ORIGINAL ARTICLE

Leptomeningeal Metastases in Patients with NSCLC with *EGFR* Mutations

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ABSTRACT

Introduction: Leptomeningeal metastases (LM) have increased in patients with NSCLC, and prognostic factors and outcomes for LM with *EGFR* gene mutations have not been well studied.

Methods: We retrospectively analyzed patients with lung cancer from January 2011 to June 2015 at our institute. Treatments and clinical outcomes of LM were reviewed.

Results: LM were diagnosed in 184 (3.4%) of 5387 patients with lung cancer. Patients with LM harboring *EGFR* mutations (9.4%) were significantly more frequent than those with wild-type *EGFR* (1.7% [$p < 0.001$]). The median overall survival (OS) after LM was 8.7 months (95% confidence interval [CI]: 7.3–10.1). Among the 109 patients with common *EGFR* mutations, the 88 patients who received tyrosine kinase inhibitor (TKI) therapy demonstrated longer OS than those who did not (10.0 months versus 3.3 months [$p < 0.001$]), but 42 patients who underwent whole brain radiotherapy (WBRT) did not show longer OS than those without WBRT, and a combination of WBRT and TKIs did not add any survival benefit beyond that in patients receiving only TKIs. A multivariate analysis indicated that TKI therapy ($p < 0.001$, hazard ratio = 0.218) was an independent predictor of favorable survival, whereas poor Eastern Cooperative Oncology Group performance status ($p < 0.001$, hazard ratio = 3.657) was a predictor of poor survival.

Conclusions: LM were much more frequent in patients with NSCLC harboring *EGFR* mutations. EGFR TKIs were the optimal treatment for LM, and active treatment with WBRT did not prolong OS for *EGFR*-mutated patients.

Keywords: Leptomeningeal metastases; *EGFR* mutations; Epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC

Introduction

Leptomeningeal metastases (LM) occur in 1% to 9.1% of all patients with solid tumors; they are a devastating complication associated with poor survival, and optimal therapeutic approaches remain a challenge.[1–5] Lung and breast cancer are the most common types of primary solid tumors with LM,[4,6] and LM in patients with NSCLC have increased during the past 10 years.[7] The use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has markedly prolonged survival in patients with *EGFR* mutations, and frequent *EGFR* mutations have been reported in central nervous system (CNS) metastases in patients with NSCLC.[8,9] However, there are only a few studies of LM that have provided a small subset of data on the *EGFR* gene mutation status.[7,10–13]

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Drs. Li and Jiang contributed equally to this work.

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There are no standard guidelines or any consensus on treatment options for patients with NSCLC with LM, although EGFR TKIs, chemotherapy, whole brain radiotherapy (WBRT), intrathecal chemotherapy, surgery, and ventriculoperitoneal shunt operations have been described.[3,7,11,14,15] Most previous studies were performed in unselected patients, and data on LM cases with *EGFR* mutations are lacking. LM usually occur during TKI therapy; high-dose TKIs and switching TKIs have been recommended in small series studies.[16–21] Patients with LM usually have poor performance status and most of them fail to accept systematic chemotherapy. Regarding WBRT, its role remains controversial; some authors claimed that it predicts favorable survival, but others disagreed, and research on WBRT alone in LM with *EGFR* mutations is lacking.[3,7,14] A previous phase II trial indicated that erlotinib was well tolerated in combination with WBRT and had a favorable objective response rate in patients with brain metastases[22]; however, its role in LM is unknown.

Given that previous studies of LM included subjects with different gene status, it is difficult to identify optimal treatments and prognostic factors for patients with NSCLC harboring *EGFR* mutations. Thus, we performed this study to examine the prevalence of *EGFR* mutations in patients with NSCLC with LM and sought to identify prognostic factors and clinical outcomes in those with *EGFR* mutations.

Patients and Methods

Patients

We retrospectively screened 5387 consecutive patients with lung cancer at Guangdong Lung Cancer Institute, Guangdong General Hospital, from January 2011 to June 2015. Patients with NSCLC with specified presence or absence of *EGFR* mutations, and LM diagnosed by a cerebrospinal fluid (CSF) cytologic test or gadolinium-enhanced brain magnetic resonance imaging (MRI) were included in the study.

Parameters

We reviewed the medical records of the database patients, including their demographic data, tumor-related features, and major treatments for LM. Tumor-related features included histological type, gene profiles of *EGFR* mutations, and interval from diagnosis of metastatic lung cancer/previous TKIs to LM. Main treatments including TKIs, chemotherapy, and WBRT were evaluated. WBRT was usually performed at a dose of 30 Gy in 10 daily fractions. The therapeutic regimens were performed after multidisciplinary discussions in most cases. This retrospective study adhered to the rules and regulations of clinical studies with respect to protection of human subjects.

Statistical Analysis

Overall survival (OS) was defined as the period from diagnosis of LM to death or last follow-up. OS status was classified as censored if a patient was unavailable for follow-up or survived beyond the last follow-up (October 16, 2015). Survival was estimated using the Kaplan-Meier method and is presented as a median value with a two-sided 95% confidence interval (CI). A two-sided log-rank test was used to compare survival between the two arms. Multivariable predictors were assessed with a forward stepwise likelihood ratio Cox proportional hazard model, and the χ^2 test was used to analyze the incidence of LM in *EGFR* mutations and patients with *EGFR* wild type. A p value less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using the SPSS for Windows software package, version 13.0 (SPSS, Inc., Chicago, IL).

Results

Incidence of LM

Of the 5387 consecutive lung cancer patients with complete electronic records who were screened, 3775 were tested for their *EGFR* gene status. Overall, 2517 had wild-type *EGFR*, whereas 1258 patients were confirmed as having *EGFR* mutations, including 576 patients who harbored the exon 19 deletion (del 19) and 511 patients who had the exon 21 Leu858Arg mutation (L858R) (Fig. 1). The incidence of LM in all patients was 3.4% (184 of 5387). Among the 184 patients with LM, 160 had known *EGFR* status (4.2% [160 of 3775]). The percentage of patients with LM harboring *EGFR* mutations (9.4% [118 of 1258]) was significantly higher than that of patients with a wild-type *EGFR* status (1.7% [42 of 2517], $\chi^2 = 122.9$, $p < 0.001$). In total, 109 patients with LM harbored common *EGFR* mutations; the incidence of patients with LM harboring del 19 (9.2% [53 of 576]) was similar to that of L858R (11.0% [56 of 511], $\chi^2 = 0.927$, $p = 0.336$).

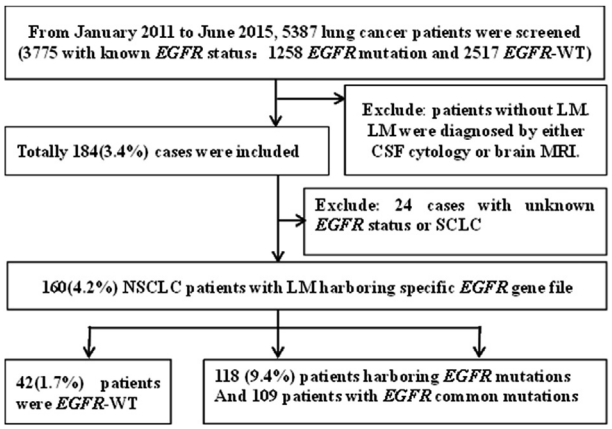

Figure 1. Study flowchart. LM, leptomeningeal metastases; WT, wild type; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

Patient Characteristics

The characteristics of the 160 patients with NSCLC and LM with a known *EGFR* gene status are summarized in Table 1. All patients were Chinese and their median age was 57 years (range 28–78 years). In patients with *EGFR* mutations, LM occurred most frequently in females (62.7%, $p = 0.002$), nonsmokers (73.7%, $p = 0.045$), patients with adenocarcinoma (99.2%, $p < 0.001$), and patients with stage IV lung cancer (89.0%, $p = 0.042$) among those with *EGFR* mutations. All the patients received brain MRI scans and 70 patients underwent a lumbar puncture. LM were diagnosed by brain MRI alone in 110 patients (68.8%) and by both MRI and cytologic tests in 42 patients (26.2%). Interestingly, there were eight patients (5%) in whom carcinoma cells were found in the CSF but with no positive presentation on brain MRI. In total, LM developed as widespread events in 150 patients (93.7%), 116 patients (72.5%) showed neurological symptoms, and both LM and brain metastases were diagnosed in 103 patients, with brain metastases developing before LM in 43 of them. In 59 patients, brain metastases were diagnosed at the same time as LM, and in one patient, brain metastases were diagnosed after LM. Also, 93 patients (58.1%) had a good Eastern Cooperative Oncology Group performance status (ECOG PS) (<2) at diagnosis of LM.

Clinical Presentation and Treatment of Patients with LM Harboring Common EGFR Mutations

LM were diagnosed in 109 patients with common *EGFR* mutations (Table 2). The median time from the diagnosis of metastatic lung cancer to diagnosis of LM was 13.3 months (range 0–81.8 months), whereas the median interval from the first day of previous TKIs to LM

Table 1. Characteristics of the 160 Patients with NSCLC

Factors	Total (N = 160), n (%)	*EGFR* Mutation (n = 118[a]), n (%)	*EGFR* Wild Type (n = 42[b]), n (%)	*p* Value
Median age (range), y	57 (28-78)	58 (32-78)	54 (28-74)	0.928
Sex				
Male	71 (44.4)	44 (37.3)	27 (64.3)	0.002
Female	89 (55.6)	74 (62.7)	15 (35.7)	
Smoking status				
Smoker	49 (30.6)	31 (26.3)	18 (42.9)	0.045
Never-smoker	111 (69.4)	87 (73.7)	24 (57.1)	
Histological type				
Adenocarcinoma	151 (94.4)	117 (99.2)	34 (81.0)	<0.001
Nonadenocarcinoma	9 (5.6)	1 (0.8)	8 (19.0)	
Stage of disease at initial lung cancer diagnosis				
Stage I-III	23 (14.4)	13 (11.0)	10 (23.8)	0.042
Stage IV	137 (85.6)	105 (89.0)	32 (76.2)	
ECOG PS at diagnosis of LM				
<2	93 (58.1)	67 (56.8)	26 (61.9)	0.563
≥2	67 (41.9)	51 (43.2)	16 (38.1)	
LM diagnosed				
By MRI only	110 (68.8)	76 (64.4)	34 (81.0)	0.027
By cytologic test only	8 (5.0)	5 (4.2)	3 (7.1)	
By both MRI and cytologic test	42 (26.2)	37 (31.4)	5 (11.9)	
Type of spread for LM				
Isolated event	10 (6.3)	7 (5.9)	3 (7.1)	0.781
Widespread event	150 (93.7)	111 (94.1)	39 (92.9)	
LM with brain metastases[c]				
Brain metastases before LM	43 (41.7)	35 (47.3)	8 (27.6)	0.06
Concurrent LM and brain metastases	59 (57.3)	38 (51.4)	21 (72.4)	
Brain metastases after LM	1 (1.0)	1 (1.3)	0	
Neurological symptoms	116 (72.5)	89 (75.4)	27 (64.3)	0.165

[a]Of the 118 patients, 109 harbored common *EGFR* mutations (53 patients with del 19 and 56 patients with L858R) and nine harbored uncommon *EGFR* mutations.
[b]A total of 16 patients harbored other driver genes: 10 patients with echinoderm microtubule associated protein like 4 gene (*EML4*)-anaplastic lymphoma receptor tyrosine kinase gene (*ALK*) rearrangement, three patients with mesenchymal-epithelial transition factor (c-MET) overexpression, one patient with both *EML4-ALK* rearrangement and c-MET overexpression, one patient with *ROS1* rearrangement, and one patient with both c-MET overexpression and *ROS1* rearrangement.
[c]Both LM and brain metastases were diagnosed in 103 patients.
ECOG PS, Eastern Cooperative Oncology Group performance status; LM, leptomeningeal metastases; MRI, magnetic resonance imaging.

Table 2. Clinical Presentation and Treatment of Patients with LM Harboring Common *EGFR* Mutations (n = 109)

Factors	n (%)
Time from diagnosis of metastatic lung cancer to development of LM, mo	13.3 (range 0-81.8)
Time from previous *EGFR* TKIs to development of LM, mo	14.2 (range 1.0-43.4)
Treatments before diagnosis of LM	
EGFR TKIs alone	32 (29.4)
Chemotherapy alone	6 (5.5)
Combination therapy[a]	51 (46.8)
No treatments	20 (18.3)
Treatments modalities for LM	
EGFR TKIs alone	49 (45.0)
WBRT alone	6 (5.5)
Chemotherapy alone	1 (0.9)
Combination therapy[b]	42 (38.5)
Best supportive care	11 (10.1)
EGFR-TKIs regimens for LM[c]	
The same administration	32 (50.0)
Switch to another EGFR TKI	26 (40.6)
High-dose EGFR TKI	6 (9.4)

[a]Including three patients who received combinations of TKIs, chemotherapy, and WBRT; 44 patients received TKIs and chemotherapy, two received TKIs and WBRT, and two received both chemotherapy and WBRT.
[b]Including four patients who received combinations of TKIs, chemotherapy, and WBRT; 29 patients received both TKIs and WBRT, six patients received both TKIs and chemotherapy, and three patients received chemotherapy and WBRT.
[c]Of 88 patients, 64 received TKIs both before and after development of LM; 24 patients had not undergone previous TKI therapy, including patients who received chemotherapy before development of LM and those treated with TKIs as first-line therapy for both lung cancer and LM.
LM, leptomeningeal metastases; TKI, tyrosine kinase inhibitor; WBRT, whole brain radiotherapy.

was 14.2 months (range 1.0–43.4 months [*previous TKIs* means that the patients received a TKI at any line of therapy before development of LM]).

Regarding treatment before diagnosis of LM, 32 patients (29.4%) were treated with TKI therapy alone, six (5.5%) received chemotherapy alone, and 51 (46.8%) received combination therapy; among them, seven patients underwent WBRT for brain metastases before LM. TKIs were given as second-line therapy or after adjuvant chemotherapy to patients receiving combination therapy. Therefore, in total, 81 patients were receiving TKI therapy at the time of diagnosis of LM. Regarding treatments for LM, 49 patients(45.0%) received TKI therapy alone, six (5.5%) received WBRT alone, and 42 (38.5%) received combination modalities; overall, 33 patients received both TKI therapy and WBRT. In total, 64 patients received TKIs both before and after development of LM: 50.0% of them continued to receive the same regimen, 40.6% of them switched to another EGFR TKI, and 9.4% changed to high-dose TKI therapy. Regarding the specific TKIs that 88 patients received after development of LM, 36.4% received gefitinib, 40.9% received erlotinib, 17.0% received icotinib, and 5.7% received other drugs (including afatinib and sorafenib).

As for patients with a wild-type *EGFR* status, there were limited treatment options for LM; 16 of them underwent WBRT, seven received second- or third-line chemotherapy, six received TKI therapy, and 13 received best support care.

Survival Analysis

The median OS after diagnosis of LM was 8.7 months (95% CI: 7.3–10.1) in 160 patients (Fig. 2), and OS for patients with *EGFR* mutations was 8.9 months (95% CI: 7.2–10.7), which was slightly longer than that in patients with wild-type *EGFR* (7.3 months, 95% CI: 4.6–10.0, $p = 0.686$) but not significantly different. Prognostic factors and outcomes of the 109 patients harboring common *EGFR* mutations were assessed in this study. The 88 patients who received TKIs for LM demonstrated longer OS than did those not receiving TKIs (10.0 months [95% CI: 8.9–11.1] versus 3.3 months [95% CI: 0.5–6.1], $p < 0.001$) (Fig. 3*A*), and TKIs before LM seemed to influence the efficacy of continuing TKIs: 24 patients not receiving TKIs before development of LM showed longer OS than did those who failed treatment with initial TKIs (12.2 months [95% CI: 9.7–14.8] versus 9.2 months [95% CI: 7.8–10.5], $p = 0.016$). Regarding the role of WBRT, the 42 patients who underwent WBRT for LM did not achieve longer OS than did those not receiving WBRT (9.3 months [95% CI: 8.4–10.3] versus 8.1 months [95% CI: 4.8–11.4], $p = 0.448$). Furthermore, 33 patients treated with both WBRT and TKIs did not show longer survival periods than those who received only TKIs (9.7 months [95% CI: 8.7–10.8] versus 10.1 months [95% CI: 7.1–13.1], $p = 0.778$) (Fig. 3*B*). Chemotherapy seemed to be correlated with prolonged survival (21.0 months [95% CI: 14.8–27.1] versus 8.7 months [95% CI: 6.8–10.6],

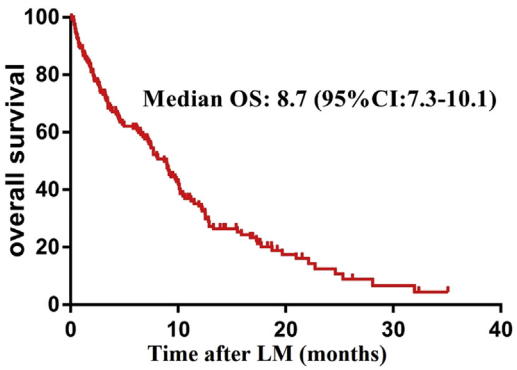

Figure 2. Overall survival after the diagnosis of leptomeningeal metastases (LM) (n = 160). CI, confidence interval; OS, overall survival.

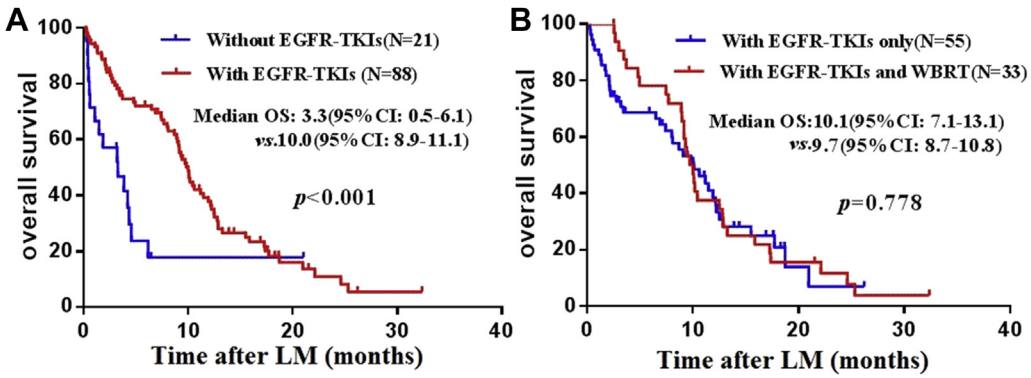

Figure 3. Survival curves for the 109 patients harboring common *EGFR* mutations. (*A*) Efficacy of EGFR tyrosine kinase inhibitors (TKIs) after leptomeningeal metastases (LM); (*B*) Efficacy of the combination of EGFR TKIs and whole brain radiotherapy (WBRT) for LM. OS, overall survival; CI, confidence interval.

$p = 0.001$), but only 14 patients received chemotherapy after development of LM. Patients with different *EGFR* gene mutations (del19 versus L858R) had similar OS times (9.1 months [95% CI: 6.1–12.1] versus 9.2 months [95% CI: 7.4–10.9], $p = 0.63$).

Certain clinical characteristics, tumor-related characteristics, and main treatment options that were thought to be useful in predicting OS were included in a multivariate analysis (Table 3). Poor ECOG PS ($p < 0.001$, hazard ratio [HR] = 3.657, 95% CI: 2.267–5.898) and being female ($p = 0.04$, HR = 1.629, 95% CI: 1.022–2.596) were prognostic factors for poor OS. Factors that were significantly associated with favorable survival were TKIs ($p < 0.001$, HR = 0.218, 95% CI: 0.116–0.411) and chemotherapy ($p < 0.001$, HR = 0.206, 95% CI: 0.092–0.460) after development of LM.

Discussion

To the best of our knowledge, this study of 118 NSCLC with LM harboring *EGFR* mutations represents the largest reported series of its kind to date. The incidence of LM was 3.4% (184 of 5387) in all screened patients with lung cancer, and LM were more frequent in NSCLC with *EGFR* mutations (9.4%) than in those with wild-type *EGFR* (1.7%). Recently, Liao et al.[3] reported 212 patients (3.8%) with LM in NSCLC and 75 patients with *EGFR* mutations; however, treatments and OS were largely analyzed in the whole population; the present study adds more data on LM in patients with *EGFR* mutation.

The mechanisms responsible for the higher frequency of LM in patients with *EGFR* mutations were multifactorial. Longer survival and insufficient penetration of TKIs into the CSF are likely to be the main explanations. With the application of TKIs, OS of metastatic NSCLC with *EGFR* mutations was improved from 19.3 months (EURTAC trial) to 35.5 months (WJTOG3405 trail), whereas the OS of patients with *EGFR* wild type was approximately 1 year.[23–26] Moreover, an increased frequency of CNS metastases had been observed in various tumor types associated with prolonged survival,[9,27] which may provide enough time for malignant cells to overcome the blood brain barrier (BBB) and metastasize to the CNS. Lower concentrations of TKIs in the CSF are

Table 3. Multivariate Analysis of OS (n = 109)

	Univariate		Multivariate	
Variables	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age (<65 vs. ≥65)	0.943 (0.543-1.639)	0.836		
ECOG PS (<2 vs. ≥2)	3.984 (2.417-6.566)	<0.001	3.657 (2.267-5.898)	**<0.001**
Sex (male vs. female)	2.571 (1.226-5.393)	0.012	1.629 (1.022-2.596)	**0.04**
Smoking (nonsmoker vs. smoker)	1.848 (0.856-3.992)	0.118		
Concurrent brain metastases (no vs. yes)	0.679 (0.420-1.096)	0.113		
EGFR mutations (del 19 vs. L858R)	0.769 (0.480-1.232)	0.274		
EGFR TKIs for LM (no vs. yes)	0.217 (0.112-0.420)	<0.001	0.218 (0.116-0.411)	**<0.001**
Combined WBRT (no vs. yes)	0.962 (0.594-1.558)	0.873		
Chemotherapy for LM (no vs. yes)	0.182 (0.078-0.425)	<0.001	0.206 (0.092-0.460)	**<0.001**

Note: Boldface indicates statistical significance.
OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; LM, leptomeningeal metastases; TKI, tyrosine kinase inhibitor; WBRT, whole brain radiotherapy.

another potential explanation.[9,28] The ratio of the CSF to plasma concentration of gefitinib or erlotinib was approximately 1.13 to 2.77%[28,29] on account of incomplete penetration of the BBB. With TKI treatment, sensitive tumor clones harboring driver genes were eradicated whereas resistant tumor cells predominated and metastasized; however, the insufficient TKI levels in CSF failed to kill micrometastases, resulting in a poor prognosis. Continuing lower stimulation with TKIs may also favor resistance, but much lower frequencies of T790M in CSF than in extracranial lesions have been described.[30,31] This discrepancy suggests the existence of other resistance mechanisms. More efforts are needed to better understand the metastatic process in LM with *EGFR* mutations.

The median OS after diagnosis of LM was 8.7 months in all patients in the present study; this was longer than the OS in previous studies, which ranged from 3 to 6 months.[3,7,11,12,14,15] This may be due to the frequent follow-ups and early identification of LM by brain MRI; in addition, the development of targeted therapy also played an important role. Patients with LM harboring different *EGFR* gene mutation status (del19 versus L858R) showed similar median OS and incidences in our larger population, suggesting that the different types of *EGFR* mutations may share similar resistance mechanisms in LM.

There is no doubt that TKIs are the first-line treatments for NSCLC with *EGFR* mutations; nevertheless, there is no consensus for treating LM. Several previous studies have claimed that TKIs could achieve survival benefits in unselected patients[3,7,12,14,15]; however, their roles in patients with *EGFR* mutations were unclear. In the present study, the 88 patients who received TKIs after LM demonstrated significantly longer survival than those who did not (10.0 versus 3.3 months). Moreover, TKI therapy was also a predictor for favorable survival in the multivariate analysis. Liao et al.[3] recently reported that unselected patients who received TKI therapy for LM shown longer OS than those who did not (median 9.5 versus 1.7 months),[3] and these findings were consistent with previous studies.[3,7,12,14,15] These results could be explained by the frequency of *EGFR* mutations in LM, although these studies only provided a small subset of *EGFR* statuses. We also found that TKIs before the diagnosis of LM seemed to influence the efficacy of continuing TKI treatment, as TKI treatment-naive patients receiving TKIs for LM showed longer survival than those who had experienced an initial TKI failure. This may be explained by the theory that a greater effect on activated tumor cells may be seen on the first exposure to TKIs because the acquired resistance clones did not predominate at that time.

High-dose TKIs and switching TKIs were recommended in several small series for LM with *EGFR* mutations after development of resistance to the initial TKIs.[16–21] If the concentration of TKIs in plasma is high enough, it may be more likely to reach a therapeutic concentration in the CSF, which is why high-dose TKIs were suggested.[18,21,32] It has been reported that the concentration of erlotinib penetrating into the CSF was higher than that of gefitinib.[29] A small sample series indicated that erlotinib may offer better control for LM than gefitinib does,[33] and in a case report two patients in whom LM developed during gefitinib therapy were also shown to benefit from erlotinib.[34] After failure of an initial TKI, icotinib, was reported to be effective in improving the ECOG PS score and demonstrated a median OS of 10.1 months in LM with *EGFR* mutations.[16] Moreover, afatinib was suggested for CNS metastases, with a cerebral disease control rate of 66%,[20] and its combination with cetuximab may also create a novel treatment option.[35] Osimertinib, a third-generation EGFR TKI, was designed to overcome T790M resistance mutation[36] and proved to be dramatically effective, with a response rate of 61%[37]; however, its activity against CNS metastases requires more clinical study. A study[38] based on an in vivo imaging model showed that osimertinib could be more efficient for LM after development of resistance to previous TKIs. Another promising agent, AZD3759, which is designed to pass through BBB to treat CNS metastases, showed excellent CNS penetration and resulted in profound regression of brain metastases in a mouse model in a phase 1 clinical trial.[39] Although these treatments demonstrated favorable results, which TKI is the best option remains unclear owing to the small sample sizes and retrospective designs. Overall, TKIs were the optimal strategy for patients with LM and *EGFR* mutations, especially for TKI treatment–naive patients.

Systemic chemotherapy could improve OS in our study, and this was consistent with previous studies performed in unselected populations.[3,7] Patients with LM usually had a poor ECOG PS score, and most of them failed to accept chemotherapy. However, for those with good ECOG PS scores, chemotherapy may be a better choice, especially for those with dramatic progression after development of acquired resistance to TKIs,[40] and it may also provide sufficient intervals for rechallenge with TKIs. The role of systematic chemotherapy in LM patients with *EGFR* mutations requires further confirmation because only a small sample received them in this setting.

Regarding local treatment of LM, the efficacy of WBRT remains controversial.[3,7,14] In this study, WBRT alone did not bring any survival benefit for LM harboring *EGFR* mutations. This result was consistent with a

previous study, which reported that 46 patients who received WBRT did not show improved survival.[14] Nevertheless, some retrospective studies have claimed that WBRT did bring clinical benefits in the whole population.[3,7] In fact, as some patients were likely to suffer a reduced quality of life after application of WBRT, even failing to complete the radiation schedule, clinicians should consider carefully whether they can recommend WBRT for LM on the basis of current evidence. According to clinical modes of TKI failure,[40] for patients with local progression, the optimal treatment was continuation of TKIs combined with local intervention. However, in our study, those receiving a combination of WBRT and TKIs did not survive longer than those receiving TKIs alone. There has been no reported study focusing on the efficacy of WBRT combined with TKIs in LM, but research on brain metastases has shown that escalated doses of WBRT increased the permeability of gefitinib into the CSF,[41] and erlotinib was well tolerated in combination with WBRT and had a favorable objective response rate.[22] The intracranial lesions were relatively stable for brain metastases, whereas carcinoma cells that dropped into CSF could circulate and implant anywhere in the leptomeninges and spinal cord in patients with LM, resulting in a more devastating prognosis; this may be one of the explanations for the smaller benefit of WBRT. There was a limited effect of WBRT in patients with LM, and its combination with TKIs was not an ideal treatment option.

This study had some limitations. The precise roles of treatments for LM need to be validated because we did not use a prospective design. Most of the therapeutic regimens were performed after multidisciplinary discussions, so the results are convincing to some extent. There were some censored cases in our study. Although we failed to record the actual time of death in these patients, most of them had a very poor performance status at the last follow-up and the censored cases were randomly distributed and did not influence the outcomes.

In conclusion, OS after LM was longer than that in previous reports, and LM were much more frequent in patients with NSCLC harboring *EGFR* mutations. EGFR TKIs were the optimal strategy for LM with *EGFR* mutations, especially in TKI treatment–naive patients. Nevertheless, active treatment with WBRT, with or without EGFR TKIs, was not supported by our study.

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