Cancer Treatment Communications (2014) 2, 4–7

Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.elsevier.com/locate/ctrc

Progressive brain metastases in an EGFR mutated adenocarcinoma of the lung: Response to gefitinib after progression on erlotinib

C. Leitner[a,*], R. von Moos[a], M. Mark[a], M. Früh[b], R. Cathomas[a]

[a]*Division of Oncology, Kantonsspital Graubünden, Switzerland*
[b]*Department of Oncology, Kantonsspital St. Gallen, Switzerland*

Received 10 March 2014; accepted 16 March 2014

KEYWORDS
Brain metastases;
EGFR mutation;
Lung adenocarcinoma;
Gefitinib;
Erlotinib

Abstract
We report a case of a 59-year-old woman with brain metastases from an EGFR mutated adenocarcinoma of the lung. She was initially treated with erlotinib and two times whole brain radiation therapy. After a second relapse within the CNS the therapy was switched to gefitinib and a partial remission of the brain metastases could be achieved. Our case demonstrates that patients can respond to a switch of the EGFR TKI also within the CNS despite heavy pretreatment. The article reviews the literature regarding the efficacy of tyrosine kinase inhibitors in brain metastases from lung cancers.

1. Case presentation

A 59-year-old female patient presented with progressive headaches over the course of two years. Magnetic resonance imaging showed multiple brain metastases in the cerebrum and cerebellum. Positron emission tomography-computed tomography of the chest and abdomen revealed a primary tumor in the medial lobe of the right lung and multiple enlarged hilar, subcarinal and supraclavicular lymph nodes. Furthermore, multiple bone metastases and a right sided adrenal metastasis were described. Bronchoscopic fine needle aspiration of a mediastinal lymph node showed adenocarcinoma cells. The activating mutation L858R in the epidermal growth-factor-receptor (EGFR) gene within exon 21 could be detected by PCR-based assay. We initiated a therapy with the tyrosine kinase inhibitor (TKI) erlotinib at a dosage of 150 mg once daily. In addition a concomitant whole brain radiation therapy (WBRT) with 5×4 Gy and a radiation of the cervical spine with 5×4 Gy was applied. Severe fatigue (grade 3) persisted after the WBRT for several

*Corresponding author at: Division of Oncology, Kantonsspital Graubünden, CH-7000 Chur, Switzerland. Tel.: +41 81 256 66 46; fax: +41 81 256 66 68.
E-mail address: christoph.leitner@ksgr.ch (C. Leitner).

http://dx.doi.org/10.1016/j.ctrc.2014.03.001

months. Due to skin toxicity grade 3 the erlotinib dose had to be reduced to 100 mg/d. Repeated computed tomography 2, 5, 8 and11 months after initiation of therapy showed sustained partial remission in the lung and mediastinum as well as in the CNS. The patient's overall condition markedly improved over time with improvement of the headaches as well as the dizziness and fatigue. A first relapse with multiple new brain metastases had to be diagnosed after 13 months of therapy with erlotinib. At this point, repeated WBRT with 10×2 Gy was performed. Treatment with erlotinib was interrupted during the course of radiotherapy. The local response to treatment was good with a marked reduction of the cerebral metastases. However, 4 months later, on continued erlotinib therapy and 18 months after starting treatment with erlotinib, a second relapse was noted. At this point, the patient suffered from a deterioration of the performance status (ECOG PS: 2–3), progressive cephalea and dizziness. Computed tomography showed further progression in the CNS and extensive new hepatic and pulmonary metastases. Neither the continuation of erlotinib nor conventional chemotherapy seemed a reasonable treatment option. The patient however desired further treatment and we decided to switch the anti-EGFR-therapy to gefitinib 250 mg once daily. Within a few weeks, the patient's general condition improved and a partial remission of all tumor lesions including the CNS was noted in a follow up CT scan after 3 months (Figure 1). A total of 5 months after the initiation of gefitinib, further hepatic and cerebral progression was noted. A last therapeutic attempt with afatinib (30 mg/d) over eight weeks within a named patient program remained without success and the patient died of her disease 27 months after the initial diagnosis.

2. Discussion

Lung cancer is still the most common malignancy with estimated 1.3 million deaths per year worldwide [1]. More than 80% of all cases are caused by non-small lung cancer (NSCLC) [2]. About 20–30% of patients with NSCLC present with brain metastases [3]. The prognosis of these patients is generally poor with a median survival of less than 6 months [4]. More than 60% of NSCLCs overexpress epidermal growth factor receptor (EGFR) [5]. These transmembrane tyrosine kinases transduce important growth factor signals from the extracellular compartment into the cell. The tyrosine kinase inhibitors (TKI) erlotinib and gefitinib target the intracellular kinase domain of EGFR. They have been shown to be particularly effective in tumors harboring activating mutations in the tyrosine kinase domain of the EGFR gene, mainly exon 19 deletions and exon 21 L858R point mutation [6]. Testing for these mutations in all patients with metastatic non-squamous carcinoma of the lung is therefore recommended and today standard practice [7]. Erlotinib and gefitinib have both been compared against standard chemotherapy regimens in several randomized phase III trials in

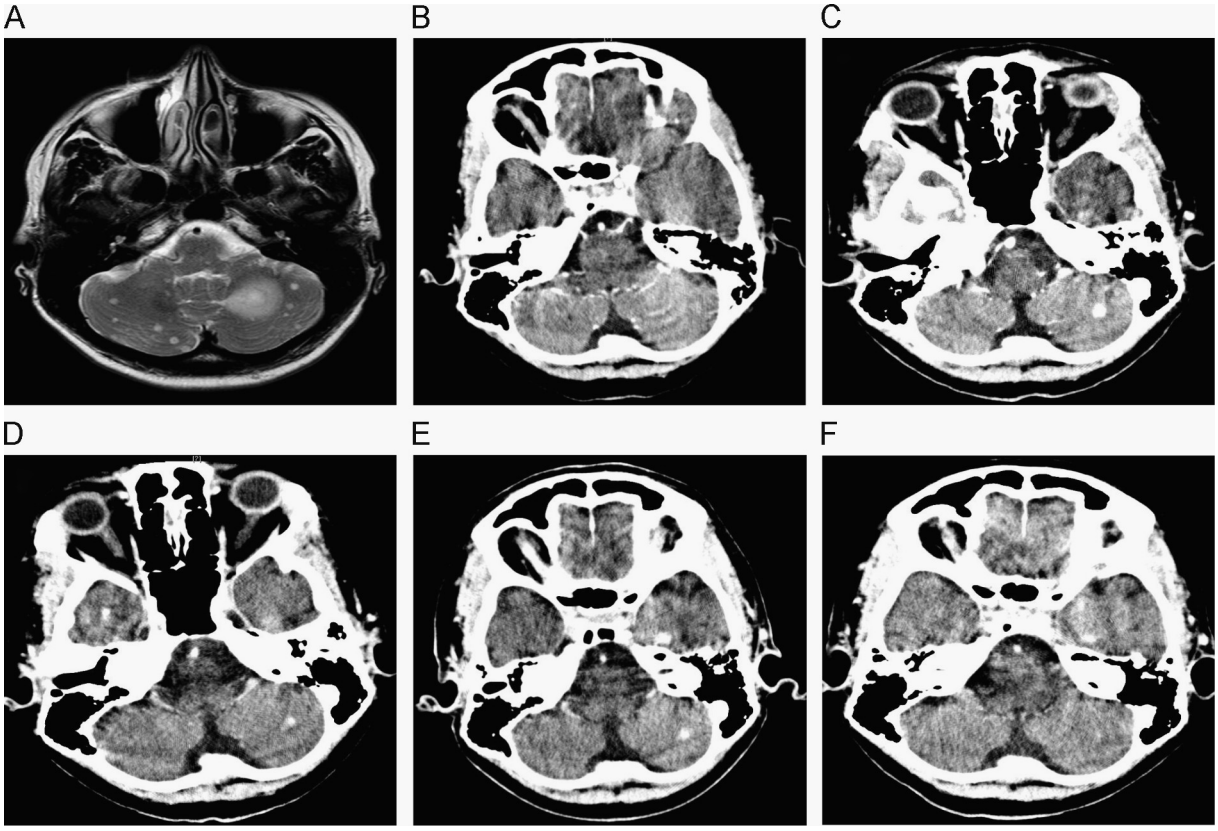

Figure 1 Magnetic resonance imaging (MRI) and computed tomography (CT) scans showing the process of brain metastases: at initial diagnosis (A), after first line therapy with whole brain radiation therapy (WBRT) and erlotinib (B), at first relapse (C), after repeated WBRT and continued erlotinib (D), at second relapse (E), after therapy with gefitinib (F).

EGFR mutated patients and they demonstrated significantly improved response rate, progression free survival and quality of life [8-11]. Therefore all guidelines recommend initial therapy with a TKI instead of chemotherapy as the best choice of treatment for patients with advanced NSCLC and an activating EGFR mutation. In patients with brain metastases from an EGFR mutated lung cancer, primary treatment with gefitinib or erlotinib has also demonstrated response in the CNS [12-15]. Porta et al. retrospectively examined efficacy and tolerability of erlotinib in 69 NSCLC patients with brain metastases. Objective response rate in patients with EGFR mutations ($n=17$) was 82.4% and 8 patients achieved a complete remission [12]. Therefore WBRT can be postponed in patients with asymptomatic brain metastases and an activating EGFR mutation if patients respond to gefitinib or erlotinib. The radiosensitivity of lung cancer cells with mutant EGFR has been demonstrated in in vitro studies [16]. In addition synergistic antitumor effects between EGFR inhibitors and radiation have been demonstrated in preclinical studies [17,18]. In a recent phase II study concomitant WBRT and erlotinib was evaluated in 40 patients with brain metastases from NSCLC regardless of the EGFR mutation status [19]. Overall response rate was 86% and median survival was 11.8 months. The therapy was safe and particular benefit was evident for patients with EGFR mutations. The combination of TKIs and WBRT therefore seems to be a safe and reasonable treatment strategy. Regarding the question of switching from one TKI to another TKI in case of progression of EGFR mutated NSCLC the only prospective data derive from the LUX Lung 1 trial [20]. This trial tested the irreversible TKI afatinib in patients who had previously received erlotinib or gefitinib and one or two lines of chemotherapy. The trial included an unselected patient population. The subgroup analysis of the EGFR mutated patients ($N=96$) showed a significantly longer progression-free survival for patients receiving afatinib compared to those who received placebo (3.3 months vs 1.0 months). A recently reported retrospective study showed that patients with advanced NSCLC and activating mutations could benefit from re-administration of the same TKI after failure of erlotinib or gefitinib [21]. In all of these patients ($N=33$), a conventional chemotherapy was performed between the first and second TKI therapy. Switching of TKI or reintroduction of the same TKI might therefore represent an option in previously responding patients. Our case demonstrates, that patients can not only respond to a switch of the TKI outside but also within the CNS despite heavy pretreatment including two times WBRT. The fact that a direct switch of TKI lead to this result in the CNS is particularly unusual. The effectiveness of TKIs on brain lesions is depending on drug penetration to the CNS through the blood-brain-barrier (BBB). It is unclear, whether one or the other TKI has better penetration through the blood-brain barrier. In one report, erlotinib demonstrated a response in patients with brain metastases from NSCLC that appeared after good initial response of extracranial disease to gefitinib [22] assuming different penetration of the two agents. Several retrospective studies examined drug concentrations in the cerebrospinal fluid (CSF) of patients with CNS metastases from NSCLC [23-25]. The results suggest higher CSF concentrations and better control rates for erlotinib than for gefitinib. However, larger intracranial lesions may cause disruption of the BBB and cause an ineffective barrier [26,27]. Moreover, radiotherapy has been shown to increase the BBB permeability [28]. One possible explanation for the unexpected success of gefitinib in our patient could therefore be an increased disruption of the BBB by tumor invasion and by post-radiogenic effects. Only two case reports were found in our literature research that showed a cross-over response of brain metastases to one TKI after failure of another TKI [29,30]. The two most common mechanisms of tumor resistance to TKIs are T790M secondary mutation and MET gene amplification. Cells with these transformations are both resistant to erlotinib and gefitinib [31]. The discordant response between erlotinib and gefitinib was in one of the mentioned reports [30] attributed to the EGFR mutation E884K. Also in our case another mutation or an altered proportion of resistant or sensitive tumor cells could be responsible for the resistance to erlotinib and the continuing efficacy to gefitinib. However such considerations remain speculative, as post-mortem CNS tumor specimens were not examined. A further explanation of our unusual result could be the dosage of TKIs. It is known that higher doses may overcome resistance to standard doses. Favorable effectiveness especially toward intracranial metastases from NSCLC is described in several reports [32,33]. In fact we used standard dosed gefitinib (250 mg/d) whereas erlotinib had to be dose-reduced (100 mg/d) because of severe skin rash. However, erlotinib was still dosed closer to its maximal tolerated dosis (150 mg/d) than gefitinib (750 mg/d). Finally, our patient has had a relatively long benefit from treatment with EGFR TKIs without chemotherapy (27 months). We hypothesize that in these patients a switch from one TKI to the other could be of particular value.

3. Conclusion

We report a case with good response of brain metastases to gefitinib in an EGFR mutated adenocarcinoma of the lung after progression on erlotinib and two times WBRT.

Conflicts of interest statement

Richard Cathomas: member of advisory board for Boehringer Ingelheim, Roche, Astra Zeneca. Roger von Moos: member of advisory board for Roche and Astra Zeneca; unrestricted research grant Roche. For the remaining authors no conflicts of interests are declared. No sources of funding are declared.

Consent

The patient we describe in our case report died of her disease prior to writing and submission of our manuscript. Therefore no written and signed consent could be obtained from the patient. Informed consent was obtained from the patient's husband for publication of this case report and accompanying images.

References

[1] World Health Organization, Cancer [online]. Available at: ⟨http://www.who.int/mediacentre/factsheets/fs297/en/index.html⟩ (accessed 21.01.14).

[2] K.M. Pisters, W.K. Evans, C.G. Azzoli, et al., Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non small-cell lung cancer guideline, J. Clin. Oncol. 25 (2007) 5506–5518.

[3] J.B. Sorensen, H.H. Hansen, M. Hansen, et al., Brain metastases in adenocarcinoma of the lung, J. Clin. Oncol. 6 (1988) 1474–1480.

[4] L. Gaspar, C. Scott, M. Rotman, et al., Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trial, Int. J. Radiat. Oncol. Biol. Phys. 37 (1997) 745–751.

[5] G. Da Cunha Santos, F.A. Shepherd, M.S. Tsao, EGFR mutations and lung cancer, Annu. Rev. Pathol. 6 (2011) 49–69.

[6] T.J. Lynch, D.W. Bell, R. Sordella, et al., Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib, N. Engl. J. Med. 350 (21) (2004) 2129–2139.

[7] V.L. Keedly, S. Temin, M.R. Somerfield, et al., American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy, J. Clin. Oncol. 29 (15) (2011) 2121–2127.

[8] M. Fukuoka, Y.L. Wu, S. Thongprasert, et al., Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS), J. Clin. Oncol. 29 (21) (2011) 2866–2874.

[9] M. Maemondo, A. Inoue, K. Kobayashi, et al., Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR, N. Engl. J. Med. 362 (2010) 2380–2388.

[10] C. Zhou, Y.L. Wu, G. Chen, et al., Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR-mutation positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study, Lancet Oncol. 12 (8) (2011) 735–742.

[11] R. Rosell, E. Carcereny, R. Gervais, 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. 13 (3) (2012) 239–246.

[12] R. Porta, J.M. Sanchez-Torres, L. Paz-Ares, et al., Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation, Eur. Respir. J. 37 (2011) 624–631.

[13] H. Bai, B. Han, The effectiveness of erlotinib against brain metastases in non-small cell lung cancer patients, Am J. Clin. Oncol. 36 (2) (2013) 110–115.

[14] S.J. Park, H.T. Kim, D.H. Lee, et al., Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation, Lung Cancer 77 (3) (2012) 556–560.

[15] C. Grommes, G.R. Oxnard, M.G. Kris, et al., Pulsatile high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer, Neuro Oncol. 13 (2011) 1364–1369.

[16] A.K. Das, M. Sato, M.D. Story, et al., Non-small-cell lung cancers with kinase domain mutations in the epidermal growth factor receptor are sensitive to ionizing radiation, Cancer Res. 66 (2006) 9601–9608.

[17] H.Q. Zhuang, J. Sun, Z.Y. Yuan, et al., Radiosensitizing effects of gefitinib at different administration times in vitro, Cancer Sci. 100 (2009) 1520–1525.

[18] P. Chinnaiyan, S. Huang, G. Vallabhaneni, et al., Mechanisms of enhanced radiation response following epidermal growth factor receptor signalling inhibition by erlotinib (Tarceva), Cancer Res. 65 (2005) 3328–3335.

[19] J.W. Welsh, R. Komaki, A. Amini, 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. 31 (2013) 895–902.

[20] V.A. Miller, V. Hirsh, J. Cadranel, et al., Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (Lux-Lung1): a phase 2/3b randomised trial, Lancet Oncol. 13 (5) (2012) 528–538.

[21] S. Zhengbo, Y. Xinmin, H. Chunxiao, et al., Re-administration after the failure of gefitinib or erlotinib in patients with advanced non-small cell lung cancer, J. Thorac. Dis. 5 (4) (2013) 400–405.

[22] T. Katayama, J. Shimizu, K. Suda, et al., Efficacy of erlotinib for brain and leptomeningeal metastases in patients with lung adenocarcinoma who showed initial good response to gefitinib, J. Thorac. Oncol. 4 (11) (2009) 1415–1419.

[23] E. Lee, B. Keam, D.W. Kim, et al., Erlotinib versus gefitinib for control of leptomeningeal carcinomatosis in non-small-cell lung cancer, J. Thorac. Oncol. 8 (8) (2013) 1069–1074.

[24] Y. Togashi, K. Masago, M. Fukudo, et al., Cerebrospinal fluid concentration of erlotinib and its active metabolite OSI-240 in patients with central nervous system metastases of non-small cell lung cancer, J. Thorac. Oncol. 5 (7) (2010) 950–955.

[25] Y. Togashi, K. Masago, S. Masuda, et al., Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer, Cancer Chemother. Parmacol. 70 (3) (2012) 399–405.

[26] L.L. Muldoon, C. Soussain, K. Jahnke, et al., Chemotherapy delivery issues in central nervous system malignancy: a reality check, J. Clin. Oncol. 25 (16) (2007) 2295–2305.

[27] J.F. Deeken, W. Loscher, The blood-brain barrier and cancer: transporters, treatment, and Trojan horses, Clin. Cancer Res. 13 (2007) 1663–1674.

[28] M. van Vulpen, H.P. Kal, M.J. Taphoorn, et al., Changes in blood-brain barrier permeability induced by radiotherapy: implications for timing of chemotherapy? Oncol. Rep. 9 (4) (2002) 683–688.

[29] J.C. Walther, M. Khorshid, A. Gaya, et al., Cross-over response to erlotinib of brain metastatic disease from bronchial adenocarcinoma after gefitinib failure, and an unusual rash, Clin. Oncol. (R. Coll. Radiol.) 18 (8) (2006) 637–639.

[30] N.W. Choong, S. Dietrich, T.Y. Seiwert, et al., Gefitinib response of erlotinib-refractory lung cancer involving meninges-role of EGFR mutation, Nat. Clin. Pract. Oncol. 3 (1) (2006) 50–57.

[31] S.H. Sim, S.W. Han, D.Y. Oh, et al., Erlotinib after Gefitinib failure in female never-smoker Asian patients with pulmonary adenocarcinoma, Lung Cancer 65 (2009) 204–207.

[32] J.L. Kuiper, E.F. Smit, High-dose, pulsatile erlotinib in two NSCLC patients with leptomeningeal metastases – one with a remarkable thoracic response as well, Lung Cancer 80 (1) (2013) 102–105.

[33] D.M. Jackman, A.J. Holmes, N. Lindeman, et al., Response and resistance in a non-small-cell lung cancer patient with an epidermal growth factor receptor mutation and leptomeningeal metastases treated with high-dose gefitinib, J. Clin. Oncol. 24 (2006) 4517–4520.