Case Report **Open Access**

Tao Wang, Ruimin Wang, Zhouhuan Dong, Naichao Liang, Ping Chang*

Complete remission through icotinib treatment in Non-small cell lung cancer epidermal growth factor receptor mutation patient with brain metastasis: A case report

DOI 10.1515/med-2016-0003
received September 7, 2015; accepted December 2, 2015

Abstract: Brain metastasis (BM) has been universally recognized as a poor prognostic factor in non-small cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have shown efficacy in treating BM with an EGFR mutation. This paper reports a case of BM patient with EGFR-mutated NSCLC. According to the findings, a complete remission (CR) of the BM was achieved by icotinib treatment without conducting a radiotherapy, which was followed by a resection of the primary lung cancer lesion and lymph nodes. After one-year follow-up, the disease progressed to liver metastasis and liver lesion biopsy showed a T790M mutation. The patient responded well to the combination treatment of AZD9291 and icotinib after the failure of transcatheter arterial chemoembolization (TACE). This case report suggests that icotinib has a sustainable anticancer response to BM and the combination with icotinib and AZD9291 is effective for liver metastasis with T790M.

Keywords: Non-small cell lung cancer, brain metastases, epidermal growth factor receptor, tyrosine kinase inhibitor

***Corresponding author: Ping Chang,** Department of Oral and Maxillofacial Surgery, PLA General Hospital, 28 Fuxing Road, Haidian District, Beijing 100853, China, Tel.:+86 10 66875514, Fax:+86 10 67817113, Email: changping301@sina.com
Tao Wang, Naichao Liang, Department of Thoracic Surgery, PLA General Hospital, Beijing 100853, P.R. China
Ruimin Wang, Department of Nuclear Medicine, PLA General Hospital, Beijing 100853, P.R. China
Zhouhuan Dong, Department of Pathology, PLA General Hospital, Beijing 100853, P.R. China

1 Introduction

The incidence of brain metastases (BM) is approximately 20%–40% in patients with non-small cell lung cancer (NSCLC) [1]. A number of clinical trials and retrospective analyses were conducted in order to compare the efficacy and safety among different treatment approaches used to control BM status [2–7]. Medical management, including surgical treatments, radiation therapy (whole brain radiation, focal beam and stereotactic radiation therapy, radiosurgery), chemotherapy, and combined therapies, remained as the major treatment options. In selected cases, complete remission of a single BM provides a surgical opportunity to remove primary lung cancer lesions, which consequently prolongs survival times [8-9].

EGFR-TKIs are a standard treatment for advanced NSCLC patients with EGFR mutations, and their role in the treatment of BM is less well established. Previous clinical studies found that EGFR TKIs [2,10], either in monotherapy or in combination with brain radiotherapy, had potential efficacy for NSCLC BM patients with EGFR mutations. The third generation of EGFR TKIs (e.g. AZD9291) is currently under development or in clinical trials to target mutant genes related with TKI tolerance [11], its interaction with the first generation EGFR TKIs is unclear and should be investigated in future.

We report herein a male NSCLC patient with BM who has achieved CR in BM and partial remission (PR) in lung lesion after 4 months' icotinib administration. Icotinib was continued for another 10 months after lung tumor resection until a liver metastasis was detected, and T790M mutation was observed. The patient later received AZD9291 combined with icotinib after TACE failed. He has been responding well to the combination treatment for 4 months.

© 2016 Tao Wang *et al* published by De Gruyter Open
This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivs 3.0 License.

2 Case presentation

The patient was a 59-year old man, who in October 2013, was diagnosed a lung cancer (NSCLC, cT3N2M1). He complained of having cough, headache, left limb paralysis, and gradual weakness for one month. The patient had a smoking history of 40 years and 2 years of hypertension. At the initial assessment in October 2013, the Karnofsky performance status was 80, the neurological test determined the left limb muscle strength of grade 4 (scores run from 0 to 5, where grade 0 is the most severe and grade 5 is normal), and an elevated carcinoembryonic antigen (CEA) was noted (13.56 μg/L, normal range 0-5 μg/L). According to findings of Computer Tomography (CT), primary lung lesion and a brain lesion was identified at the junctional zone between the temporal and parietal lobes of the left hemisphere (Figs. 1 A-B). A sample specimen, which was collected using transthoracic needle aspiration, was pathologically confirmed as an adenocarcinoma with a deletion of exon 19 of EGFR gene. The test also confirmed a negative result for T790M and ALK mutation. In October 2013, icotinib was administrated orally by 125 mg/d, three times daily.

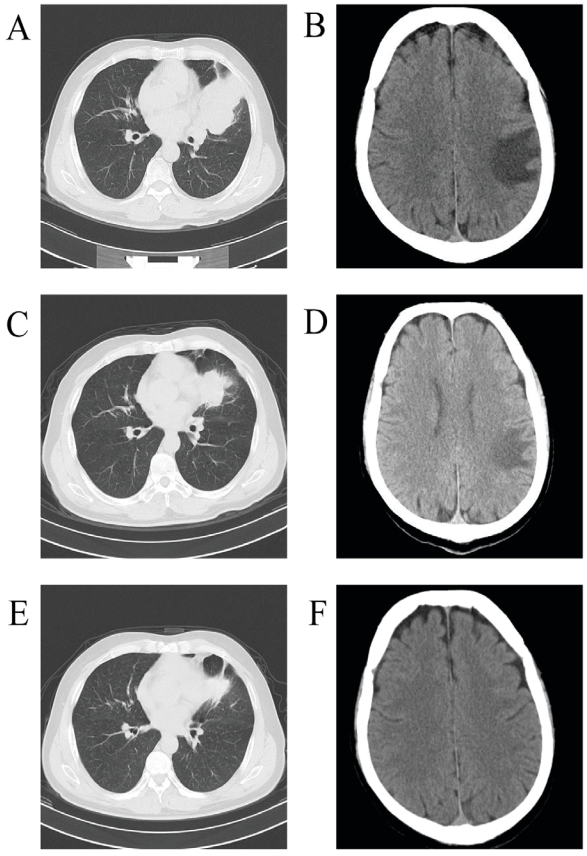

Figure 1: Computer tomography (CT) scans of lung lesion and brain metastasis before and after icotinib treatment. (A and B) At diagnosis of the metastases (Oct 12, 2013); (C and D) After 16 days of icotinib therapy (Oct 28, 2013), revealing a good response to treatment; (E and F) After 47 days of icotinib treatment (Nov 26, 2013), revealing brain lesion completed resolved.

The patient reported a significant improvement of neurological symptoms after receiving icotinib treatment for 10 days and had a completed relief after 6 weeks. The only adverse effect was skin rash at 1 degree according to Common terminology criteria for adverse events 4.0 after 2 weeks' administration. According to RECIST 1.1 (Figs.1 C-D), a significant improvement regarding partial response (PR) was observed, as evidenced by a 37.1% reduction in the size of lesion on average, and a quick absence in brain metastasis after 46 days of treatment (Figs.1 F). Considering the brain tumor had complete remission, we decided to monitor brain tumors by every 2 months using CT scan rather than a brain radiation therapy.

Given the good performance status, moderate increase of the lung lesions, and no evidence of BM recurrence, the patient underwent a left upper lobe resection on February 19, 2014. Similar pathological and molecular testing results were reported on the operative samples, which was EGFR exon 19 deletion and ALK-negative. Icotinib was interrupted for 10 days during perioperative period.

The lab results showed a continuous rise in CEA level, with a double increase observed after 6 months. Icotinib was increased to 250 mg tid and showed controlling effects on CEA for 8 months. CEA could not be controlled by doubled dose of icotinib, and PET/CT scan confirmed metastases in liver and lymph node lesions along the duodenum and inferior vena cava (Fig.2 A-B) on December 24, 2014. After a week, a liver lesion biopsy was performed to further confirmed a diagnosis of poorly differentiated metastatic adenocarcinoma and T790M mutation.

TACE was prescribed to the patient on January 7, 2015 and Icotinib was administrated 3 days later with dose of 125 mg tid. Unfortunately, on March 24, 2015, a poor clinical response to the TACE was reported, along with new liver metastases (Fig.2 C-D).

The patient received AZD9291 20 mg twice daily on March 27, 2015, in combination icotinib treatment 125 mg tid. Three weeks later, we observed a significant reduction in liver lesions and lymph node lesions, and an average shrinkage of 35.1% in target lesion size (Fig.2 E-F). CEA gradually decreased, but remained above the normal range. The rationale behind a continuation of icotinib administration was that the brain lesion still was in completed remission with it. The combination of AZD9291 and icotinib continued to show acceptable efficacy and safety as of this paper's writing for more than 4 months.

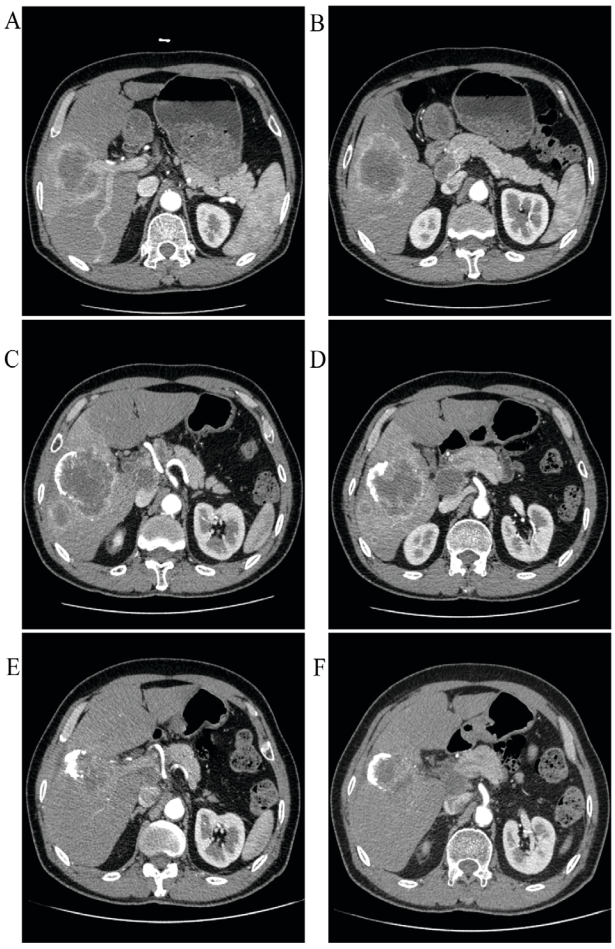

Figure 2: Abdominal computed tomography (CT) imaging of metastatic live lesion lymph node lesions before and after AZD9291 treatment. (A and B) At diagnosis of the metastases after administrating icotinib for 14 months (Dec 23, 2014); (C and D)After 2 months of transcatheter arterial chemoembolization, revealing disease progression (Mar 27, 2015); (E and F)After 20 days of combination treatment of icotinib and AZD9291, revealing a dramatic response(Apr 3, 2015).

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

3 Discussion

EGFR TKIs, as suggested by previous phase II trials, were found to significantly improve the efficacy in treating brain metastasis among patients with EGFR-mutated NSCLC. The intracranial response rate was 52%–89% and the median progression-free survival was 6.6–23.2 months in EGFR mutant patients, [12–15] indicating that EGFR TKIs could be considered as an alternative to chemotherapy prior to radiotherapy in patients suffering from asymptomatic brain metastases. However, whether TKIs could delay or obviate the need of Whole-Brain Radiotherapy (WBRT) in symptomatic brain metastases remains unclear at this point. Several cases have been reported in patients with neurological symptoms treated with high doses of gefitinib or erlotinib to control their disease [16-19], suggesting that EGFR-TKIs may also play an important role in controlling symptomatic BM.

Icotinib is a small-molecule EGFR-TKI developed by a local pharmaceutical company in China. The efficacy and safety of icotinib have been verified to be comparable to gefitinib by a randomized phase III study as 2nd line therapy for NSCLC [20]. In 2015, the first line indication for NSCLC patients with EGFR mutation of icotinib was approved by the China Food and Drug Administration [21]. Several phase I and II studies of icotinib in treatment of BM have been published recently. Zhou et al reported that icotinib could be well tolerated at dose of 375mg tid/day concurrent with WBRT in a phase I study, and found that the mean icotinib cerebrospinal fluid (CSF) penetration rate was 4.04% (range: 1.23%-9.71%) [22]. A phase II study of icotinib combined with WBRT treatment found that the CSF concentration and penetration rate were 11.6 ± 9.1 ng/mL and 1.4 ± 1.1 % respectively at a dose of icotinib 125mg tid. In the study, 10 patients with EGFR mutation had PFS and median overall survival times were 12.0 and 22.0 months, respectively [23]. The efficacy was consistent with the results of genfitinib and erlotinib published studies [12,15]. Zeng et al reported the efficacy of icotinib monotherapy for recurrent or progressive brain metastases after radiation in patients with end-stage NSCLC. 17 unselective patients, 9 patients had PR, 4 patients had SD and 4 patients had PD, and among 11 patients with EGFR mutation, 7 of 8 patients with 19DEL had PR [24]. The results suggested that intracranial metastasis tumors with 19 DEL were high sensitive to EGFR-TKIs as well. Zhang et al reported a patient with lung adenocarcinoma, with multiple lesions in the brain, controlled by icotinib more than 1 year with satisfactory health-related quality of life [25]. Can icotinib be used as a first-line single-drug treatment in BM patients with activating EGFR mutations? A

phase III randomized controlled study is currently being conducted in BM patients with EGFR mutations in China to compare the PFS between the first line icotinib and WBRT treatments [26]. The results of this phase III study might solve the issue of selecting the first-line treatment for BM patients with EGFR mutations.

The present case demonstrated profound effects against BM within a short period of treatment. After complete remission of BM, the patient became a candidate for surgical resection of lung lesions and underwent an operation to achieve a complete removal of the lesions. The results suggested that a remarkable clinical response to icotinib among patients with BM from an EGFR mutated NSCLC, which further indicate an opportunity to surgically eradicate the residual tumors.

The main mechanism of acquired resistance to EGFR TKIs is T790M mutation, which accounts for two thirds of all post-TKI tumor samples [27]. Phase I–II studies of the third generation EGFR TKIs as AZD9291 and rociletinib have demonstrated potential therapeutic effects in NSCLC patients who failed in the first generation TKI treatment and subsequently showed T790M mutation [28,29]. Interestingly, due to the heterogeneity of the tumors, multiple site rebiopsies revealed T790M status was frequently distinct between CNS (especially CSF) and thoracic lesions in individual patients. Some patients even exhibited an intrathoracic T790M heterogeneity [30]. Based on these findings, it is warrant to investigate the combination of different generation TKIs utilized to overcome EGFR resistance or improve the efficacy. In this case, considering the consistent benefits of icotinib in treating BM, icotinib was not discontinued during the AZD 9291 treatment. The patient showed good response and acceptable tolerance to the combination treatment.

4 Conclusion

In conclusion, this case indicated an impressive clinical response to icotinib and multimodality therapy in treating BM with EGFR-mutated NSCLC, subsequently developed T790M in live metastasis and controlled by AZD9291. It also demonstrated an impressive clinical response to EGFR-TKIs and warranted a development of new strategies of multimodality therapy for IV stage NSCLC with EGFR sensitive mutations.

Competing interests: The authors declare that they have no competing interests.

Acknowledgements: The authors acknowledge all the ward staff that took care of the patient.

Authors' contributions: PC and TW drafted the manuscript. RW, ZD and NL contributed to patients information collection and helped to draft the manuscript. All authors read and approved the final manuscript

Reference

[1] Langer CJ and Mehta MP: Current management of brain metastases, with a focus on systemic options. J Clin Oncol 2005; 23: 6207-6219

[2] Welsh JW, Komaki R, Amini A, Munsell MF, Unger W, Allen PK, 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: 895-902

[3] Endo C, Hasumi T, Matsumura Y, Sato N, Deguchi H, Oizumi H, et al: A prospective study of surgical procedures for patients with oligometastatic non-small cell lung cancer. Ann Thorac Surg 2014; 98: 258-264

[4] Lee SM, Lewanski CR, Counsell N, Bates A, Patel N, et al. Randomized Trial of Erlotinib Plus Whole-Brain Radiotherapy for NSCLC Patients With Multiple Brain Metastases. JNCI Journal of the National Cancer Institute. 2014;106(7):dju151. doi:10.1093/jnci/dju151

[5] Ojerholm E, Lee JY, Thawani JP, Miller D, O'Rourke DM, Dorsey JF, Geiger GA, Nagda S, Kolker JD, Lustig RA, Alonso-Basanta M.: Stereotactic radiosurgery to the resection bed for intracranial metastases and risk of leptomeningeal carcinomatosis. J Neurosurg 2014; 121 Suppl 2: 75-83

[6] Parlak C, Mertsoylu H, Güler OC, Onal C and Topkan E: Definitive chemoradiation therapy following surgical resection or radiosurgery plus whole-brain radiation therapy in non-small cell lung cancer patients with synchronous solitary brain metastasis: a curative approach. Int J Radiat Oncol Biol Phys 2014; 88: 885-891

[7] Putora PM, Ess S, Panje C, Hundsberger T, van Leyen K, Plasswilm L, and Früh M. et al: Prognostic significance of histology after resection of brain metastases and whole brain radiotherapy in non-small cell lung cancer (NSCLC). Clin Exp Metastasis 2015; 32: 143-149

[8] Li Z, Zhang X, Jiang X, Guo C, Sai K, Yang Q, et al: Outcome of surgical resection for brain metastases and radical treatment of the primary tumor in Chinese non-small-cell lung cancer patients. Onco Targets Ther 2015; 8: 855-860

[9] Qin H, Wang C, Jiang Y, Zhang X, Zhang Y, and Ruan Z: Patients with single brain metastasis from non-small cell lung cancer equally benefit from stereotactic radiosurgery and surgery: a systematic review. Med Sci Monit 2015; 21: 144-152

[10] Hoffknecht P, Tufman A, Wehler T, Pelzer T, Wiewrodt R, Schütz M, et al: Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. J Thorac Oncol 2015; 10: 156-163

[11] Janne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al: AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 2015; 372:1689-1699
[12] Iuchi T, Shingyoji M, Sakaida T, Hatanoc K, Naganoe O, Itakurab M, Kageyamad H, Yokoid S, Hasegawaa Y, Kawasakia K and Iizasab T: Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. Lung Cancer 2013; 82:282-287
[13] Porta R, Sánchez-Torres JM, Paz-Ares L, Massutí B, Reguart N, Mayo C, et al: Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. Eur Respir J 2011; 37:624-631
[14] Park SJ, Kim HT, Lee DH, Kim KP, Kim SW, Suh C, and Lee JS: 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; 77:556-560
[15] Wu YL, Zhou C, Cheng Y, Lu S, Chen GY, Huang C, 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; 24:993-999
[16] Jackman DM, Holmes AJ, Lindeman N, Wen PY, Kesari S, Borras AM, Bailey C, de Jong F, Jänne PA, and Johnson BE: 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; 24:4517-4520
[17] Hata A, Kaji R, Fujita S, and Katakami N: High-dose erlotinib for refractory brain metastases in a patient with relapsed nonsmall cell lung cancer. J Thorac Oncol 2011; 6:653-654,
[18] Clarke JL, Pao W, Wu N, Miller VA, and Lassman AB: High dose weekly erlotinib achieves therapeutic concentrations in CSF and is effective in leptomeningeal metastases from epidermal growth factor receptor mutant lung cancer. J Neurooncol 2010; 99:283-286
[19] Kuiper JL, and Smit EF: High-dose, pulsatile erlotinib in two NSCLC patients with leptomeningeal metastases: one with a remarkable thoracic response as well. Lung Cancer 2013; 80: 102-105
[20] Kuiper JL, and Smit EF: High-dose, pulsatile erlotinib in two NSCLC patients with leptomeningeal metastases: one with a remarkable thoracic response as well. Lung Cancer 2013; 80: 102-105
[21] Shi Y, Zhang L, Liu X, Zhou CC, Zhang SC, Wang D, Li Q, Qin SK, et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomized, double-blind phase 3 non-inferiority trial. Lancet Oncol. 2013; 14:953-961
[22] Qin N, Yang X, Zhang Q, Li X, Zhang H, Lv J, Wu Y, Wang J. and Zhang, S. Efficacy of Icotinib treatment in patients with stage IIIb/IV non-small cell lung cancer. Thoracic Cancer 2014; 5: 243-249
[23] Zhou L, He J, Xiong W, Yu Q, Xiang J, Liang MZ, Liu YM, Ding ZY, Gong YL and Lu Y : Phase I trial of icotinib combined with whole brain radiotherapy for EGFR-mutated non-small cell lung cancer patients with brain metastases. J Clin Oncol 2014; 32 Suppl 14:8110
[24] Fan Y, Huang Z, Fang L, Miao L, Gong L, Yu H, Yang H, Lei T, and Mao W: A phase II study of icotinib and whole-brain radiotherapy in Chinese patients with brain metastases from non-small cell lung cancer. Cancer Chemother Pharmacol 2015; 76:517-523
[25] Zeng YC, Wu R, Chi F, Xing R, Cai WS, Xiao YP, Xin Y and Wang NQ: Analysis of icotinib hydrochloride in the treatment for recurrent or progressive brain metastases after radiation in patients with end-stage non-small cell lung cancer. Clinical Medicine of China 2014; 30:804-807
[26] Zhang Y, Tang H, Li J, and Li M: An active treatment of lung adenocarcinoma cancer with brain metastases: icotinib. Onco Targets Ther 2015; 8:1351-1354
[27] Icotinib treat the patient with brain metastases epidermal growth factor receptor (EGFR) mutant non small cell lung cancer comparing with whole brain radiotherapy. http://www.ClinicalTrials.gov (NCT01724801)
[28] Su KY, Chen HY, Li KC, Kuo ML, Yang JC, Chan WK, Ho BC, et al: Pretreatment epidermal growth factor receptor (EGFR) T790M mutation predicts shorter EGFR tyrosine kinase inhibitor response duration in patients with non–small-cell lung cancer. J Clin Oncol 2012; 30:433-440
[29] Jänne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al: AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 2015; 372: 1689-1699
[30] Sequist LV, Soria JC, Goldman JW, Wakelee HA, Gadgeel SM, Varga A, et al: Rociletinib in EGFR-mutated non-small-cell lung cancer. N Engl J Med 2015; 372: 1700-1709
[31] Boyer M, Tsao MS, Jänne P, Ramalingam, S, Pitman Lowenthal S. and Alam, M. Preparing for tomorrow: Molecular diagnostics and the changing nonsmall cell lung cancer landscape. Asia-Pacific Journal of Clinical Oncology 2014,10: 2010