J Med Sci 2018;38(6):247-251
DOI: 10.4103/jmedsci.jmedsci_41_18

ORIGINAL ARTICLE

The Clinical Outcome of Brain Metastases in Nonsmall Cell Lung Cancer Patients with Epidermal Growth Factor Receptor Mutation- A Retrospective Single-Institution Analysis

Cho-Hao Lee[1], Tzu-Chuan Huang[1], Yung-Chih Wang[2,3], Yi-Ying Wu[1], Ching-Liang Ho[1], Jia-Hong Chen[1,4]

[1]Department of Medicine, Division of Hematology-Oncology, National Defense Medical Center, Tri-Service General Hospital, [4]Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, [2]Department of Internal Medicine, Division of Infectious Diseases and Tropical Medicine, National Defense Medical Center, Tri-Service General Hospital, [3]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan

Introduction: Nonsmall cell lung cancer (NSCLC) is the leading cause of cancer-related deaths in many countries. Brain metastases (BM) from NSCLC are poor prognosis, with a median survival of 6 months following whole-brain radiotherapy. NSCLC patients harboring activating epidermal growth factor receptor (EGFR) mutations have generally responded to afatinib with good objective response rate, progression-free survival (PFS), and overall survival (OS), and platinum-double chemotherapy. These findings demonstrate the potential effectiveness of afatinib for the treatment of EGFR-positive with BM. The aim of this retrospective study is to present data on the prognostic effect of afatinib versus gefitinib in an unselected population with newly diagnosed NSCLC with BM collected. **Patients and Methods:** Data were obtained from our electronic database from 48 patients with newly diagnosed EGFR mutative NSCLC with BM and treated from January 2007 to December 2017, in which data on EGFR mutation was all available at the time of diagnosis. **Results:** Thirteen of forty-eight were treated with afatinib, and the other was treated with gefitinib. There were seven Exon 19 deletion and six were Exon 21 mutation ([p.Leu858Arg, (c.2573T>G)]:4; [p.Leu861Gln, (c.2582T>A)]:2). There was 18 Exon 19 deletion, and 16 were Exon 21 mutation ([p.Leu858Arg, (c.2573T>G)]:16) and the other one was Exon 18 mutation [p.Gly719Ser (c.2155G>A)]. There was no significant difference between two groups included PFS (afatinib: 12.0 months vs. gefitinib: 10.1 months, $P = 0.766$) and OS (afatinib: 20.6 months vs. gefitinib: 14.5 months, $P = 0.362$). **Conclusion:** From the K–M survival curve evaluation, neither the PFS nor OS have the statistical significance between gefitinib and afatinib. We provided a real-world data to compare the efficacy of EGFR-TKI in NSCLC. Due to relative small sample size, we urged large clinical trial to provide more precise results.

Key words: Brain metastases, nonsmall cell lung cancer, epidermal growth factor receptor mutation

INTRODUCTION

Lung cancer is the leading cause of cancer death and the second most common cancer among both men and women in Taiwan as well as in the United States. Nonsmall cell lung cancer (NSCLC) is the leading cause of cancer-related deaths in many countries.[1] Brain metastases (BM) from NSCLC are poor prognosis, with a median survival of 6 months following whole-brain radiotherapy (RT).[2] NSCLC patients harboring activating epidermal growth factor receptor (EGFR) mutations have generally responded to afatinib with good objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and platinum-double chemotherapy. A recent analysis of 81 patients with BM from LUX-Lung 3 and 6 revealed a median PFS of 8.2 or 5.4 months.[3] These findings demonstrate the potential effectiveness of Giotrif

Received: April 09, 2018; Revised: June 25, 2018; Accepted: July 30, 2018
Corresponding Author: Dr. Jia-Hong Chen, Department of Medicine, Division of Hematology-Oncology, National Defense Medical Center, Tri-Service General Hospital, No 325, Section 2, Cheng-Kung Road, Neihu 114, Taipei, Taiwan. Tel: 886-2-87927213; Fax: 886-2-87927134. E-mail: ndmc_tw.tw@yahoo.com.tw

How to cite this article: Lee CH, Huang TC, Wang YC, Wu YY, Ho CL, Chen JH. The clinical outcome of brain metastases in nonsmall cell lung cancer patients with epidermal growth factor receptor mutation- A retrospective single-institution analysis. J Med Sci 2018;38:247-51.

for the treatment of EGFR-positive with BM. However, the central nervous system (CNS) is a common site of recurrence, probably owing to the low penetration of agents into the CNS.[4] Cerebrospinal fluid (CSF) concentration of gefitinib was poor, with a CSF penetration rate of 1.2%. CSF concentration of erlotinib is better than gefitinib, with penetration rate of erlotinib was 2.7%–4.4%.[5] Afatinib penetrates blood–brain barrier in NSCLC BM mice and contributes to the brain tumor response. The results support for the potential application of Giotrif in NSCLC patients with BM.[6] The median CSF penetration rate (1.7%) of afatinib in this study by Akihiro Tamiya was higher than that reported previously (0.7%).[7,8] The aim of this retrospective study is to present data on the prognostic effect of afatinib versus gefitinib in an unselected population with newly diagnosed NSCLC with BM collected.

PATIENTS AND METHODS

Study population and diagnosis of cancer

Inclusion criteria include that we searched the electronic database of our hospital for patients with newly diagnosed EGFR mutative NSCLC with BM and treated from January 2007 to December 2017. The study comprised a retrospective cohort of patients and was approved by the Institutional Review Board (IRB) of Tri-Service General Hospital. NSCLC was confirmed by clinical, radiological, and pathological features in all cases. The stage procedure included a comprehensive laboratory panel, bronchoscopy, the chest and abdominal computed tomography (CT), magnetic resonance imaging (MRI), or CT of the brain and bone scan. Patient characteristics and laboratory data were collected at initial diagnosis including demographic features (gender and age), accompanying medical history (hypertension and diabetes), smoking history, serum laboratory data, and survival time. The demographic features, medical, and smoking histories were evaluated by review of the medical records. The OS was defined as the time from the date of diagnosis to the date of death. The duration of PFS was defined as the time interval between the day of diagnosis and the day of locoregional recurrence or distant metastasis. Disease progressions are diagnosed by computed tomography or MRI. Death was also taken as disease progression. However, exclusion criteria contained the EGFR mutative NSCLC patients with recurrent BM later and the NSCLC patients using target therapy in the past.

This study was performed under the guidelines of the Helsinki Declaration and approved by the IRB of Tri-Service General Hospital.

Treatment of cancer

First-line therapy was performed with tyrosine kinase inhibitors (TKI) agent for all enrolled patients.[3,5-7] Afatinib was dosed at 40 mg per day, and gefitinib was dosed at 100 mg per day. The cranial irradiation was also administered with 30 Gy divided into 10 fractions.[9,10]

Measurement of covariates and statistical assessment

The differences in study variables between treatment with afatinib and gefitinib were tested using Chi-square test where appropriate. For compared with survival status in treatment with afatinib and gefitinib, Kaplan–Meier curve, and log-rank test were used to test their difference. We considered a $P < 0.05$ as statistically significant for all analyses. The survival time was defined as the time from the time of diagnosis to the date of death. Statistical analyses were carried out with R 3.0.1 software (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/) and "survival" package.

RESULTS

Forty-eight patients with newly diagnosed EGFR mutative NSCLC with BM were identified. The results of EGRF mutation data were available in all patients. Thirteen of forty-eight were treated with afatinib, and the other was treated with gefitinib. There were seven Exon 19 deletion and six were Exon 21 mutation ([p.Leu858Arg, (c.2573T>G)]:4; [p.Leu861Gln, (c.2582T>A)]:2) in the afatinib group. There was 18 Exon 19 deletion, and 16 were Exon 21 mutation ([p.Leu858Arg, (c.2573T>G)]:16) and the other one was Exon 18 mutation [p.Gly719Ser (c.2155G>A)] in the gefitinib group. The difference of EGFR between treatment with afatinib and gefitinib was not statistically significant [$P = 0.815$, Table 1].

The median age of the patient with afatinib was 65.38 years, and the male-to-female ratio was 0.625; median age of the patient with gefitinib was 63.89 years, and the male-to-female ratio was 0.75. Patient characteristics and data are shown in Table 1. Distribution of age and gender did not differ significantly in the two study groups; however, the distribution of the tumor location differ statistically significant in the two study groups ($P = 0.029$).

The prognosis of treatment with afatinib was compared with that of gefitinib. The Kaplan–Meier curves and results of the log-rank tests are shown in Figure 1a and b, and the difference of PFS between treatment with afatinib and gefitinib was not statistically significant (12.0 vs. 10.1 months, P of log-rank test = 0.766); the difference of OS between treatment with afatinib and gefitinib was not

Table 1: Patient characteristics and data collected at initial diagnosis

Variable	Gefitinib (%)	Giotrif (%)	*P*
Gender			
Female	20 (57.1)	8 (61.5)	0.784
Male	15 (42.9)	5 (38.5)	
Age	63.89±13.34	65.38±8.52	0.416
ECOG			
0	10 (28.6)	2 (15.4)	0.519
1	14 (40.0)	8 (61.5)	
2	5 (14.3)	3 (23.1)	
3	3 (8.6)	0 (0.0)	
4	3 (8.6)	0 (0.0)	
Location			
LLL	10 (28.6)	0 (0.0)	0.029*
LUL	6 (17.1)	7 (53.8)	
RLL	7 (20.0)	2 (15.4)	
RUL	12 (34.3)	4 (30.8)	
EGFR			
Exon 18 mutation	1 (2.9)	0 (0.0)	0.815
Exon 19 mutation	18 (51.4)	8 (61.5)	
Exon 21 mutation	16 (45.7)	5 (38.5)	
Clinical T stage			
12	12 (34.3)	2 (15.4)	0.292
34	23 (65.7)	11 (84.6)	
Clinical N stage			
12	24 (68.6)	7 (53.8)	0.498
3	11 (31.4)	6 (46.2)	
Pathological grade			
Well	3 (8.6)	2 (15.4)	0.559
Intermediate	22 (62.9)	6 (46.2)	
Poor	10 (28.6)	5 (38.5)	
Numbers of brain tumors			
Single	20 (57.1)	7 (53.8)	0.838
Multiple	15 (42.9)	6 (46.2)	
Symptomatic			
Yes	16 (45.7)	7 (53.8)	0.666
No	19 (54.3)	6 (46.2)	
Radiotherapy			
No	6 (17.1)	4 (30.8)	0.666
Stereotactic radiosurgery	3 (8.6)	1 (7.7)	
Whole brain radiotherapy	26 (74.3)	8 (61.5)	

LUL=Left upper lung; LLL=Left lower lung; RUL=Right upper lung; RLL=Right lower lung; ECOG=Eastern Cooperative Oncology Group; EGFR=Epidermal growth factor receptor

statistically significant (20.6 vs. 14.5 months, *P* of log-rank test = 0.362).

DISCUSSION

Lung cancer is the leading cause of cancer mortality worldwide and is representing 18.2% of total deaths from cancer.[11] Among those, nearly 7.4% of NSCLC patients will have BM at appearance,[9] and 25%–30% will develop BM during their disease. Life expectancy for these patients is poor, with a median survival of only 3.4 months. Besides, numerous will suffer considerable loss of autonomy due to neurocognitive and functional deficits, as well as morbidity.[10,12]

The use of drugs targeting the proteins of mutated EGFR has become standard of care in the systemic treatment of metastatic NSCLC.[13] In addition, large international Phase III trials comparing EGFR TKI against platinum-doublet chemotherapy have achieved significant PFS benefits of >4 months with hazard ratios (HRs) ranging from 0.37 to 0.58 and improvements to symptoms and quality of life.[14-17]

In first-line clinical trials of the EGFR-targeted drugs gefitinib, erlotinib, and afatinib, ORR of 55%–83% were observed, mostly clustering above 70%.[18] Our study has shown a trend that the PFS (12.0 vs. 10.1 months) and OS (20.6 vs. 14.5 months) effects of the first line of afatinib may be better than gefitinib in EGFR mutative NSCLC with BM. However, the sample size was small, and there was no significant difference between the two groups. The present study showed that there was no statistical difference in the median PFS (11.3 vs. 10.8 months, $P = 0.2030$) and OS (13.8 vs. 13.5 months, $P = 0.3185$) between the gefitinib and the erlotinib groups.[19]

Since there are more effective molecular-targeted agents in the treatment for some subsets of NSCLC compared to the conventional therapy, increasing attention has been paid to the potential role of EGFR-TKI in BM from NSCLC in recent years. Nonetheless, BM was usually considered as exclusion criteria in most previous clinical studies involving EGFR-TKI and accounts of its use in intracranial lesions are available only in a few case reports or some small studies with limited number of patients. Therefore, the role of EGFR-TKI in this setting remains unclear. The purpose of this retrospective study was to further explore the antitumor efficacy of EGFR-TKI therapy against BM from NSCLC harboring EGFR mutation.

The median PFS was 12.0 months in afatinib or 10.1 months in gefitinib in the present study was better than others (the median PFS of 11.1 months in afatinib or 5.4 months in chemotherapy form LUX-Lung 3 and the median PFS of

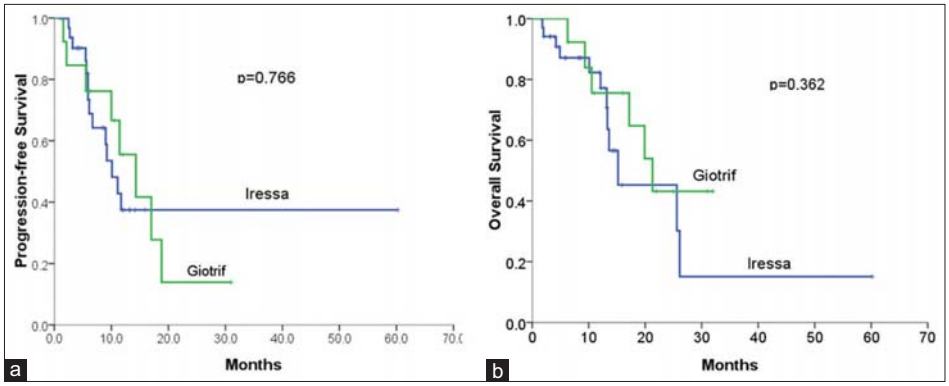

Figure 1: Kaplan-Meier survival plot of Giotrif and Iressa (a) progression free survival (b) overall survival

8.2 months in afatinib or 4.7 months in chemotherapy form LUX-Lung 6 LUX-Lung 6). However, the prognostic factors have been identified, which can be patient or disease related; the patient-related factors include age and performance status (ECOG, neurological findings, estimated prognosis, comorbidities, and patient preferences) and disease-related factors include primary tumor type, and chemosensitivity, systemic disease burden, and single versus multiple BM.

New outcome again demonstrated the advantage of frontline osimertinib in patients with EGFR-positive advanced NSCLC and CNS metastases at baseline, according to data presented at the 2017 ESMO Asia Congress. The subgroup analysis from the Phase III FLAURA trial included 128 patients with at least one measurable and/or nonmeasurable CNS lesion at baseline. Among 61 patients who received osimertinib, the CNS ORR was 66%, compared to 43% (odds ratio, 2.5; 95% CI 1.2–5.2; $P = 0.011$) in 67 patients who received standard EGFR TKI therapy with erlotinib or gefitinib. Osimertinib reduced the risk of CNS disease progression or death by 52% (HR, 0.48; 95% CI, 0.26–0.86; nominal $P = 0.014$). The rate of disease progression resulting from the development of new CNS lesions was also lower with osimertinib, at 12% versus 30%. In October 2017, the FDA awarded a breakthrough therapy designation to osimertinib for the first-line treatment of patients with metastatic EGFR mutation-positive NSCLC. The drug is approved as a treatment for patients with metastatic EGFR *T790M* mutation-positive NSCLC following prior treatment with an EGFR TKI. Thus, our study did not include the treatment of osimertinib.[20,21]

However, there were still some limitations inherent in our study. First, due to the retrospective study, design and small sample size, heterogeneity of patients, and the prognostic effect of TKI agents in EGFR mutative NSCLC patients with BM need to be confirmed by large, prospective cohort studies. Second, there were few patients who received afatinib for fewer months in our analysis. The duration of follow-up was too short to evaluate the survival benefit of treatment. Third, a disease progression of BM in NSCLC was noted after TKI, and rebiopsy form CNS tissue was difficult in our study.

CONCLUSION

Our results quantify the relationships more precisely than previously. From the K–M survival curve evaluation, neither the PFS nor OS have the statistical significance between gefitinib and afatinib. We provided a real-world data to compare the efficacy of EGFR-TKI in NSCLC. Due to relative small sample size, we urged large clinical trial to provide more precise results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A, *et al.* Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Gaspar LE, Mehta MP, Patchell RA, Burri SH, Robinson PD, Morris RE, *et al.* The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:17-32.
3. Schuler M, Wu YL, Hirsh V, O'Byrne K, Yamamoto N, Mok T, *et al.* First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. J Thorac Oncol 2016;11:380-90.

4. Lee YJ, Choi HJ, Kim SK, Chang J, Moon JW, Park IK, *et al.* Frequent central nervous system failure after clinical benefit with epidermal growth factor receptor tyrosine kinase inhibitors in korean patients with nonsmall-cell lung cancer. Cancer 2010;116:1336-43.
5. Togashi Y, Masago K, Masuda S, Mizuno T, Fukudo M, Ikemi Y, *et al.* Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. Cancer Chemother Pharmacol 2012;70:399-405.
6. Zhang SR, Zhu LC, Jiang YP, Zhang J, Xu RJ, Xu YS, *et al.* Efficacy of afatinib, an irreversible erbB family blocker, in the treatment of intracerebral metastases of non-small cell lung cancer in mice. Acta Pharmacol Sin 2017;38:233-40.
7. Tamiya A, Tamiya M, Nishihara T, Shiroyama T, Nakao K, Tsuji T, *et al.* Cerebrospinal fluid penetration rate and efficacy of afatinib in patients with EGFR mutation-positive non-small cell lung cancer with leptomeningeal carcinomatosis: A Multicenter prospective study. Anticancer Res 2017;37:4177-82.
8. Solca F, Dahl G, Zoephel A, Bader G, Sanderson M, Klein C, *et al.* Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible erbB family blocker. J Pharmacol Exp Ther 2012;343:342-50.
9. Schuette W. Treatment of brain metastases from lung cancer: Chemotherapy. Lung Cancer 2004;45 Suppl 2:S253-7.
10. Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. J Clin Oncol 2005;23:6207-19.
11. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D, *et al.* Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
12. Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI, *et al.* Identification of prognostic factors in patients with brain metastases: A review of 1292 patients. Int J Radiat Oncol Biol Phys 1999;43:795-803.
13. Ettinger DS, Akerley W, Borghaei H, Chang AC, Cheney RT, Chirieac LR, *et al.* Non-small cell lung cancer, version 2.2013. J Natl Compr Canc Netw 2013;11:645-53.
14. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, *et al.* Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
15. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, *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;13:239-46.
16. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, *et al.* Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
17. Yang JC, Hirsh V, Schuler M, Yamamoto N, O'Byrne KJ, Mok TS, *et al.* Symptom control and quality of life in LUX-lung 3: A phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3342-50.
18. Köhler J, Schuler M. Afatinib, erlotinib and gefitinib in the first-line therapy of EGFR mutation-positive lung adenocarcinoma: A review. Onkologie 2013;36:510-8.
19. Bai H, Xiong L, Han B. The effectiveness of EGFR-TKIs against brain metastases in EGFR mutation-positive non-small-cell lung cancer. Onco Targets Ther 2017;10:2335-40.
20. Vansteenkiste J, Reungwetwattana T, Nakagawa K, Cho BC, Dols MAC, Cho EK, *et al.* CNS response to osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFR-TKI sensitising mutation (EGFRm)-positive advanced non-small cell lung cancer (NSCLC): Data from the FLAURA study. Ann Oncol 2017;28: doi: 10.1093/annonc/mdx782.
21. Ramalingam S, Reungwetwattana T, Chewaskulyong B, Dechaphunkul A, Lee KH, Imamura F N, *et al*. Osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFRm advanced NSCLC: FLAURA. Presented at: 2017 ESMO Congress; Madrid, Spain; 2017.