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ORIGINAL PAPER

Survival of patients with brain metastases from non-small cell lung cancer harboring EGFR mutations treated with epidermal growth factor receptor tyrosine kinase inhibitors

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Abstract Brain metastases (BM) is one of the most crucial distant metastases in patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (*EGFR*) mutations. There is no consensus about which EGFR tyrosine kinase inhibitor (TKI) is most effective against BM in such patients. Here, we compared prognoses of patients with EGFR-TKI naïve *EGFR*-positive BM treated with erlotinib or gefitinib after BM diagnosis. Of 269 patients with NSCLC treated with EGFR-TKIs at a single institution, we reviewed medical records of 205 patients with documented *EGFR* mutations. Eleven patients were administered erlotinib, and 52 patients were administered gefitinib as the first-line EGFR-TKI treatment after diagnosis. We used propensity score matching to balance patient backgrounds between groups, and the log-rank test to compare survival curves. Patients with BM at the induction of chemotherapy had a poorer prognosis than those without BM [median overall survival (OS) 18.5 vs. 28.0 months]. Meanwhile, there was no significant difference in OS between those with or without BM at the initiation of EGFR-TKI treatment (20.3 vs. 23.8 months). Median OS of patients treated with erlotinib was not significantly longer than that of patients treated with gefitinib (25.0 vs. 18.1 months). The presence of BM at the initiation of EGFR-TKI treatment had no apparent effect on survival. Erlotinib was deemed more effective than gefitinib in preventing intracranial lesions and prolonging survival; however, prospective studies are needed to confirm these results.

Keywords Brain metastases · Gefitinib · Erlotinib · Epidermal growth factor receptor · Lung cancer

Abbreviations

BM	Brain metastases
NSCLC	Non-small cell lung cancer
EGFR	Epidermal growth factor receptor
TKI	Tyrosine kinase inhibitors
OS	Overall survival
PS	Performance status
BMCP	BM controlled period
CNS	Central nervous system
PD	Progressive disease

Introduction

Brain metastases (BM) occur in up to 25–40 % of patients with non-small cell lung cancer (NSCLC) and considerably impair patients' quality of life [1]. Specific gene mutations that lead to BM remain unclear; however, a high correlation between BM and epidermal growth factor receptor (*EGFR*) mutations has been suggested [2]. A previous study showed that BM prevalence was higher in Japanese patients with NSCLC harboring *EGFR* mutations than in those with wild-type *EGFR* (31.4 vs. 19.7 %) and that approximately 40 % of patients with BM had an *EGFR* mutation [2].

Tyrosine kinase inhibitors (TKIs) targeting EGFR are widely used to treat advanced NSCLC patients harboring *EGFR* mutations; however, resistance to EGFR-TKIs is often acquired via a mutation in *EGFR* or in another oncogenic

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gene during treatment with these agents [3]. A report of a patient who developed BM after EGFR-TKI treatment demonstrated that although the primary lesion harbored an exon 20 T790M mutation—the most common TKI-resistant *EGFR* mutation—the BM specimen was negative for the mutation [4]. This case indicates that the biological characteristics of BM may differ from those of the primary or other metastatic lesion. The first-generation EGFR-TKIs erlotinib and gefitinib are effective against BM [5–10]. At clinical doses, erlotinib achieves higher blood concentrations and penetrates the blood–brain barrier more effectively than gefitinib [11]. Another retrospective study showed that erlotinib was more effective than gefitinib in the cytologic ablation of the cerebrospinal fluid in patients with leptomeningeal carcinomatosis caused by NSCLC [12]. Overall survival (OS) of patients with BM was reportedly affected by erlotinib administration but not by gefitinib administration [13]; however, there are no reports comparing these two EGFR-TKIs with respect to the OS of patients with BM from NSCLC.

We therefore hypothesized that EGFR-TKIs treatment at sufficient doses may effectively control BM in patients with *EGFR* mutations and prolong survival, even in patients with evidence of BM at the initiation of treatment. We also hypothesized that patients with BM from NSCLC would achieve longer survival if treated with erlotinib instead of gefitinib as the first-line treatment. In this study, we reviewed patient with NSCLCs treated with EGFR-TKIs at Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital. We then compared the survival of patients with *EGFR* mutations stratified according to the presence of BM at the initiation of chemotherapy or EGFR-TKIs and the type of EGFR-TKI first administered after BM diagnosis.

Patients and methods

Data acquisition

A total of 269 consecutive patients with advanced or recurrent NSCLC, diagnosed between 2007 and 2015, were treated with EGFR-TKI (Fig. 1). Among them, 205 were genetically diagnosed as harboring *EGFR* mutations ("*EGFR* mutation analysis" section). Fifty patients were then diagnosed with BM at the initiation of chemotherapy, including EGFR-TKIs and cytotoxic agents. The remaining 13 patients had no evident BM at the initiation of treatment, but they developed BM after cytotoxic chemotherapy. Thus, 63 patients with BM received EGFR-TKI treatment. Eleven patients were administered erlotinib, and 52 patients were treated with gefitinib as the first-line EGFR-TKI after diagnosis. We extracted information regarding sex, age, histological type of the primary lesion, locus of the *EGFR* mutation, smoking history, primary tumor stage, Eastern Cooperative Oncology Group scale performance status (PS) at the time of diagnosis of lung cancer, lesion recurrence after surgery, date of initiation and withdrawal of EGFR-TKIs, date of last follow-up, and patient outcome from the records. In this study, the term "chemotherapy" includes both EGFR-TKIs and cytotoxic agents.

This study was approved by the institutional review committee of Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital.

EGFR mutation analysis

EGFR mutations were evaluated in biopsy specimens or bronchoalveolar lavage fluid from each patient at a commercial central laboratory (SRL, Tokyo, Japan). From June 1, 2007, outsourcing of *EGFR* genetic testing was funded by government insurance. The screening was performed by direct sequencing, the peptide nucleic acid-locked nucleic acid polymerase chain reaction (PCR) clamp method [14], or the PCR invader assay [15]. Presence of exon 19 deletion and exon 21 L858R point mutations was determined. The exon 20 T790M mutation of *EGFR* correlates with resistance to EGFR-TKIs; therefore, patients harboring this mutation were not treated with EGFR-TKIs [3] and were excluded from the present study.

Statistical analysis

Descriptive statistics were used to summarize the patients' baseline characteristics. OS was defined as the time from the date of NSCLC diagnosis to the date of death by any reason. The BM controlled period (BMCP) was defined as the time from the date of initiation of EGFR-TKI treatment to the date of BM progression or death. Cases in which EGFR-TKI treatment was terminated because of EGFR-TKI toxicity or patient refusal were considered censored.

Categorical variables were compared using Pearson's Chi-squared or Fisher's exact test. Log-rank analysis was performed to compare OS estimated using the Kaplan–Meier method. To minimize background intergroup differences, we calculated propensity scores based on patient characteristics. A two-sided p value less than 0.05 was considered statistically significant. All statistical analyses were performed using the R version 3.2.2.

Results

Patients' characteristics

The characteristics of patients with *EGFR* mutations are summarized in Table 1. The median age of patients was

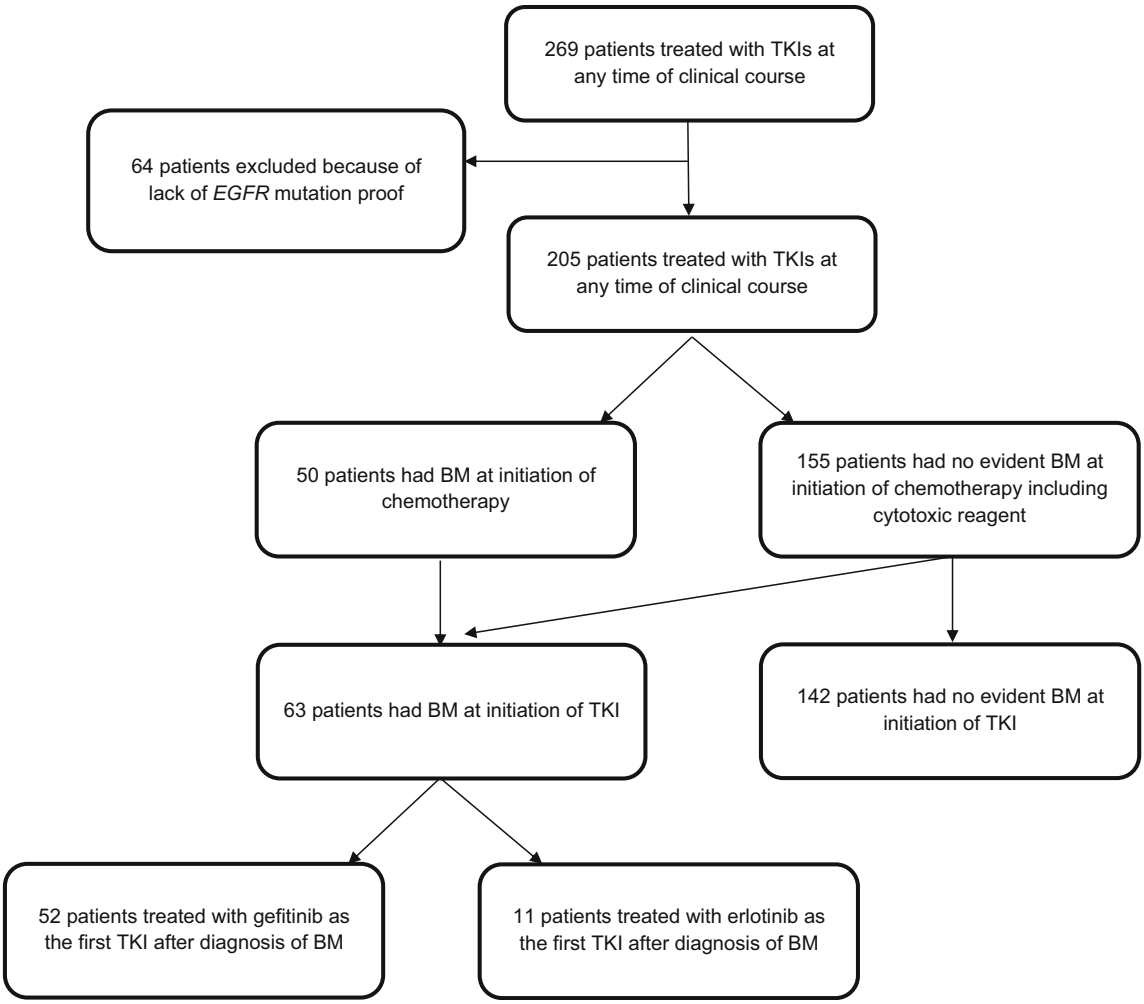

Fig. 1 Study profile. *BM* brain metastasis, *TKI* tyrosine kinase inhibitor

67.3 years, and both types of *EGFR* mutations—exon 21 L858R point mutation and exon 19 in-frame deletion—were found at almost the same frequency (45.4 vs. 50.7 %). Table 2 shows the characteristics of patients with and without BM at the initiation of chemotherapy. The number of cases of recurrence and those lost to follow-up was statistically different between BM-positive and BM-negative group, whereas these differences became insignificant after propensity score matching (PSM). Patient characteristics at the initiation of EGFR-TKI treatment are shown in Table 3. There were no statistically significant differences between patients with and without BM except for age, which diminished after PSM. Table 4 shows the characteristics of patients treated with EGFR-TKIs after diagnosis. Except for the gene mutation status (exon 21 L858R point mutation was more prevalent in patients in the erlotinib group than in the gefitinib group, $p = 0.04$), almost all aspects of baseline characteristics were equally distributed between the groups. Five patients in the erlotinib group (45.5 %) and 14 in the gefitinib group (26.9 %) were lost to follow-up.

Survival analysis

Impact of BM on patient survival among the matched cohort

The median OS of 50 patients with BM at the initiation of chemotherapy was 18.5 months, which was significantly shorter than that of patients with no evident BM (29.4 months, $p = 0.0002$). We then used matched data from 50 patients with no BM in the propensity scores calculated from age, sex, gene mutation locus, recurrence, smoking history, and PS; median OS was nearly the same (BM-positive group: 18.5 months and BM-negative group: 28.0 months, $p = 0.015$; Fig. 2a). Patients with BM at the initiation of EGFR-TKI treatment ($n = 63$) also had poorer prognoses than those without BM (median OS 24.3 vs. 20.3 months, $p = 0.035$), whereas matched-pair analysis showed no significant difference between these two groups (median OS 23.8 vs. 20.3 months, $p = 0.105$, Fig. 2b).

Erlotinib and gefitinib impact on survival after BM

The median survival of patients who were administered erlotinib as the first-line treatment after diagnosis ($n = 11$) was 25.0 months and that of patients treated with gefitinib ($n = 52$) was 18.1 months; this difference was not significant ($p = 0.45$). Matched-pair analysis using propensity scores yielded nearly the same result (median OS 25.0 vs. 18.1 months, $p = 0.75$, Fig. 2c). However, almost no BM progression occurred in the erlotinib group compared with a median BMCP of 10.8 months in the gefitinib group ($p = 0.02$, Fig. 2d).

Table 1 Baseline characteristics of patients harboring EGFR mutations

Characteristics	No of patients	(%)
No. of patients	205	
Age, years (median)	67.3	
Gender		
Male	57	27.8
Female	148	72.2
Smoking status		
Never smoker	123	60.0
Smoker	82	40.0
ECOG performance status		
0–1	153	74.6
2	25	12.2
3–4	27	13.2
EGFR mutation status		
Exon 21 L858R	93	45.4
Exon 19 in-frame deletion	104	50.7
Other mutations	8	3.9
Recurrence after surgery	41	20.0

EGFR epidermal growth factor receptor, *ECOG* Eastern Cooperative Oncology Group

Discussion

NSCLC patients with BM harboring *EGFR* mutations at the initiation of chemotherapy have a poorer prognosis that those without BM; however, there was no statistically significant difference when we stratified patients according to the presence of BM at the initiation of EGFR-TKI treatment. Further, erlotinib seemed to be more effective than gefitinib in controlling BM and tended to afford a better prognosis.

In patients with NSCLC harboring *EGFR* mutations, OS in the BM-positive group was significantly shorter than that in the BM-negative group at the initiation of chemotherapy. This result is consistent with those of previous clinical trials and retrospective studies that enrolled patients regardless of the gene mutation status [16]. Matched-pair analysis yielded almost similar result. Selection bias cannot be excluded because all enrolled patients underwent at least one EGFR-TKI treatment during the retrospective

Table 2 Baseline characteristics of patients with and without BM at the initiation of chemotherapy

Characteristics	Before PSM			After PSM		
	With BM	Without BM	*p*	With BM	Without BM	*p*
No. of patients	50	155		50	50	
Age, years (median)	65.5	69	0.014	65.5	66	0.528
Sex			0.365			0.803
Male	11	46		11	9	
Female	39	109		39	41	
Smoking status			1			0.0135
Never smoker	30	93		30	42	
Smoker	20	62		20	8	
ECOG performance status			0.193			0.586
0–1	36	117		36	32	
2	4	21		4	8	
3–4	10	17		10	10	
EGFR mutation status			0.88			1
Exon 21 L858R	21	72		21	21	
Exon 19 in-frame deletion	27	77		27	27	
Other mutations	2	6		2	2	
Recurrence after surgery	4	37	0.014	4	4	1
Censored follow-ups	38	90	0.029	32	38	0.275

BM brain metastasis, *EGFR* epidermal growth factor receptor, *TKI* tyrosine kinase inhibitor, *PSM* propensity score matching, *ECOG* Eastern Cooperative Oncology Group

Table 3 Baseline characteristics of patients with and without BM at the initiation of EGFR-TKI treatment

Characteristics	Before PSM			After PSM		
	With BM	Without BM	*p*	With BM	Without BM	*p*
No. of patients	63	142		63	63	
Age, years (median)	66	69.5	0.004	66	67	0.386
Sex			0.499			0.372
Male	15	42		15	10	
Female	48	100		48	53	
Smoking status			1			0.461
Never smoker	38	85		38	42	
Smoker	25	57		25	21	
ECOG performance status			0.272			0.815
0–1	47	100		47	45	
2	5	20		5	7	
3–4	11	16		11	11	
EGFR mutation status			0.712			0.766
Exon 21 L858R	26	67		26	29	
Exon 19 in-frame deletion	34	70		34	30	
Other mutations	3	5		3	4	
Recurrence after surgery	9	32	0.191	9	8	1
Censored follow-ups	44	84	0.162	44	39	0.453

BM brain metastasis, *EGFR* epidermal growth factor receptor, *TKI* tyrosine kinase inhibitor, *PSM* propensity score matching, *ECOG* Eastern Cooperative Oncology Group

Table 4 Baseline characteristics of patients with BM at the initiation of EGFR-TKI treatment

Characteristics	Before PSM			After PSM		
	Erlotinib	Gefitinib	*p*	Erlotinib	Gefitinib	*p*
No. of patients	11	52		11	11	
Age, years (median)	67.0	65.5	0.84	67	69	0.716
Sex			0.272			1
Male	1	14		1	2	
Female	10	38		10	9	
Smoking status			0.503			0.586
Never smoker	8	30		8	10	
Smoker	3	22		3	1	
ECOG performance status			0.723			1
0–1	8	39		8	9	
2	1	4		1	0	
3–4	2	9		2	2	
EGFR mutation status			0.075			1
Exon 21 L858R	8	18		8	8	
Exon 19 in-frame deletion	3	31		3	3	
Other mutations	0	3		0	0	
Recurrence after surgery	2	7	0.72	2	1	1
Censored follow-ups	5	14	0.28	6	8	0.659

BM brain metastasis, *EGFR* epidermal growth factor receptor, *TKI* tyrosine kinase inhibitor, *PSM* propensity score matching, *ECOG* Eastern Cooperative Oncology Group

observational period, and we excluded patients who were treated with cytotoxic agents only. EGFR-TKIs are easy to administer because of their low toxicity; therefore, they are often initiated in patients with a low PS. Therefore, we should be careful in interpreting these results, considering the external validity of these results.

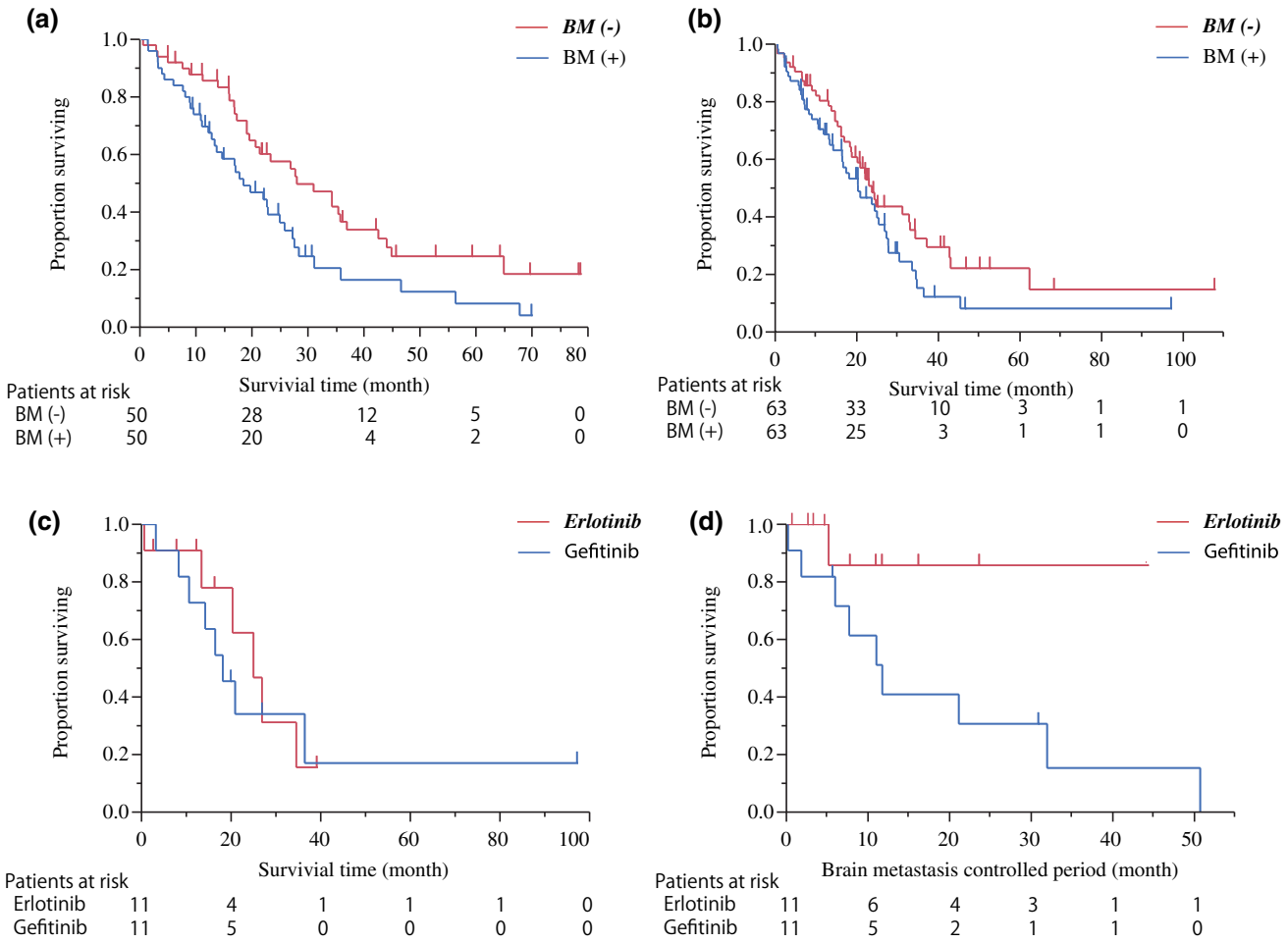

Fig. 2 Matched-pair comparisons of overall survival. Survival of patients with and without BM at the initiation of chemotherapy (**a**) and at the initiation of EGFR-TKI treatment (**b**). Comparison of survival after BM diagnosis between erlotinib and gefitinib (**c**) and of BMCP (**d**). *BM* brain metastasis, *TKI* tyrosine kinase inhibitor, *BMCP* brain metastasis controlled period

In patients with NSCLC and BM, median OS was reported to be 5–6 months, which is shorter than that in patients with stage IV NSCLC without BM [17]. In our study, the median OS of patients diagnosed with BM at the initiation of EGFR-TKI treatment was shorter than that of patients without BM, but matched-pair analysis did not show a statistically significant difference. The number of patients was reduced by matched-pair analysis; we must, therefore, accept that the power of the test also subsequently decreased. Additionally, we note that the proportion of patients with a PS of 3 or 4 is larger in patients with BM than in those without BM before PSM (17.5 and 11.2 %, respectively). Our results indicate that the presence of BM does not affect survival in patients with an *EGFR* mutation treated with an EGFR-TKI.

In patients diagnosed with BM, OS was longer in those who were administered erlotinib as the first-line treatment than in those administered gefitinib. Clinical doses of erlotinib have been reported to result in therapeutic blood levels twice as high as those of gefitinib [11]. Furthermore, some case reports have shown improvements in neurological symptoms caused by BM or leptomeningeal carcinomatosis in response to erlotinib [7–10]. A recent phase III study, which directly compared the efficacy of erlotinib and gefitinib, did not show superiority of gefitinib in progression-free survival [18]. However, to the best of our knowledge, few studies have compared erlotinib and gefitinib in the terms of survival of patients with BM. A previous retrospective study demonstrated that compared with gefitinib, erlotinib prolonged survival of patients with leptomeningeal carcinomatosis caused by NSCLC, although the results were not statistically significant [12]. Another study on patients with BM harboring *EGFR* mutations reported that erlotinib administration was a favorable prognostic factor, whereas gefitinib administration was not [13]. However, the choice of first-line EGFR-TKI treatment after BM diagnosis was not mentioned in that study. Results of prospective and retrospective studies demonstrating central nervous system

Table 5 Review of previous studies demonstrating CNS progression after erlotinib treatment

Study	*N*	BM prevalence at baseline (%)	CNS PD proportion rate (%)
JO22903/JO25567 [19]	125	1.6	4.8
Benjamin et al. [20]	172	33	8.0
ASPIRATION [21]	171	Not reported	2.9

CNS central nervous system, *BM* brain metastasis, *PD* progressive disease

(CNS) progressive disease (PD) after treatment with erlotinib are summarized in Table 5 [19–21]. The proportion of cases of CNS PD after erlotinib treatment was smaller than that of gefitinib, as shown in the NEJ005 study [22]. The CNS PD rate was less than 10 % in erlotinib studies whereas the counterpart was 25.1–39.4 % in gefitinib studies [22, 23]. On the other hand, CNS PD rate with afatinib, a second-generation pan-ErbB TKI, in patients without baseline brain metastasis was 7.2 % in LUX-Lung 3 trial and 5.4 % in LUX-Lung 6 trial [24]. The present results are consistent with those of a previous study [13]; compared with gefitinib administration, first-line erlotinib administration after BM diagnosis in patients with *EGFR* mutations prolongs survival by approximately 7 months. However, the present findings were not statistically significant. One reason for the absence of a significant difference in OS is crossover treatment: Three patients in the erlotinib group switched to gefitinib after erlotinib failure, and 16 patients in the gefitinib group were treated with erlotinib after gefitinib failure. A previous case series showed that erlotinib controlled the progression of CNS lesions during gefitinib treatment [10]. The gap might have been narrowed by data from patients who were administered erlotinib subsequent to gefitinib treatment. The number of patients in the erlotinib group was relatively small ($n = 11$), and cases in whom treatment was terminated during the observational period were considered censored. These factors may have impacted the accuracy of data.

On the other hand, BMCP was significantly different between the erlotinib and gefitinib groups. It is notable that the event of BMCP including CNS PD and death was 9.1 % in erlotinib group and 63.5 % in gefitinib group. As the need for repeated biopsies to confirm acquired resistance to EGFR-TKIs is increasing, a third-generation EGFR-TKI, which is effective in treating resistance caused by a previous EGFR-TKI treatment, is now available [25]. It is difficult to obtain tumor tissue from BM, and this may make it impossible to administer third-generation EGFR-TKIs because of the absence of a suitable biomarker. The importance of controlling BM, which drastically affects patients' PS, is growing because EGFR-TKIs are administered orally. Our results indicate that erlotinib is more effective than gefitinib in maintaining PS; therefore, patients could undergo treatment over a longer period because BMCP is a measure of the EGFR-TKI treatment period until withdrawal; in many cases, we could not assess the time from cessation of treatment until BM progression or death because of the aggravation of metastatic lesions. Therefore, BMCP might not reflect the current status of systemic or neurological symptoms. In addition, some patients continue to undergo long-term EGFR-TKI treatment, particularly erlotinib. To evaluate erlotinib's effectiveness in maintaining patients' quality of life, prospective studies examining comprehensive quality of life scores are warranted.

This study has several limitations. First, this is a retrospective study conducted at a single institution, and the number of patients is relatively small. By utilizing propensity scores, patient backgrounds were equalized as much as possible; however, the number of patients decreased. Therefore, the power of the test decreased as well. Second, we cannot exclude selection bias on the choice of the specific EGFR-TKI administered by physicians. Third, the dose of EGFR-TKIs was occasionally reduced based on patient tolerance; therefore, we might have underestimated the effect of the EGFR-TKIs. Fourth, erlotinib became available in Japan after gefitinib. This aspect of the background data was not adjusted, which may have prolonged OS and BMCP in the erlotinib group. For advanced NSCLC patients haboring EGFR mutation, the control of CNS with EGFR-TKI is crucial for treatment strategy, since it affects the patient's PS which directly influences whether he/she can continue with later-lines of chemotherapy. Therefore, thoracic oncologists should consider to take better CNS control and not only focus on toxicities, when selecting EGFR-TKIs.

Conclusion

Our study showed that prognoses of patients who undergo EGFR-TKI treatment might not be affected by the presence of BM at initiation of EGFR-TKI administration. Moreover, erlotinib may be more effective in preventing BM progression and prolonging survival than gefitinib. Larger, prospective studies are warranted to confirm these results.

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Compliance with ethical standards

Comflict of interest Y. Hosomi has received speaker fees as honoraria from Eli Lilly Japan K.K., Chugai Pharmaceutical Co., AstraZeneca K.K., Taiho Pharmaceutical Co., and Ono Pharmaceutical Co. The rest of the authors declare that they have no competing interests.

Ethical approval The study was approved by the Ethics Committee of Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital was also in accordance with the Declaration of Helsinki in 2013. The clinical information presented in the present investigation was obtained through Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital's medical records.

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