Lung Cancer 127 (2019) 1–5

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Leptomeningeal metastasis after effective first-generation EGFR TKI treatment of advanced non-small cell lung cancer

Ya-Lan Wu[a,b,1], Qian Zhao[a,c,1], Lei Deng[a,1], Yan Zhang[a], Xiao-Juan Zhou[a], Yan-Ying Li[a], Min Yu[a], Lin Zhou[a], Bing-Wen Zou[a], You Lu[a], Yong-Mei Liu[a,*]

[a] Department of Thoracic Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China
[b] Department of Oncology, Chengdu Shang Jin Nan Fu Hospital, West China Hospital, Sichuan University, Chengdu, China
[c] Department of Oncology, The First People Hospital of Zigong, Zigong, China

ARTICLE INFO

Keywords:
Non-small cell lung cancer
Leptomeningeal metastasis
Epidermal growth factor receptor tyrosine kinase inhibitor
Exon 19 deletion
L858R

ABSTRACT

Objective: To evaluate the influence of a first-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) treatment on the clinical features of leptomeningeal metastasis (LM) progression and outcome in advanced non-small cell lung cancer (NSCLC) patients.

Methods: We retrospectively evaluated advanced NSCLC patients receiving effective first-generation EGFR TKI treatment (*e.g.*, treatment > 6 months) at our institution between January 2008 and February 2014. Incidence, time to progression, and treatment outcome of LM were examined.

Results: In our cohort, 29/420 patients (6.9%) developed LM. Among the patients harboring L858R or deletion of exon 19 in *EGFR*, the incidence of LM was 10.7% (21/197) and 3.4% (7/203), respectively (P = 0.006). The median time to LM progression was 16.5 months (95% confidence interval (CI), 11.9–20.8). The median overall survival (OS) after LM diagnosis was 5.2 months (95% CI, 3.2–7.2). In a subgroup analysis, OS was improved in patients with performance status (PS) ≤ 2 *vs*. PS > 2 (14.2 months *vs.* 2.3 months, respectively; P < 0.001). OS was also improved among patients who received, rather than did not receive, anti-tumor treatment (6.0 months *vs.* 1.9 months, respectively; P < 0.001) or whole brain radiotherapy (WBRT) (6.0 months *vs*. 3.9 months, respectively; P = 0.038). Multivariate analysis indicated that WBRT is a good prognostic factor (P = 0.048), whereas best support care (P = 0.033) and PS > 2 (P = 0.034) were poor prognostic factors.

Conclusion: A greater incidence of LM was observed in NSCLC patients harboring *EGFR* mutations after effective EGFR TKI treatment. In particular, the primary mutation, L858R, potentially predicts a higher risk of LM compared with deletion of exon 19. These results highlight the importance of determining mutation status when evaluating the biological behavior of LM in NSCLC patients who positively respond to EGFR TKI treatment.

1. Introduction

Therapeutic advances in non-small cell lung cancer (NSCLC) have led to improvements in patient survival, especially in patients who harbor sensitive mutations in the epidermal growth factor receptor (*EGFR*) gene. Patients with these mutations have exhibited better disease control and prolonged survival when treated with tyrosine kinase inhibitors (TKIs) such as gefitinib [1,2]. However, these improvements in patient survival have been accompanied by an increased incidence of leptomeningeal metastasis (LM) from NSCLC. LM is an adverse condition that contributes to poor survival [3].

LM is a severe complication of malignancies and occurs in approximately 5% of patients with metastatic solid cancers [4]. The relatively low ratio of LM from NSCLC presents limited opportunities to conduct randomized controlled trials. Consequently, data regarding the characteristics and therapeutic options for NSCLC patients with LM have generally derived from retrospective studies or clinical trials with small sample sizes. Moreover, there is no evidence to date to indicate which intervention is preferred among options such as epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs), systemic chemotherapy, whole brain radiotherapy (WBRT), and intrathecal chemotherapy. To identify the best treatment strategy, it is important to understand the factors that affect LM from NSCLC. Considering the prolonged patient survival that has been achieved with EGFR TKIs, we

* Corresponding author at: Department of Thoracic Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China.
E-mail address: lymi75@163.com (Y.-M. Liu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.lungcan.2018.11.022
Received 30 July 2018; Received in revised form 16 November 2018; Accepted 19 November 2018

hypothesize that EGFR TKIs influence the clinical features and treatment outcomes of LM in NSCLC. To test this hypothesis, we conducted this retrospective study. We evaluated a large cohort of patients who underwent treatment for > 6 months with a first-generation EGFR TKI in order to assess the clinical features of LM progression and the outcomes of different treatment regimens. These findings are anticipated to provide valuable insight into the best therapeutic strategies for patients with LM from NSCLC.

2. Patients and methods

2.1. Patients and data collection

Patients with advanced NSCLC who received first- or second-line treatment with a first-generation EGFR TKI for more than six months at our institution (Cancer Center, West China Hospital, Sichuan University, Chengdu, China) between January 2008 and February 2014 were included in this study. Patients were defined as having LM if they had cytological evidence of malignant cells in cerebrospinal fluid (CSF) or had findings from a central nervous system neuroradiographic examination with gadolinium magnetic resonance imaging (MRI) and a clinical examination that were consistent with LM. Typical MRI findings included clear leptomeningeal enhancement in cerebral sulci, cerebellar foliae, the spinal cord, cauda equina, or subependymal lining. In these patients, newly developed LM was defined after response to a TKI with or without pre-existing brain parenchyma lesions. Medical records and imaging data were reviewed to obtain patient characteristics, patterns of care, and patient outcome. This study was approved by the Institutional Review Board of West China Hospital of Sichuan University.

2.2. Statistical analysis

Time to LM was defined from the start of TKI treatment to initial documentation of LM progression. Overall survival (OS) after LM was calculated from the time of LM diagnosis until death or last follow-up. Statistical analyses of categorical variables were performed using Pearson's chi-squared test or Fisher's exact test. A survival analysis was performed according to the Kaplan-Meier method, with the log-rank test applied to compare survival data. P-values less than 0.05 were considered statistically significant. All statistical analyses were performed with SPSS 20.0.

3. Results

3.1. Patient characteristics

A total of 420 patients with advanced NSCLC who received effective TKI treatment as a first- or second-line therapy were included in this study. Among these patients, 29 cases progressed to LM. Clinical characteristics of the entire cohort are summarized in Table 1. All of the patients reported neurological symptoms and signs. The most common symptoms were headache (52%), cranial nerve signs (34%), nausea/vomiting (24%), spinal symptoms (21%), seizure (17%), and ataxia (14%). Five of six patients with pre-existing brain parenchymal metastases received local therapy before, or concomitant with, gefitinib. The treatments administered to treat LM are listed in Table 2.

3.2. Incidence and median time to LM

The total incidence of LM in our cohort was 6.9% (29/420). The 1-, 2-, and 3-year incidence rates were 2.4%, 5.2%, and 6.4%, respectively. We also analyzed the proportion of patients in our cohort who harbored common *EGFR* mutations (7.0%, 28/400). Patients carrying the L858R mutation were more likely to develop LM than those with the deletion of exon 19 (Del19) (P = 0.006). The incidence of LM did not significantly differ among the other factors examined (Table 3).

The median time to LM was 16.5 months (95% confidence interval (CI), 11.9–20.8). Between the first-line TKI group and the second-line TKI group, there was no statistically significant difference in the median time to LM (P = 0.277) [21.0 months (95% CI, 9.1–31.0) *vs.* 15.9

Table 1
Characteristics of patients with leptomeningeal metastases after the treatment of EGFR-TKI.

	Patient number (%)
Gender	
Male	13 (44.8%)
Female	16 (55.2%)
Age (year, range 37-73)	
< 65	21 (72.4%)
≥ 65	8 (27.6%)
Histology	
Adenocarcinoma	28 (96.6%)
Squamous carcinoma	1 (3.4%)
EGFR mutation	
L858R mutations	21 (72.4%)
Exon 19 deletions	7 (24.1%)
Unknown	1 (3.4%)
Type of EGFT TKI	
Gefitinib	27 (93.1%)
Icotinib	2 (6.9%)
Therapy line of EGFR TKI	
First	18 (62.1%)
Second	11 (37.9%)
Treatment effect of EGFR-TKI	
SD	11 (37.9%)
PR	18 (62.1%)
Previous brain metastasis	
Yes	6 (20.7%)
No	23 (79.3%)
CSF examination	
Positive	8 (27.6%)
Negative	7 (24.1%)
Unknown	14 (48.3%)
Time to dissemination	
< 2 years	22 (76%)
≥ 2 years	7 (24%)

EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; SD, stable disease; PR, partial response.

Table 2
Treatments to LM.

Therapy	Patients number (n = 29)
Mono-therapy	
BSC	7
SC	2
WBRT	2
EGFR TKI	6
Multiple-therapy	
EGFR TKI + BSC	1
EGFR TKI + Gamma Knife	1
EGFR TKI + WBRT	6
EGFR TKI + SC	1
SC + WBRT	1
EGFR TKI + SC + WBRT	1
EGFR TKI	
Continue gefitinib	7
Change to erlotinib	10
None	12

BSC, best supportive care; SC, systemic chemotherapy; WBRT, whole brain radiotherapy; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

Table 3
The incidence of LM in patients harbored common (19-del and L858R) EGFR mutations.

Characteristics	Non-LM (n = 372)	LM (n = 28)	P
Age (year)			
< 65	289(78%)	20(71%)	0.446
≥ 65	83(22%)	8(29%)	
Gender			
Male	156(42%)	12(43%)	0.924
Female	216(58%)	16(57%)	
EGFR mutations			
L858R	176(47%)	21(75%)	0.006
19-del	196(53%)	7(25%)	
Previous brain metastasis			0.427
Yes	102(27%)	6(21%)	
No	269(73%)	22(79%)	
EGFR-TKI therapy			
First-line	275(74%)	18(64%)	0.329
Second-line	97(26%)	10(36%)	
Histology			
Adenocarcinoma	342(92%)	27(96%)	0.368
Non-adenocarcinoma	30(8%)	1(4%)	

EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

months (95% CI, 13.2–19.8)]. There was also no difference in the median time to LM between patients carrying the L858R mutation or Del19. Furthermore, the median time to LM did not significantly differ according to patient age, performance status (PS), or based on the presence or absence of previous brain metastasis events.

3.3. Survival and prognosis after LM diagnosis

The median OS after LM diagnosis was 5.2 months (95% CI, 3.2–7.2) (Fig. 1). The patients who received best support care (BSC; which included intravenous administration of mannitol, glycerol fructose, and cortisol) *vs*. anti-tumor treatment had a median OS after LM diagnosis that was significantly shorter (1.9 months *vs*. 6.0 months, respectively; P < 0.001) (Fig. 2a). In contrast, the survival time of the patients who received WBRT was significantly longer than those who did not undergo WBRT (6.0 months *vs*. 3.9 months, respectively; P = 0.038) (Fig. 2b). There was also a significant difference between the patients with PS ≤ 2 and PS > 2 (14.2 months *vs*. 2.3 months, respectively; P < 0.001) (Fig. 2c). For seven (24%) of the latter patients, treatment with gefitinib was continued after their LM diagnosis, while ten (35%) patients received erlotinib after their LM diagnosis. As shown in Fig. 2d, there were no differences in survival between the patients who stopped taking gefitinib and those who did not (5.2 months *vs*. 4.2 months, respectively; P = 0.330). Similarly, the median

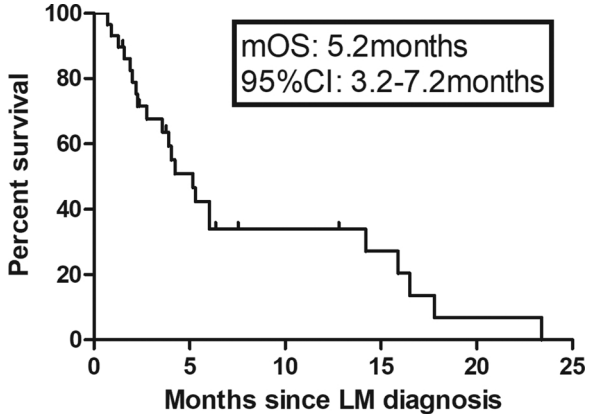

Fig. 1. Overall survival of patients in our cohort from diagnosis of LM to death.

OS after LM did not differ between the patients who continued erlotinib treatment *vs*. those who did not in our subset analysis (5.3 months *vs*. 4.0 months, respectively; P = 0.941). There was also no difference in median OS after LM between the patients with and without preexisting brain metastasis in our subset analysis (5.3 months *vs*. 4.0 months, respectively; P = 0.230).

In our multivariate analysis, BSC treatment alone and PS > 2 were identified as poor prognostic factors for extended treatment after LM, and the corresponding adjusted hazard ratio (HR) values for these factors were 1.9 (95% CI, 1.1–3.4; P = 0.033) and 4.8 (95% CI, 1.1–20.4; P = 0.034), respectively. In contrast, WBRT was identified as a good prognostic factor (P = 0.048) (Table 4).

4. Discussion

To the best of our knowledge, this is the first and largest study to report clinical features of LM in a cohort of advanced NSCLC patients after effective EGFR TKI treatment (*e.g.*, treatment for > 6 months). In previous studies, the patients examined were either diagnosed with LM or NSCLC [5–16]. Furthermore, none of these studies required the patients examined to be treated for > 6 months with a first-generation EGFR TKI.

The incidence of LM among our patients who received effective EGRF TKI treatment was 6.9% (29/420). After excluding patients who did not carry common *EGFR* mutations, the incidence of LM in patients carrying an *EGFR* mutant was 7.0% (28/400). Both of these incidence rates are higher than those previously reported for unselected NSCLC patients (3.4–3.8%) [12,15]. Our data also indicate that the incidence of LM was higher in the patients carrying an *EGFR* mutant after effective EGFR TKI treatment. We hypothesize that this result represents an aspect of prolonged survival due to treatment with an EGFR TKI. The incidence of LM in NSCLC patients carrying an *EGFR* mutant has previously been reported to range from 9.0 to 9.4% [12,16]. This range is higher than the incidence reported in the present study (7.0%). Possible reasons for this inconsistency include the subtype of the *EGFR* mutant being carried, the efficiency of the EGFR TKI treatment, and the types and sequence of treatment administered [12,16].

Interestingly, we found that patients harboring *EGFR* L858R were more likely to experience LM than those harboring Del19 (10.7% *vs*. 3.4%, respectively; P = 0.006). In a previous study in which 5387 consecutive patients with lung cancer were screened at a single institution, the incidence of patients with LM who harbored L858R was 11.0% (56/511, P = 0.336) compared to 9.2% for Del19 (53/576, P = 0.336) [12]. However, 28/109 of those patients harboring L858R or Del19 never received EGFR TKI treatment. Considering that the incidence of LM in unselected NSCLC patients has been reported to range from 3.4 to 3.8% [12,15], the present results appear to indicate that effective first-generation EGFR TKI treatment can increase the incidence of LM in patients harboring a L858R mutation.

When Ke et al. examined a cohort of patients exhibiting acquired resistance to an EGFR TKI, the prevalence of the T790 M mutation was found to be significantly higher in the Del19 subgroup than in the L858R subgroup (50.4% *vs*. 36.5%, respectively; P = 0.043) [17]. The prevalence of the T790 M mutation may also be low in NSCLC patients with LM who are responsive to EGFR TKI treatment because those patients are at a higher risk of harboring the primary mutation, L858R. In a study conducted by Fan et al., eight of eleven patients developed LM during treatment with a first-generation EGFR-TKI [18], and it was not reported if the treatment was effective. When CSF samples from these 11 patients with LM were examined, eight patients were found to carry the *EGFR* L858R mutation. In addition, 1 patient had Del19, 2 patients carried both L858R and Del19, and 1 patient carried the T790 M mutation. However, the T790 M mutation was not detected in any of the CSF samples. Jiang et al. also examined 14 patients with LM who were carrying *EGFR* mutants (9 with L858R, 5 with Del19) [19]. All of these patients were also treated with a first-generation EGFR TKI, and it was

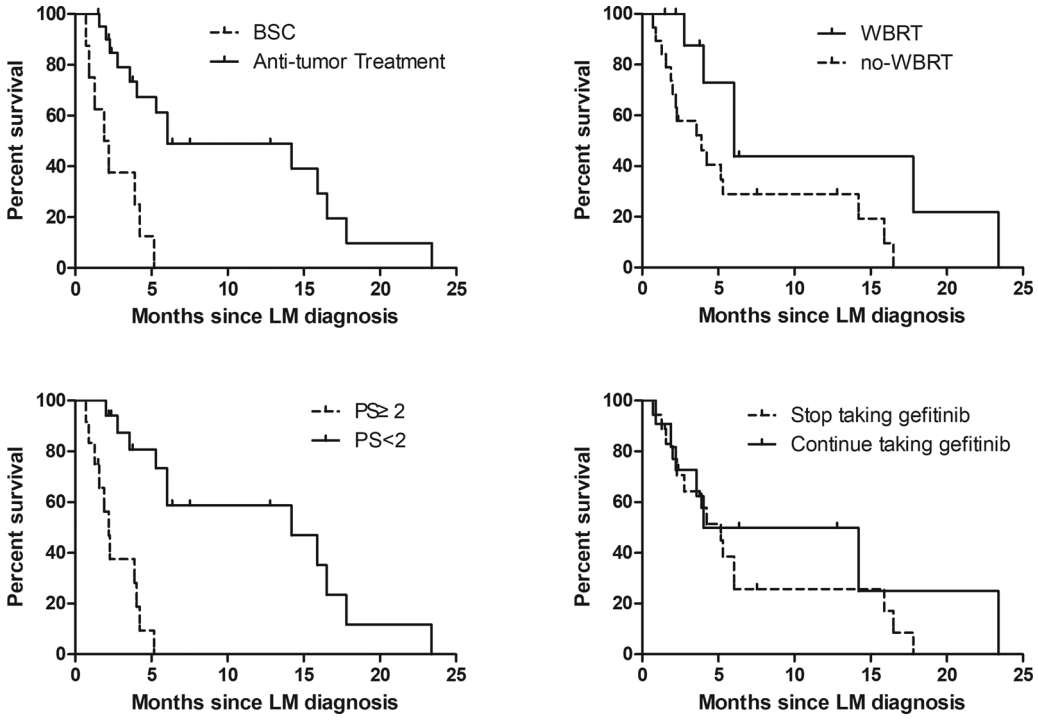

Fig. 2. Comparison of Kaplan-Meier survival curves after LM diagnosis. The patient subgroups compared include BSC and anti-tumor treatment groups (a), groups with and without WBRT (b), groups with PS ≤ 2 *vs*. PS > 2 (c), and groups with gefitinib treatment continued or discontinued (d).

Table 4
The prognosis factors of LM.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
L858R(+)	1.1 (0.3-4.2)	0.842		
≥65 years old	1.3 (0.5-3.4)	0.543		
BSC	2.7 (1.5-4.6)	0.001	1.9 (1.1-3.4)	0.033
WBRT	0.6 (0.3-0.9)	0.048		
Pre-existing BM	3.7 (1.4-11.0)	0.003	1.6 (0.4-5.8)	0.467
Stop EGFR-TKI	1.5 (0.6-4.1)	0.337	2.0 (0.7-6.0)	0.211
PS > 2	6.2 (2.1-18.5)	0.001	4.8 (1.1-20.4)	0.034

BSC, best supportive care; WBRT, whole brain radiotherapy; BM, brain metastasis; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; PS, performance status; HR: hazard ratio, CI: confidence interval.

not indicated if the treatment was effective. Furthermore, T790 M was only detected in one patient with Del19 (1/14, 7.1%). More recently, Li et al. reported the results of CSF liquid biopsies that were performed for 26 patients with LM [20]. Eighteen of these patients (4 with L858R, 14 with Del19) received first-generation EGFR TKI treatment and progressed to LM during their treatment. These authors also did not report if the treatment was effective. However, five of these 18 patients (27.8%) had T790 M detected in their CSF samples. Since these studies only included patients diagnosed with LM [18–20], they do not represent populations of NSCLC patients with LM. Despite this difference, their data still suggest an increased prevalence of T790 M in association with Del19. Moreover, this tendency supports our hypothesis that the prevalence of detecting T790 M in the CSF of LM patients harboring L858R after effective EGFR TKI treatment is low. However, it remains for the latter hypothesis to be tested in future studies.

All of the data discussed above are consistent with the possibility that the biological behavior of LM may differ compared with progression at other sites, especially in patients who receive effective EGFR TKI treatment. It remains unclear which factors may contribute to these differences, and therefore, additional studies are needed. To identify specific factors that mediate an association between LM and effective EGFR TKI treatment, a better understanding of the mechanism involved, as well as precision medicine in this specific population, are needed.

The median time to LM reported for the current cohort is longer than the median times reported by other groups (16.5 months *vs*. 13.3–13.6 months, respectively) [12,16]. It is possible that the administration of an EGFR TKI prior to the development of LM in the present study may have contributed to the prolonged time to LM. However, the median OS still varies between the present study and other studies, thereby suggesting that many factors affect OS. Our present results reveal that PS is an important prognostic factor, and this is consistent with the results of other studies [5–16]. Our results also reveal that WBRT can prolong OS, whereas EGFR TKI and systemic chemotherapy do not. However, the sample size of our LM cohort was small. In our previously published pooled analysis, intrathecal chemotherapy was identified as an effective treatment option for NSCLC patients with LM [13]. Thus, a standardized treatment regimen remains to be established for NSCLC with LM. The potential for regimens to be tailored according to the genetic profiles of patients also remains to be confirmed [21]. Cheng et al. recently proposed specific diagnostic and treatment guidelines for the management of LM in NSCLC patients carrying *EGFR* mutations or rearrangements of ALK [21]. According to these guidelines, performing a CSF liquid biopsy is not required. Moreover, they recommend that in the absence of a T790 M mutation, or when mutation status cannot be confirmed, a high concentration of osimertinib, a high dose of erlotinib, or an administration of newer generation TKIs with high penetration in CSF should be considered for patients harboring primary sensitive *EGFR* mutations (*e.g.*, L858R or Del19). However, the present results suggest that the biological behavior of LM may differ compared with progression at other sites. Furthermore, it is possible that specific mutations other than primary sensitive mutations may affect the biological features of LM and influence the effectiveness of targeted therapies. Therefore, we consider CSF liquid biopsy to be a necessary step before administering a targeted or non-targeted therapy. The information obtained may provide insight

into the biological features of LM patients and could also influence treatment decisions.

Two of our 29 LM patients received an EGFR TKI as well as systemic chemotherapy (one patient continued with gefitinib, while the other patient switched to erlotinib). Based on the results of a randomized, phase 3 multicenter IMPRESS study [22,23], physicians have been warned against continuing treatment with first-generation EGFR TKIs beyond radiologic disease progression when chemotherapy is initiated. In fact, the detriment was statistically significant in patients with T790 M mutation-positive plasma samples (HR, 1.49; 95% CI, 1.02–2.21). In contrast, statistical significance was not reached for T790 M mutation-negative patients (HR, 1.15; 95% CI, 0.68–1.94) [23]. Since these results were published after the period during which our patients were treated, we did not know which therapy program was preferable. However, based on the present results and those of other studies, we still consider that CSF liquid biopsy should be performed before treatment decisions are made. Furthermore, while the IMPRESS study confirmed the influence of an acquired T790 M mutation on the administration of a first-generation EGFR TKI for unselected disease progression in NSCLC patients, we would advocate that a small molecule-based therapy could be identified based on the results of a CSF liquid biopsy. Moreover, the latter would be a more precise and preferred treatment approach compared with systemic chemotherapy in LM patients. However, this recommendation remains to be confirmed in a clinical trial.

In conclusion, we observed an increased incidence of LM in NSCLC patients carrying a mutation in *EGFR* after they underwent effective EGFR TKI treatment. Interestingly, patients harboring a L858R mutation in *EGFR* were more likely to develop LM than patients with deletions of *EGFR* exon 19. These data indicate that LM may exhibit different biological behaviors compared with metastasis progression at other sites, especially in patients undergoing effective EGFR TKI treatment. However, additional studies are needed to confirm these phenomena, to identify relevant mechanisms, and to identify the best treatment strategies for specific patient populations. Currently, CSF liquid biopsy represents a valuable tool for investigating possible disease mechanisms and for providing guidance regarding treatment decisions. However, a more efficient and feasible protocol for performing CSF liquid biopsies is also needed.

Conflict of interest

The authors have no potential conflicts of interest to report.

Acknowledgements

This study was supported by the Projects of Health and Family Planning Commission of Sichuan Province, China (No. 16ZD005).

References

[1] A. Inoue, K. Kobayashi, K. Usui, M. Maemondo, S. Okinaga, I. Mikami, M. Ando, K. Yamazaki, Y. Saijo, A. Gemma, H. Miyazawa, T. Tanaka, K. Ikebuchi, T. Nukiwa, S. Morita, K. Hagiwara, G. North East Japan gefitinib study, first-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy, J. Clin. Oncol. 27 (9) (2009) 1394–1400.

[2] T.S. Mok, Y.L. Wu, S. Thongprasert, C.H. Yang, D.T. Chu, N. Saijo, P. Sunpaweravong, B. Han, B. Margono, Y. Ichinose, Y. Nishiwaki, Y. Ohe, J.J. Yang, B. Chewaskulyong, H. Jiang, E.L. Duffield, C.L. Watkins, A.A. Armour, M. Fukuoka, Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma, N. Engl. J. Med. 361 (10) (2009) 947–957.

[3] A.M. Omuro, M.G. Kris, V.A. Miller, E. Franceschi, N. Shah, D.T. Milton, L.E. Abrey, High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib, Cancer 103 (11) (2005) 2344–2348.

[4] S.A. Grossman, M.J. Krabak, Leptomeningeal carcinomatosis, Cancer Treat. Rev. 25 (2) (1999) 103–119.

[5] S.J. Lee, J.I. Lee, D.H. Nam, Y.C. Ahn, J.H. Han, J.M. Sun, J.S. Ahn, K. Park, M.J. Ahn, Leptomeningeal carcinomatosis in non-small-cell lung cancer patients: impact on survival and correlated prognostic factors, J Thorac Oncol 8 (2) (2013) 185–191.

[6] J.W. Riess, S. Nagpal, M. Iv, M. Zeineh, M.A. Gubens, K. Ramchandran, J.W. Neal, H.A. Wakelee, Prolonged survival of patients with non-small-cell lung cancer with leptomeningeal carcinomatosis in the modern treatment era, Clin Lung Cancer 15 (3) (2014) 202–206.

[7] J.H. Park, Y.J. Kim, J.O. Lee, K.W. Lee, J.H. Kim, S.M. Bang, J.H. Chung, J.S. Kim, J.S. Lee, Clinical outcomes of leptomeningeal metastasis in patients with non-small cell lung cancer in the modern chemotherapy era, Lung Cancer 76 (3) (2012) 387–392.

[8] P.G. Morris, A.S. Reiner, O.R. Szenberg, J.L. Clarke, K.S. Panageas, H.R. Perez, M.G. Kris, T.A. Chan, L.M. DeAngelis, A.M. Omuro, Leptomeningeal metastasis from non-small cell lung cancer: survival and the impact of whole brain radiotherapy, J Thorac Oncol 7 (2) (2012) 382–385.

[9] Y. Nakamura, T. Takahashi, A. Tsuya, T. Naito, H. Kenmotsu, A. Ono, T. Shukuya, H. Murakami, H. Harada, R. Watanabe, M. Endo, K. Mitsuya, T. Nakajima, N. Yamamoto, Prognostic factors and clinical outcome of patients with lung adenocarcinoma with carcinomatous meningitis, Anticancer Res. 32 (5) (2012) 1811–1816.

[10] S. Umemura, K. Tsubouchi, H. Yoshioka, K. Hotta, N. Takigawa, K. Fujiwara, N. Horita, Y. Segawa, N. Hamada, I. Takata, H. Yamane, H. Kamei, K. Kiura, M. Tanimoto, Clinical outcome in patients with leptomeningeal metastasis from non-small cell lung cancer: Okayama lung cancer study group, Lung Cancer 77 (1) (2012) 134–139.

[11] Q. Xu, X. Chen, D. Qian, Y. Wang, S. Meng, H. Liu, C. Zhou, Treatment and prognostic analysis of patients with leptomeningeal metastases from non-small cell lung cancer, Thorac Cancer 6 (4) (2015) 407–412.

[12] Y.S. Li, B.Y. Jiang, J.J. Yang, H.Y. Tu, Q. Zhou, W.B. Guo, H.H. Yan, Y.L. Wu, Leptomeningeal metastases in patients with NSCLC with EGFR mutations, J Thorac Oncol 11 (11) (2016) 1962–1969.

[13] Y.L. Wu, L. Zhou, Y. Lu, Intrathecal chemotherapy as a treatment for leptomeningeal metastasis of non-small cell lung cancer: a pooled analysis, Oncol Lett 12 (2) (2016) 1301–1314.

[14] Y. Lee, J.Y. Han, H.T. Kim, T. Yun, G.K. Lee, H.Y. Kim, J.S. Lee, Impact of EGFR tyrosine kinase inhibitors versus chemotherapy on the development of leptomeningeal metastasis in never smokers with advanced adenocarcinoma of the lung, J. Neurooncol. 115 (1) (2013) 95–101.

[15] J. Remon, E. Le Rhun, B. Besse, Leptomeningeal carcinomatosis in non-small cell lung cancer patients: a continuing challenge in the personalized treatment era, Cancer Treat. Rev. 53 (2017) 128–137.

[16] J.L. Kuiper, L.E. Hendriks, A.J. van der Wekken, A.J. de Langen, I. Bahce, E. Thunnissen, D.A. Heideman, Y. Berk, E.J. Buijs, E.J. Speel, F.H. Krouwels, H.J. Smit, H.J. Groen, A.M. Dingemans, E.F. Smit, Treatment and survival of patients with EGFR-mutated non-small cell lung cancer and leptomeningeal metastasis: a retrospective cohort analysis, Lung Cancer 89 (3) (2015) 255–261.

[17] E.E. Ke, Q. Zhou, Q.Y. Zhang, J. Su, Z.H. Chen, X.C. Zhang, C.R. Xu, J.J. Yang, H.Y. Tu, H.H. Yan, Y.C. Zhang, F.Y. Niu, Y.L. Wu, A Higher proportion of the EGFR T790M mutation May contribute to the better survival of patients with exon 19 deletions compared with those with L858R, J Thorac Oncol 12 (9) (2017) 1368–1375.

[18] Y. Fan, M. Hu, X.H. Zhu, M.Z. Wang, Y.J. Xu, X.S. Lv, H.Y. Hu, J.Y. Ding, Y. Ye, L. Fang, Z.Y. Huang, L.L. Miao, L. Gong, W.M. Mao, H.Y. Lu, Exploration of the underlying mechanisms of leptomeningeal metastasis in NSCLC patients through NGS of cerebrospinal fluid, J Thorac Oncol 12 (1, supplement) (2017) S271.

[19] B.Y. Jiang, Y.S. Li, W.B. Guo, X.C. Zhang, Z.H. Chen, J. Su, W.Z. Zhong, X.N. Yang, J.J. Yang, Y. Shao, B. Huang, Y.H. Liu, Q. Zhou, H.Y. Tu, H.J. Chen, Z. Wang, C.R. Xu, B.C. Wang, S.Y. Wu, C.Y. Gao, X. Zhang, Y.L. Wu, Detection of driver and resistance mutations in leptomeningeal metastases of NSCLC by next-generation sequencing of cerebrospinal fluid circulating tumor cells, Clin. Cancer Res. 23 (18) (2017) 5480–5488.

[20] Y.S. Li, B.Y. Jiang, J.J. Yang, X.C. Zhang, Z. Zhang, J.Y. Ye, W.Z. Zhong, H.Y. Tu, H.J. Chen, Z. Wang, C.R. Xu, B.C. Wang, H.J. Du, S. Chuai, H. Han-Zhang, J. Su, Q. Zhou, X.N. Yang, W.B. Guo, H.H. Yan, Y.H. Liu, L.X. Yan, B. Huang, M.M. Zheng, Y.L. Wu, Unique genetic profiles from cerebrospinal fluid cell-free DNA in leptomeningeal metastases of EGFR-mutant non-small-cell lung cancer: a new medium of liquid biopsy, Ann. Oncol. 29 (4) (2018) 945–952.

[21] H. Cheng, R. Perez-Soler, Leptomeningeal metastases in non-small-cell lung cancer, Lancet Oncol. 19 (1) (2018) e43–e55.

[22] J.C. Soria, Y.L. Wu, K. Nakagawa, S.W. Kim, J.J. Yang, M.J. Ahn, J. Wang, J.C. Yang, Y. Lu, S. Atagi, S. Ponce, D.H. Lee, Y. Liu, K. Yoh, J.Y. Zhou, X. Shi, A. Webster, H. Jiang, T.S. Mok, Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial, Lancet Oncol. 16 (8) (2015) 990–998.

[23] T.S.K. Mok, S.W. Kim, Y.L. Wu, K. Nakagawa, J.J. Yang, M.J. Ahn, J. Wang, J.C. Yang, Y. Lu, S. Atagi, S. Ponce, X. Shi, Y. Rukazenkov, V. Haddad, K.S. Thress, J.C. Soria, gefitinib plus chemotherapy versus chemotherapy in epidermal growth factor receptor mutation-positive non-small-cell lung cancer resistant to first-line gefitinib (IMPRESS): overall survival and biomarker analyses, J. Clin. Oncol. 35 (36) (2017) 4027–4034.