the BM-related symptom of headache improved, along with a remarkable reduction in the size of the primary tumor and

metastatic lesions (*Figure 3E,F*).

Discussion

To our knowledge, our results are notable for two reasons.

First, we reviewed cases of NSCLC patients with BM who had not previously received RT such as SRS or WBRT, but instead received E+B as initial treatment for BM. Moreover, this study included patients with BM-related neurologic symptoms and multiple BMs, for which radiotherapy is typically indicated. Second, this eight-case analysis was a retrospective study of consecutive data only from our institution. Although the patient population in our study was small, studies on E+B as initial treatment for BM in a single institution have not previously been reported.

The present study demonstrated three major findings. First, E+B treatment of all eight patients was found to be safe, with no severe complications or progression of BM-related neurologic symptoms, despite existing safety concerns about the use of E+B such as cerebral hemorrhage. However, a limitation of our data is that BM patients with severe brain edema were excluded from the study population. This finding supports the selection of E+B as initial treatment for BM in NSCLC patients with *EGFR* mutations, given the complication that can arise with RT such as leukoencephalopathy related to activities of daily living (ADL). Second, this study showed the effectiveness of E+B for BM in NSCLC patients with BM-related neurologic symptoms and multiple BMs. All patients had a PR, except for 1 patient that had a complete response, and 4 patients were continuing treatment at the time of writing (cases 1, 6–8). Some previously (10,11) studies have examined the effects of chemotherapy (such as cytotoxic agents or molecular targeted drugs) on BM, although none showed that chemotherapy was effective in all patients with BM. Molecular targeted drugs such as EGFR-TKIs and ALK inhibitors have recently been used to treat BM in NSCLC patients positive for driver mutations (11,12) despite the limitations posed by the blood-brain barrier. However, these previous studies excluded patients with BM-related neurologic symptoms and multiple BMs. Based on our findings, we recommend treatment with E+B for BM in patients with NSCLC and EGFR mutations, including those with BM-related neurologic symptoms and multiple BMs. BM-related neurologic symptoms can lead to a rapid decline in ADL, meaning that rapid, effective treatment, such as E+B, is recommended for BM. Moreover, treatment that reduces ADL, such as WBRT, should be avoided for NSCLC patients with driver mutations and a long-term prognosis. Third, our findings support the use of E+B as first-line therapy for BM in NSCLC patients, as E+B treatment was more effective when used as first-line therapy for BM compared with E+B after previous treatment with

EGFR-TKI. Pre-treatment with EGFR-TKI may reduce the effectiveness of E+B treatment because resistance may develop, including T790M mutations in EGFR. Recently developed EGFR-TKI such as osimertinib and AZD 3759 can more readily penetrate the blood-brain than erlotinib can (17). Future studies should therefore examine the effect of adding bevacizumab to novel EGFR-TKI.

This study indicates that E+B may be used as first-line therapy for BM in NSCLC, even in patients with BM-related neurologic symptoms and multiple BMs. In the future, next-generation EGFR-TKI plus bevacizumab may represent a new treatment strategy for BM in NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The Ethics Committee of the University of Occupational and Environmental Health Japan approved this study (H26-15). Informed consent was obtained from the patients before the study commenced.

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