

Combined action of EGFR tyrosine kinase inhibitors and whole-brain radiotherapy on *EGFR*-mutated non-small-cell lung cancer patients with brain metastasis

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Background: Lung cancer is the most common type of cancer to spread to the brain (brain metastasis [BM]). This study assessed the effect of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in combination with whole-brain radiotherapy (WBRT) on *EGFR*-mutant non-small-cell lung cancer (NSCLC) patients with BM.

Patients and methods: Thirty-nine patients, who had received different EGFR TKIs plus 30 Gy WBRT until disease progression, were retrospectively analyzed between 2010 and 2014. Treatment response was evaluated and survival data were collected and analyzed.

Results: Among the 39 patients, 18 had an *EGFR* exon 19 deletion and 21 had an *EGFR* exon 21 point mutation. After therapy, 19 (48.7%) patients had complete remission, 12 (30.8%) had partial remission, and eight (20.5%) had stable disease in the intracranial lesions. Besides, there was no single case of complete remission, 21 (53.8%) had partial remission, and 18 (46.2%) had stable disease of the extracranial lesions. The median progression-free survival (PFS) of intracranial lesions and extracranial lesions was 18 and 12 months, respectively. The median overall survival (OS) was 26 months. The univariate analysis showed that graded prognostic assessment ($P=0.006$) and Karnofsky Performance Scale ($P=0.045$) were associated with intracranial progression-free survival (iPFS), while recursive partitioning analysis ($P=0.049$) was associated with OS of patients.

Conclusion: EGFR TKIs plus concomitant WBRT controlled intracranial lesions of lung cancer metastasis and significantly improved OS of patients. Further studies will be needed to confirm whether this combination treatment could be used as a standard therapy for *EGFR*-mutated NSCLC patients with BM.

Keywords: non-small-cell lung cancer, brain metastases, epidermal growth factor receptor, tyrosine kinase inhibitors, whole-brain radiotherapy

Introduction

Lung cancer remains the leading cause of cancer-related deaths throughout the world.¹ The 2013 China Tumor Registration Annual Report estimated that the People's Republic of China has ~60,000 new lung cancer cases to be diagnosed. Globally, non-small-cell lung cancer (NSCLC) accounts for 80%–90% of all lung cancer cases, and adenocarcinoma is the most common histological type of NSCLC.² Most NSCLC patients are diagnosed at the advanced stages of disease, at which point surgical resection is not a possible option. For such patients, platinum-based chemotherapy is often used as the first-line treatment; however, such treatments may not significantly reduce NSCLC mortality and the 5-year survival rate remains less than 5% with median

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survival of much less than 1 year.^{3,4} Clinically, lung cancer metastasizing to the brain (brain metastasis [BM]) has the highest incidence rate, ranging between 20% and 65% in all NSCLC cases,^{5,6} significantly contributing to a high NSCLC mortality rate. Among patients who are initially diagnosed with NSCLC, the prevalence rates of BM ranges from 7.4% to 10% initially but further increases to 30%–50% during the course of the disease.^{7–11} Despite therapy, the prognosis of NSCLC patients with BM is very poor and the 1-year survival rate is only ~20%, while the median overall survival (OS) of such patients is ~7 months.¹² Thus, further studies are needed to develop novel treatment options to control NSCLC and BM, which will be the key to prolong the survival of NSCLC patients.

Over the last decade, lung cancer research has focused on molecular target therapy; for example, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been used to treat *EGFR*-mutated NSCLC.^{13–20} To date, EGFR TKIs have been successfully employed to control *EGFR*-mutated NSCLC with an efficacy of ~70% in patients with EGFR mutations and only 5% in patients with wild-type *EGFR* NSCLC.^{21,22} A recent study also showed that EGFR TKIs were able to effectively control BM in *EGFR*-mutated NSCLC patients.²³ Other studies reported that patients with *EGFR*-mutated NSCLCs were more sensitive to radiotherapy.^{24–29} Together, these studies indicate that the combination of EGFR TKIs with whole-brain radiotherapy (WBRT) could effectively control BM lesions in patients with *EGFR*-mutated NSCLC. Thus, in this study, we assessed the effect of EGFR TKIs in combination with WBRT on *EGFR*-mutated NSCLC patients with BM. We expected to provide evidence for use of this treatment combination as the standard clinical therapy protocol for NSCLC patients.

Patients and methods

Patients

In this study, we retrospectively enrolled and analyzed 39 *EGFR*-mutated NSCLC patients with BM after they received EGFR TKIs (icotinib, gefitinib, or erlotinib) plus WBRT between 2010 and 2014 at Zhejiang Cancer Hospital (Hangzhou, People's Republic of China). All patients were histologically diagnosed with NSCLC, and EGFR mutations were detected by the amplification refractory mutation system analysis, which identified tumor lesions that had EGFR mutations (exon 19 deletion or exon 21 point mutation). BM in these patients was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). Patient follow-up by telephone was done until April 2015 and the

median follow-up time was 25 months (ranged between 7 and 55 months). This study was approved by The Ethics Committee of Zhejiang Cancer Hospital and all patients or guardians signed informed consent forms before participation in this study.

Clinicopathological data, including sex, age, history of tobacco smoking, histology, number of brain metastatic lesions, active extracranial metastases at baseline, interval of BM, prior chemotherapy before BM, EGFR mutation type, EGFR TKIs treatment, data on recursive partitioning analysis (RPA),⁴ graded prognostic assessment (GPA),³⁰ Karnofsky Performance Scale (KPS),³¹ and treatment responses, were retrieved from patients' medical records.

Treatment and evaluation of treatment responses

All patients received oral administration of EGFR TKIs (125 mg/day, three times a day: icotinib; 250 mg gefitinib; 150 mg erlotinib) until there was detectable progressive disease (PD), symptomatic deterioration (SD), or unacceptable toxicity. The dose of concomitant WBRT was 30 Gy administered in ten fractions (3 Gy fractions once a day, 5 days a week).

Treatment responses were assessed using chest CT and brain MRI every 2 or 3 months until disease progression. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, including complete remission (CR), partial remission (PR), SD, and PD of the intracranial lesions. The objective response rate (ORR) included the combination of CR and PR, and the disease control rate (DCR) included CR, PR, and SD.³² Treatment outcome was OS defined as the time from starting EGFR TKIs treatment until death from any cause or last follow-up day. Progression-free survival (PFS) was defined as the time from starting EGFR TKIs to occurrence of either clinically symptomatic BM (intracranial progression-free survival [iPFS]) or confirmed morphologically proven intracranial PD (presence of at least one key symptom in combination with radiologic evidence including CT or MRI of PD in the brain on follow-up) or extracranial PD (extracranial progression-free survival [ePFS]). Systemic PD was defined as disease progression based on RECIST version 1.1.³²

Evaluation of treatment toxicity

Treatment toxicity was evaluated based on the National Cancer Institute Common Toxicity Criteria (NCICTC) version 2.0³³ and was assessed every month.

Statistical analysis

The impact of the potential variables affecting PFS and OS was assessed by univariate analysis with the log-rank test. The Cox regression method was used to identify the most important independent prognostic factors and estimate the hazard ratio (HR). In a multivariate analysis, the following variables were included: sex, age, tobacco smoking history, KPS, tumor histology, numbers of BM lesions, active extracranial metastasis at the baseline, interval of BM, prior chemotherapy before BM, types of EGFR mutations, EGFR TKIs, RPA, and GPA. All tests and confidence intervals (CIs) were two-sided, and the significance level of statistical analysis was set at $P < 0.05$. All statistical analyses were performed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of patients

There were 39 patients who had histologically confirmed NSCLC and radiographically diagnosed with BM. Moreover, all NSCLC lesions had an EGFR mutation (Table 1). The median age of these patients was 56 years (ranged between 39 and 73 years); 15 patients were male and 24 were female. Thirteen patients were tobacco smokers and 26 were nonsmokers. These NSCLC cases included 36 adenocarcinomas and three nonadenocarcinoma cases, 28 of which had KPS ≥ 70 , eleven had KPS < 70 . Twelve patients had a single intracranial lesion, while seven had two lesions and 20 had three or more lesions. EGFR exon 19 deletion mutation occurred in 18 patients and exon 21 point mutation in 21 patients. RPA showed that 13 patients were in RPA class I, 22 in class II, and four in class III. GPA showed that 14 patients were between scores 0 and 1.0, 15 between 1.5 and 2.0, six between 2.5 and 3.0, and four between 3.5 and 4.0.

Efficacy of treatment and survival

Survival analysis showed that the median iPFS was 18 months (95% CI, 16.1–19.9 months) and the median ePFS was 12 months (95% CI, 9.07–14.93 months). The median OS was 26 months (95% CI, 22.8–29.3 months). We evaluated brain tumor variables by dividing EGFR mutations into exon 19 and exon 21, but found no statistical difference in OS between the groups (Figure 1A). All patients had a similar OS after being treated with different EGFR TKIs in combination with the same WBRT dose (Figure 1B).

Taking into account intracranial lesions, 19 patients (48.7%) had CR, 12 had (30.8%) PR, and eight had (20.5%) SD. The ORR and DCR were 79.5% and 100.0%, respectively

Table 1 Patient baseline characteristics (n=39)

Characteristics	Patients, n (%)
Median age, years (range)	56 (39–73)
Age, years, n (%)	
<56	19 (48.7)
≥ 56	20 (51.3)
Sex, n (%)	
Male	15 (38.5)
Female	24 (61.5)
Smoking status, n (%)	
Never	26 (66.7)
Former or current	13 (33.3)
ECOG PS, n (%)	
KPS ≥ 70	28 (71.8)
KPS < 70	11 (28.2)
Histology, n (%)	
Adenocarcinoma	36 (92.3)
Squamous carcinoma	1 (2.6)
Other	2 (5.1)
Number of brain metastases, n (%)	
1	12 (30.8)
2	7 (17.9)
≥ 3	20 (51.3)
Extracranial metastases, n (%)	
No	16 (41.0)
Yes	23 (59.0)
Interval of brain metastases, n (%)	
Synchronous	21 (53.8)
Heterochronous	18 (46.2)
Prior chemotherapy before brain metastases, n (%)	
Yes	13 (33.3)
No	26 (66.7)
EGFR mutation, n (%)	
Exon 19	18 (46.2)
Exon 21	21 (53.8)
TKIs type, n (%)	
Erlotinib	23 (59.0)
Gefitinib	7 (17.9)
Icotinib	9 (23.1)
RPA class, n (%)	
Class I	13 (33.3)
Class II	22 (56.4)
Class III	4 (10.3)
GPA grade, n (%)	
0–1	14 (35.9)
1.5–2.5	15 (38.4)
3	6 (15.4)
3.5–4	4 (10.3)

Abbreviations: KPS, Karnofsky Performance Scale; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; RPA, recursive partitioning analysis; GPA, graded prognostic assessment.

(Table 2). At the last follow-up, 18 patients were deceased and 21 were alive. The 6-month, 1-year, and 2-year survival rates were 97.4%, 89.7%, and 33.3%, respectively.

The univariate analysis data showed that GPA ($P=0.006$) and KPS ($P=0.045$) were significantly associated with iPFS, but not with ePFS. RPA ($P=0.049$) was significantly

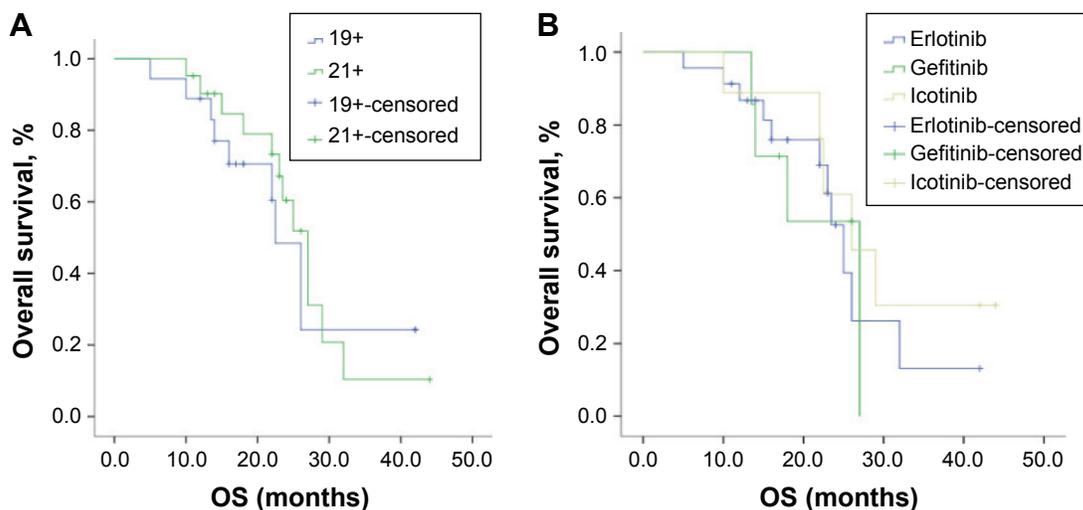


Figure 1 Kaplan–Meier curve analyses of overall survival (OS) of patients after EGFR TKI and WBRT.

Notes: (A) Kaplan–Meier curve was stratified by EGFR mutation types (exon 19 vs exon 21). (B) Kaplan–Meier curves were stratified by different EGFR TKI treatments.

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy.

associated with OS (Table 3). The multivariate analysis did not show any statistically significant associations with OS of these patients.

Toxicity and safety

All 39 patients were included in the toxicity analysis. The combination of EGFR TKIs with WBRT was well tolerated. There was no radiation-enhanced EGFR TKIs related rash in the portal treatment area. During the concurrent EGFR TKIs with combination WBRT phase, none of the patients required a reduction in the dose of EGFR TKIs, although skin toxicity did occur in 33.3% of patients. Other toxicities included diarrhea in 5.1% of patients, constipation in one patient, and hepatotoxicity in 7.7% of patients. The long-term follow-up showed that some patients developed neurotoxicity that was deemed possibly related to treatment. Alopecia occurred in 82.1% of patients, headache in 30.8%, and vomiting in 46.2%. However, nausea and fatigue were rarely observed. There was no grade 5 treatment-related toxicity in this cohort of patients (Table 4).

Table 2 Treatment response of the intracranial lesion (n=39)

Response	TKI + WBRT, n (%)
CR	19 (48.7)
PR	12 (30.8)
SD	8 (20.5)
PD	0 (0)
ORR	31 (79.5)
DCR	39 (100.0)

Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy.

Discussion

To date, treatment of patients with advanced stages of NSCLC and BM remains a significant clinical challenge. Therapeutic modalities to control BM include WBRT, stereotactic radiosurgery (SRS), surgery, and chemotherapy, but efficacy of these treatments remains poor and prognosis of such patients with BM is still poor. Specifically, SRS or surgery is only used to alternatively treat a small subset of NSCLC patients with oligoplastic BM lesion and palliative systemic chemotherapy may not cross the blood–brain barrier (BBB), making this treatment less effective. Thus, WBRT has been used as a standard treatment in NSCLC patients with BM resulting in an OS ranging between 3 and 6 months.^{34,35} Our current study evaluated the efficacy of EGFR TKIs plus WBRT on controlling BM of patients with *EGFR*-mutant NSCLC. Our data showed that 48.7% had CR, 30.8% had PR, and 20.5% had SD in the intracranial lesions. The median PFS of intracranial lesions and extracranial lesions was 18 and 12 months, respectively, and the median OS was 26 months. In the univariate analysis, the GPA and KPS data were associated with iPFS and RPA was associated with OS, whereas the multivariate analysis did not show any independent indicator for OS of these patients. Our current study did indicate that EGFR TKIs plus concomitant WBRT could effectively control intracranial lesions in NSCLC patients and significantly improve OS of these patients. After further confirmation by a future prospective clinical trial, this treatment regimen could be used as a standard therapy for *EGFR*-mutated NSCLCs with BM.

It has been previously demonstrated that systemic chemotherapy failed to control BM lesions,³⁶ because most

Table 3 Univariate analysis for overall survival and progression-free survival

Clinical variables	N	Median OS (months)	95% CI	Log rank (P-value)	Median iPFS (months)	95% CI	Log rank (P-value)	Median ePFS	95% CI	Log rank (P-value)
Age, years, n (%)				0.80			0.58			0.72
<55	19	27.0	20.24–33.75		14.0	12.10–15.89		12.0	9.16–14.84	
≥55	20	26.0	22.86–29.13		18.0	17.06–18.94		8.5	1.39–15.61	
Sex, n (%)				0.17			0.67			0.62
Male	15	32.0	14.55–49.44		17.0	10.09–23.90		12.0	7.21–16.78	
Female	24	25.0	21.47–28.52		18.0	15.04–20.95		11.0	6.53–15.46	
Smoking status, n (%)				0.64			0.22			0.72
Never	26	25.0	22.17–27.82		18.0	14.87–21.12		12.0	8.59–15.40	
Former or current	13	32.0	17.86–46.13		17.0	8.68–25.31		11.0	8.06–13.96	
KPS				0.17			0.05			0.223
KPS ≥70	28	22.0'	12.30–31.70		23.0	13.41–32.59		23.0'	–	
KPS <70	11	18.0	6.31–29.69		14.0'	6.45–21.55		11.0'	3.42–18.58	
Histology, n (%)				0.74			0.33			0.48
Adenocarcinoma	36	25.0	22.30–27.69		18.0	15.23–20.77		12.0	8.51–15.48	
Squamous carcinoma	1	32.0	–		18.0	–		18.0	–	
Other	2	15.0	–		11.0'	–		7.0'	–	
Number of brain metastases, n (%)				0.92			0.89			0.64
1	12	26.0	22.36–29.63		17.0'	15.30–18.69		12.5	0.00–25.23	
2	7	–	–		24.0	–		14.0	6.30–21.69	
≥3	20	23.0	17.91–28.08		18.0	11.99–24.00		10.0'	6.71–13.28	
Extracranial metastases, n (%)				0.69			0.87			0.67
No	16	26.0	20.37–29.62		17.0'	13.19–20.80		10.0'	7.083–12.917	
Yes	23	25.0	22.67–29.32		18.0	15.49–20.50		12.5	9.57–15.42	
Interval of brain metastases, n (%)				0.75			0.86			0.31
Synchronous	21	26.0	23.20–28.79		17.0	10.71–23.29		10.0'	6.07–13.92	
Heterochronous	18	27.0'	23.30–30.69		18.0	17.10–18.89		12.5	7.36–17.63	
Prior chemotherapy before brain metastases, n (%)				0.18			0.16			0.22
Yes	13	27.0	25.72–28.27		22.0	17.86–26.13		12.0'	9.72–14.27	
No	26	23.5	15.27–31.72		14.0'	11.89–16.10		10.0'	5.11–14.88	
EGFR mutation, n (%)				0.68			0.89			0.11
Exon 19	18	22.5	19.21–25.78		18.0	14.49–21.50		9.0'	6.92–11.07	
Exon 21	21	27.0	23.78–30.21		17.0	13.98–20.01		15.0'	9.40–20.59	
TKIs type, n (%)				0.65			0.30			0.83
Erlotinib	23	25.0	22.30–27.69		18.0	14.46–21.53		11.0'	7.21–14.78	

(Continued)

Table 3 (Continued)

Clinical variables	N	Median OS (months)	95% CI	Log rank (P-value)	Median iPFS (months)	95% CI	Log rank (P-value)	Median ePFS	95% CI	Log rank (P-value)
Gefitinib	7	27.0	–	–	17.0	13.48–20.51	–	12.5'	8.65–16.34	–
Icotinib	9	26.0	18.09–33.90	0.049	23.0	18.89–27.10	0.70	12.0'	6.15–17.84	0.34
RPA class, n (%)										
Class I	13	25.0	21.60–28.38		17.0	9.63–24.36		10.0'	6.56–13.43	
Class II	22	26.0	22.75–29.24		18.0	17.20–18.79		13.0'	8.85–17.14	
Class III	4	12.0	3.10–20.82		12.0	2.20–21.80	0.006	6.5	0.00–14.83	0.73
GPA grade, n (%)										
0–1	14	22.5	12.21–32.78	0.39	14.0'	3.554–24.44		11.0'	5.92–16.07	
1.5–2.5	15	27.0	19.57–34.42		18.0'	17.50–18.49		12.0	8.41–15.58	
3	6	23.5	20.56–26.44		10.5	5.69–15.30		10.0'	1.59–18.40	
3–5.4	4	26.0	–		26.0'	13.19–38.80		8.5	–	

Abbreviations: KPS, Karnofsky Performance Scale; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; RPA, recursive partitioning analysis; GPA, graded prognostic assessment; CI, confidence interval; OS, overall survival; iPFS, intracranial progression-free survival; ePFS, extracranial progression-free survival; –, not available.

Table 4 Treatment toxicities (n=39)

Adverse events	Grade 1/2, n (%)	Grade 3/4, n (%)	Total, n (%)
Skin toxicity	12 (30.8)	1 (2.6)	13 (33.3)
Diarrhea	1 (2.6)	1 (2.6)	2 (5.1)
Constipation	1 (2.6)	0 (0)	1 (2.6)
Hepatotoxicity	2 (5.1)	1 (2.6)	3 (7.7)
Nausea	0 (0)	0 (0)	0 (0)
Vomiting	18 (46.2)	0 (0)	18 (46.2)
Neuropathy	0 (0)	0 (0)	0 (0)
Fatigue	3 (7.7)	0 (0)	3 (7.7)
Leukopenia	0 (0)	0 (0)	0 (0)
Alopecia	24 (61.5)	8 (20.5)	32 (82.1)
Headache	10 (25.6)	2 (5.1)	12 (30.8)

chemotherapeutic agents are unable to cross the BBB. However, EGFR TKIs, especially EGFR TKIs plus WBRT, can better penetrate the brain parenchyma.^{36,37} Furthermore, gefitinib sensitized tumor cells to radiation in vitro.²⁹ Huang et al reported that the combined treatment of radiation with gefitinib synergistically inhibited tumor growth in lung cancer xenografts of nude mouse.²⁵ Van et al showed that radiation was able to disrupt the BBB,³⁷ which improved penetration of chemotherapeutic agents or molecular targeted drugs into the brain. Zeng et al demonstrated that gefitinib increased the BBB permeability after an escalated dose of WBRT, which was consistent with that of other previous studies.^{38–42} Compared to chemotherapy, previous studies showed that *EGFR*-mutated NSCLC patients with BM who received EGFR TKIs alone had an ORR of 60%–88% and a median OS of 6.6–18.9 months.^{23,36,43–49} Other studies reported that after the failure of radiotherapy, ORR and DCR of patients with *EGFR*-mutated NSCLC and BM, who received EGFR TKIs, were found to be 20%–89% and 80%–89%, respectively.^{47,50,51} In our current retrospective study, the ORR and DCR of intracranial lesions reached 79.5% and 100.0%, respectively, which is consistent with the previous studies. In addition, Luo et al reported that 125 NSCLC patients with BM who underwent WBRT and 12% of patients with intracranial tumors had CR, 68% had PR, 10% had SD, and 10% had PD, and the median OS was 7.1 months.⁵² Another study assessed nine patients with *EGFR*-mutated NSCLC and BM after erlotinib and WBRT treatment, and the data showed a 19.1-month median OS, and the 6-month, 1-year, and 2-year cumulative survival rates were 88.9%, 55.6%, and 44.4%, respectively.⁴⁷ Zeng et al reported that the ORR and DCR of seven patients with *EGFR*-mutated NSCLC and BM who had gefitinib and WBRT treatment reached 71.4% and 85.7%, respectively, with a median OS of 23.4 months.⁵¹ In our

current study, the median PFS and median OS of patients treated with EGFR TKIs plus WBRT reached more than 10 and 26 months, respectively, which were significantly better than those obtained for chemotherapy, EGFR TKIs, or WBRT alone and better than the values reported in previous similar studies.^{47,51,53} These results may be due to the fact that high proportion of our patients received fully individualized treatments.

Furthermore, our current study demonstrated that patients tolerated the combined treatment of EGFR TKIs and WBRT well. Specifically, there was no radiation-enhanced EGFR TKIs related rash in the portal treatment area. No adjustments were needed in EGFR TKIs or WBRT doses given to the patients. One-third of the patients did develop skin toxicity, but other toxicities were rare, although the long-term follow-up data showed that alopecia occurred in 32 patients, headache in 12, and vomiting in 18. Welsh et al also showed that erlotinib and radiation therapy of BM in NSCLC patients was safe and well tolerated.⁴⁷ We assumed that the addition of WBRT might increase the concentration of TKIs in the patients with BM. However, WBRT may induce neurotoxicity and lead to leukodystrophy. Thus, SRS or routine surgery could be used to remove a single metastatic brain NSCLC lesion followed by molecular target or chemotherapy. This strategy is proposed because intracranial lesions usually progress in a short period of time after SRS or routine surgery. Further studies are needed to reduce side effects and increase treatment efficacy to control BM in NSCLC patients.

Limitations

Our current study does have some limitations; for example, this was a single-arm study and retrospective in nature. BM was not confirmed pathologically or genetically. *EGFR* mutation status was evaluated only in primary tumor specimens. However, discordance of *EGFR* mutation status between the primary and metastatic sites has been reported and reached up to 28%.^{54,55} Thus, future studies are needed to evaluate *EGFR* mutation status in BM. Moreover, WBRT and EGFR TKI was not precisely determined and controlled in this retrospective study. Shukuya et al showed that this kind of therapy was effective when continuous EGFR TKIs were administered following WBRT in NSCLC patients with isolated central nervous system failure.⁵⁶ To date, there are no clinical trials to compare concomitant and sequential therapy of EGFR TKIs and WBRT. Future clinical trials should investigate the optimal regimen of EGFR TKIs in combination with WBRT in NSCLC patients with BM.

Conclusion

In conclusion, the current retrospective study of concurrent EGFR TKIs and WBRT for control of *EGFR*-mutated NSCLC with BM showed that this combination was safe and well tolerated. Survival rate of the patients exceeded that of those treated with EGFR TKIs or WBRT alone from historical controls. However, a large prospective randomized clinical trial is needed to validate our current findings.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69–90.
2. Yamanashi K, Marumo S, Miura K, et al. Long-term survival in a case of pleomorphic carcinoma with a brain metastasis. *Case Rep Oncol*. 2014;7(3):799–803.
3. Sampsonas F, Ryan D, McPhillips D, et al. Molecular testing and personalized treatment of lung cancer. *Curr Mol Pharmacol*. 2014;7(1):22–32.
4. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997;37(4):745–751.
5. Preusser M, Capper D, Ilhan-Mutlu A, et al. Brain metastases: pathobiology and emerging targeted therapies. *Acta Neuropathol*. 2012;123(2):205–222.
6. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol*. 2004;22(14):2865–2872.
7. Smedby KE, Brandt L, Backlund ML, et al. Brain metastases admissions in Sweden between 1987 and 2006. *Br J Cancer*. 2009;101(11):1919–1924.
8. Sorensen JB, Hansen HH, Hansen M, et al. Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. *J Clin Oncol*. 1988;6(9):1474–1480.
9. Komaki R, Cox JD, Stark R. Frequency of brain metastasis in adenocarcinoma and large cell carcinoma of the lung: correlation with survival. *Int J Radiat Oncol Biol Phys*. 1983;9(10):1467–1470.
10. Schouten LJ, Rutten J, Huvneers HA, et al. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer*. 2002;94(10):2698–2705.
11. Hubbs JL, Boyd JA, Hollis D, et al. Factors associated with the development of brain metastases: analysis of 975 patients with early stage nonsmall cell lung cancer. *Cancer*. 2010;116(21):5038–5046.
12. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol*. 2012;30(4):419–425.
13. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947–957.
14. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol*. 2011;29(21):2866–2874.

15. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362(25):2380–2388.
16. Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann Oncol*. 2013;24(1):54–59.
17. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11(2):121–128.
18. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13(3):239–246.
19. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15(2):213–222.
20. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12(8):735–742.
21. Ding K, Pater J, Whitehead M, et al. Validation of treatment induced specific adverse effect as a predictor of treatment benefit: a case study of NCIC CTG BR21. *Contemp Clin Trials*. 2008;29(4):527–536.
22. Gang C. Molecular targets therapy for non-small cell lung cancer. *Chin J Cancer Prev Treat*. 2007;14(5):387–391.
23. Park SJ, Kim HT, Lee DH, et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. *Lung Cancer*. 2012;77(3):556–560.
24. Bianco C, Tortora G, Bianco R, et al. Enhancement of antitumor activity of ionizing radiation by combined treatment with the selective epidermal growth factor receptor-tyrosine kinase inhibitor ZD1839 (Iressa). *Clin Cancer Res*. 2012;8(10):3250–3258.
25. Huang SM, Li J, Armstrong EA, et al. Modulation of radiation response and tumor-induced angiogenesis after epidermal growth factor receptor inhibition by ZD1839 (Iressa). *Cancer Res*. 2002;62(15):4300–4306.
26. Bonner JA, Harari PM, Giralat J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006;354(6):567–578.
27. Shimato S, Mitsudomi T, Kosaka T, et al. EGFR mutations in patients with brain metastases from lung cancer: association with the efficacy of gefitinib. *Neuro Oncol*. 2006;8(2):137–144.
28. Das AK, Chen BP, Story MD, et al. Somatic mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) abrogate EGFR-mediated radioprotection in non-small cell lung carcinoma. *Cancer Res*. 2007;67(11):5267–5274.
29. Park SY, Kim YM, Pyo H. Gefitinib radiosensitizes non-small cell lung cancer cells through inhibition of ataxia telangiectasia mutated. *Mol Cancer*. 2010;9:222.
30. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. *Int J Radiat Oncol Biol Phys*. 2010;77(3):655–661.
31. Fan Y, Huang Z, Fang L, et al. Chemotherapy and EGFR tyrosine kinase inhibitors for treatment of brain metastases from non-small-cell lung cancer: survival analysis in 210 patients. *Onco Targets Ther*. 2013;6:1789–1803.
32. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247.
33. Kaba H, Fukuda H, Yamamoto S, et al. [Reliability at the National Cancer Institute-Common Toxicity Criteria version 2.0]. *Gan To Kagaku Ryoho*. 2004;31(8):1187–1192.
34. Diener-West M, Dobbins TW, Phillips TL, et al. Identification of an optimal subgroup for treatment evaluation of patients with brain metastases using RTOG study 7916. *Int J Radiat Oncol Biol Phys*. 1989;16(3):669–673.
35. Borgelt B, Gelber R, Kramer S, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. 1980;6(1):1–9.
36. Eichler AF, Kahle KT, Wang DL, et al. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. *Neuro Oncol*. 2010;12(11):1193–1199.
37. van Vulpen M, Kal HB, Taphoorn MJ, et al. Changes in blood-brain barrier permeability induced by radiotherapy: implications for timing of chemotherapy? (Review). *Oncol Rep*. 2002;9(4):683–688.
38. Zeng YD, Liao H, Qin T, et al. Blood-brain barrier permeability of gefitinib in patients with brain metastases from non-small-cell lung cancer before and during whole brain radiation therapy. *Oncotarget*. 2015;6(10):8366–8376.
39. Jackman DM, Holmes AJ, Lindeman N, et al. Response and resistance in a non-small-cell lung cancer patient with an epidermal growth factor receptor mutation and leptomeningeal metastases treated with high-dose gefitinib. *J Clin Oncol*. 2006;24(27):4517–4520.
40. Fukuhara T, Saijo Y, Sakakibara T, et al. Successful treatment of carcinomatous meningitis with gefitinib in a patient with lung adenocarcinoma harboring a mutated EGF receptor gene. *Tohoku J Exp Med*. 2008;214(4):359–363.
41. Zhao J, Chen M, Zhong W, et al. Cerebrospinal fluid concentrations of gefitinib in patients with lung adenocarcinoma. *Clin Lung Cancer*. 2013;14(2):188–193.
42. d'Avella D, Ciccirello R, Albiero F, et al. Quantitative study of blood-brain barrier permeability changes after experimental whole-brain radiation. *Neurosurgery*. 1992;30(1):30–34.
43. Ceresoli GL, Cappuzzo F, Gregorc V, et al. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. *Ann Oncol*. 2004;15(7):1042–1047.
44. Porta R, Sanchez-Torres JM, Paz-Ares L, et al. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. *Eur Respir J*. 2011;37(3):624–631.
45. Iuchi T, Shingyoji M, Sakaida T, et al. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. *Lung Cancer*. 2013;82(2):282–287.
46. Song Z, Zhang Y. Gefitinib and erlotinib for non-small cell lung cancer patients who fail to respond to radiotherapy for brain metastases. *J Clin Neurosci*. 2014;21(4):591–595.
47. Welsh JW, Komaki R, Amini A, et al. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. *J Clin Oncol*. 2013;31(7):895–902.
48. Hsiao SH, Lin HC, Chou YT, et al. Impact of epidermal growth factor receptor mutations on intracranial treatment response and survival after brain metastases in lung adenocarcinoma patients. *Lung Cancer*. 2013;81(3):455–461.
49. Wu YL, Zhou C, Cheng Y, et al. Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG-0803). *Ann Oncol*. 2013;24(4):993–999.
50. Bai H, Han B. The effectiveness of erlotinib against brain metastases in non-small cell lung cancer patients. *Am J Clin Oncol*. 2013;36(2):110–115.
51. Zeng YD, Zhang L, Liao H, et al. Gefitinib alone or with concomitant whole brain radiotherapy for patients with brain metastasis from non-small-cell lung cancer: a retrospective study. *Asian Pac J Cancer Prev*. 2012;13(3):909–914.
52. Luo J, Zhu H, Tang Y, et al. Analysis of prognostic factors and comparison of prognostic index scores in patients with brain metastases after whole-brain radiotherapy. *Int J Clin Exp Med*. 2014;7(12):5217–5225.
53. Gow CH, Chien CR, Chang YL, et al. Radiotherapy in lung adenocarcinoma with brain metastases: effects of activating epidermal growth factor receptor mutations on clinical response. *Clin Cancer Res*. 2008;14(1):162–168.

54. Gow CH, Chang YL, Hsu YC, et al. Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naive non-small-cell lung cancer. *Ann Oncol*. 2009;20(4):696–702.
55. Kalikaki A, Koutsopoulos A, Trypaki M, et al. Comparison of EGFR and K-RAS gene status between primary tumours and corresponding metastases in NSCLC. *Br J Cancer*. 2008;99(6):923–929.
56. Shukuya T, Takahashi T, Naito T, et al. Continuous EGFR-TKI administration following radiotherapy for non-small cell lung cancer patients with isolated CNS failure. *Lung Cancer*. 2011;74(3):457–461.

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