

# Epidermal growth factor receptor tyrosine kinase inhibitors with conventional chemotherapy for the treatment of non-small cell lung cancer

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**Abstract:** We report a Chinese male patient with advanced stage lung squamous cell carcinoma who developed brain metastases after responding to treatment comprising six cycles of conventional chemotherapy with docetaxel and cisplatin. The patient was then treated with oral erlotinib (150 mg/day) and whole-brain radiation therapy followed by four cycles of docetaxel and carboplatin chemotherapy. The patient then received gefitinib (250 mg/day) as a maintenance therapy until the end of the follow-up period. In this patient, progression-free survival, defined as the interval from the initiation of first-line chemotherapy to the cessation of erlotinib due to progressive disease or death from any cause, was 3 months. Overall survival, defined as the interval from the initiation of first-line chemotherapy to death from any cause, was 75 months. Erlotinib was well tolerated in combination with whole-brain radiation therapy and a favorable objective response rate was observed. Furthermore, targeted drug treatment warrants consideration in patients with a negative epidermal growth factor receptor mutation status and male patients with a history of smoking.

**Keywords:** EGFR tyrosine kinase inhibitors, chemotherapy, non-small cell lung cancer

## Introduction

Lung cancer, of which non-small cell lung cancer (NSCLC) is the most common form, remains the leading cause of cancer-related mortality worldwide, and many NSCLC patients present with advanced disease at the time of initial diagnosis.<sup>1</sup> Recent advancements in chemotherapy and targeted therapy have provided new treatment options for this disease.

NSCLC research has increasingly focused on efforts to identify biomarkers that can predict increased clinical benefit from new agents in specific patient subgroups to enable clinicians make informed treatment decisions regarding the most appropriate initial treatment option for individual patients. The most promising biomarker to date is the epidermal growth factor receptor (EGFR) mutation status; recent data suggest that compared to patients with tumors lacking such mutations, patients with tumors harboring activating mutations in EGFR achieve a substantially increased benefit from treatment with EGFR tyrosine kinase inhibitors (TKIs).<sup>2-7</sup> Notably, EGFR mutations occur with greater frequency in Asian patients than in European patients, with typical mutation rates of ~30% and 8%, respectively.<sup>3,8,9</sup> Therefore, approximately one in three Asian patients is positive for a biomarker predicting an exceptional response to EGFR TKI therapy. One such EGFR TKI is the orally administered targeted agent erlotinib, which inhibits the tyrosine kinase domain of EGFR. Erlotinib was approved for second-line use based on the positive results of the Phase III BR.21 trial,<sup>10</sup> in which erlotinib,

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compared with best supportive care, improved overall survival. In Phase II studies, erlotinib has also been shown to have clinical benefit as a first-line therapy for advanced NSCLC, resulting in tumor response rates of 10%–20% and median survival durations of 10.9–12.9 months.<sup>11,12</sup> However, despite important new additions to the therapeutic arsenal for NSCLC, the 5-year survival rate for patients with this disease remains disappointingly low, at <20%.<sup>13</sup> The implementation of accurate EGFR mutation testing is a key component of biomarker-based treatment strategies in clinical practice; however, thus far, the selection or identification of patients with activating EGFR mutations based on clinical characteristics has been unsatisfactory.<sup>2,14</sup>

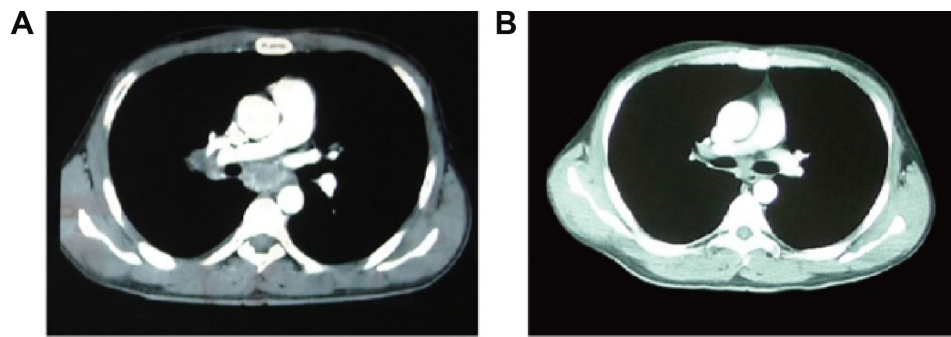
Unfortunately, despite treatment advances, the prognosis of patients with advanced lung cancer remains poor, and the vast majority of patients die as a result of uncontrolled systemic disease. Among patients with NSCLC, ~20%–40% ultimately develop brain metastases.<sup>15,16</sup> Treatment options for brain metastases from NSCLC include whole-brain radiation therapy (WBRT), stereotactic radiosurgery, surgical resection, or some combination of these three treatments. The median survival duration after WBRT strongly correlates with patient age, Eastern Cooperative Oncology Group performance status, and the number and location of the metastatic lesions, and it generally ranges from 3 to 6 months.<sup>17–21</sup>

The present study describes a 34-year-old male with NSCLC and brain metastases that were incidentally identified during a histopathological examination. This study also includes a review of the relevant literature to provide clinicians with information concerning a novel treatment program for NSCLC that achieved a longer overall survival. Written informed consent was obtained from the patient. The Research Ethics Committee of the Shandong Cancer Hospital and Institute approved this study.

## Case report

A 34-year-old male was admitted to the local hospital in April 2007 complaining of hacking cough of unknown cause. The patient had no symptoms of bosom frowsty, chest pain, anhelation, fever, or weakness, and the patient had not experienced appetite or weight loss. However, the patient showed no evident improvement upon hospitalization. A chest computed tomography (CT) scan in May 2007 at the Affiliated Hospital of Binzhou Medical College (Binzhou, People's Republic of China) revealed a mass in the hilum of the right lung, swollen lymph nodes in the mediastinum, and pleural effusion. Furthermore, fiberoptic bronchoscopy

revealed the tumor pathology: moderately differentiated squamous cell carcinoma (SCC) in the middle and lower lobes of the lung. After 3 days, the patient visited the Chinese PLA General Hospital in Beijing, and an abdominal CT scan revealed a suspicious mass, which was considered to be either a metastatic tumor or an adenocarcinoma, in the right adrenal gland. Brain magnetic resonance imaging and bone emission CT showed no evidence of distant metastasis. The patient's medical history was unremarkable, and SCC was staged as T4N2M0 (IIIB) according to the International Union Against Cancer 1997 Tumor Node Metastasis staging criteria.<sup>22</sup> After several discussions, the oncologists chose not to perform surgery. The patient's alanine aminotransferase level was between 2- and 2.5-fold above normal after admission to the hospital; therefore, treatments to protect the liver were initiated after the patient was admitted. The patient's carcinoembryonic antigen level was 7.6 ng/mL, and carbohydrate antigen 19-9 (CA 19-9) level was 13.4 ng/mL. From May 28, 2007 to September 12, 2007, the patient received six cycles of adjuvant chemotherapy consisting of 300 mg of paclitaxel and 750 mg of dicycloplatin on day 1 of each 2-week cycle. The evident side effects of this adjuvant chemotherapy regimen were myelosuppression with grade 0–2 neutrocytopenia and a grade 1 gastrointestinal reaction. The patient demonstrated a partial response (PR) after four cycles and a complete response (CR) after six cycles according to the chest CT scan, which showed a streaky or coarse reticular pattern of opacities in the upper right lobe under the pleura and small nodules in the right hilum (Figure 1). The patient did not receive any additional therapy until February 18, 2008, when a chest CT scan demonstrated lung cancer with mediastinal lymph node metastasis, a right lower lobe lesion (4.4×3.1 cm), and mediastinal lymph node enlargement. Brain CT showed abnormal enhancement in the right occipital lobe with evidence of metastatic disease. Abdominal ultrasound revealed medium-low echo in the right adrenal gland nodules and did not rule out adrenal metastasis. These findings indicated local recurrence and brain metastases. Therefore, from February 26, 2008 to June 14, 2008, the patient underwent six additional cycles of chemotherapy for progressive disease (PD) according to the following medication schedule: 1,000 mg of pemetrexed disodium on day 1; 50 mg of cisplatin on days 1 and 2; and 40 mg of cisplatin on day 3. This cycle was repeated every 2 weeks. For the first 12 cycles, 140 mg of cisplatin was administered on day 1. Grade 0–1 myelosuppression and grade 0–1 gastrointestinal reactions were observed. A potential PR was assessed after cycle 8, and the patient was evaluated after cycle 10



**Figure 1** A complete response after six cycles of chemotherapy according to the contrast-enhanced chest computed tomography scan.

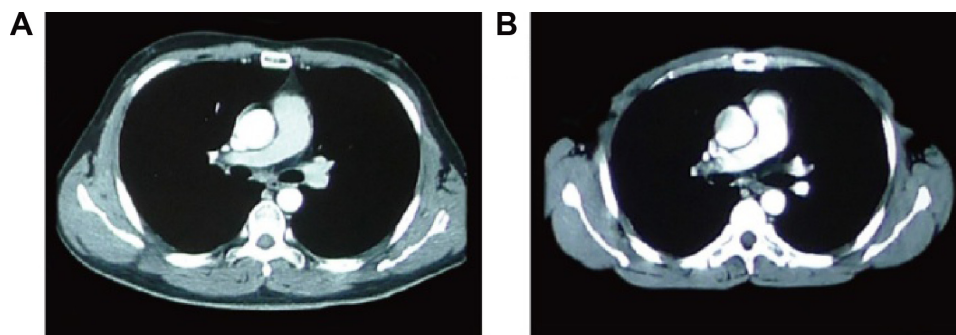
**Notes:** Contrast-enhanced chest computed tomography scan showing a mass located in the hilum of the right lung (**A**). This mass exhibited evident shrinkage following six cycles of chemotherapy (**B**).

for stable disease (SD) (Figure 2). Beginning on March 7, 2008, sequential adjuvant radiotherapy was performed via 40 Gy/20 F irradiation of the whole brain and 60 Gy/20 F irradiation of the right occipital metastasis; no side effects were observed after the six cycles of maintenance radiotherapy. Oral erlotinib (150 mg/day) was administered from July 2008 to December 2009 (Figure 3). At the scheduled follow-up on December 7, 2009, the abdominal CT scan showed liver and adrenal metastases. On December 11, 2009, a brain magnetic resonance imaging scan revealed abnormal enhancement in the nodules of the right occipital lobe (ovular shape with a diameter of ~12 cm) with a history of suspected metastases, a right cerebellar lesion without abnormal enhancement, and a lesion with a slight increase in contrast compared with that of the original film. Emission CT showed no signs of bone metastases (Figure 4). From December 11, 2009 to January 3, 2010, the patient underwent retreatment according to chemotherapy cycles 1 and 2 using the following medications: 140 mg of docetaxel intravenously (iv) on day 1 and 500 mg of carboplatin iv on day 1. The patient experienced grade 0–2 side effects, bone marrow suppression, gastrointestinal reactions, nausea and vomiting. On January 22, 2010, an abdominal CT scan revealed multiple

liver lesions (potential metastatic disease) and right adrenal metastases (4.6×3.7 cm). On December 7, 2009, a focused abdominal CT with contrast was performed to evaluate the patient for a PR. From January 23, 2010 to February 20, 2010, the patient was re-treated according to chemotherapy cycles 3 and 4 using the following medications: 140 mg of docetaxel iv on day 1 and 500 mg of carboplatin iv on day 1 (Figure 5). The patient experienced bone marrow suppression, grade 0–2 side effects, gastrointestinal reactions, nausea, and vomiting. Oral gefitinib treatment was initiated in June 2010 and continued until the patient died of pulmonary infection and cachexia in August 2013 (Figure 6).

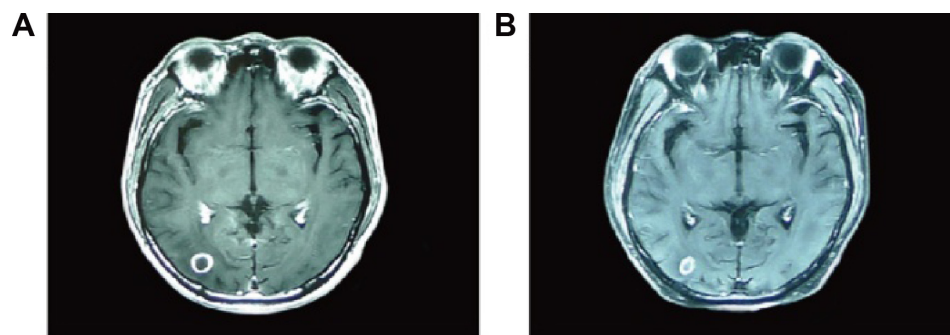
## Discussion

Erlotinib was initially used in combination with chemotherapy as a first-line treatment for advanced NSCLC but was found to be ineffective.<sup>23,24</sup> This lack of efficacy could be explained by the hypothesis that a negative interaction occurs between EGFR TKIs and cytotoxic agents when they are administered concurrently and by the fact that no molecular biomarkers exist to identify appropriate patients for this combination treatment. Subsequently, several randomized studies, including the BR.21 and TRUST studies,



**Figure 2** A stable disease after six additional cycles of chemotherapy according to the contrast-enhanced chest computed tomography scan.

**Notes:** Enhanced chest computed tomography scan on February 18, 2008, showing lung cancer with mediastinal lymph node metastasis, a right lower lobe lesion, and mediastinal lymph node enlargement (**A**). The lesion was significantly reduced and remained stable after six additional cycles of chemotherapy (**B**).

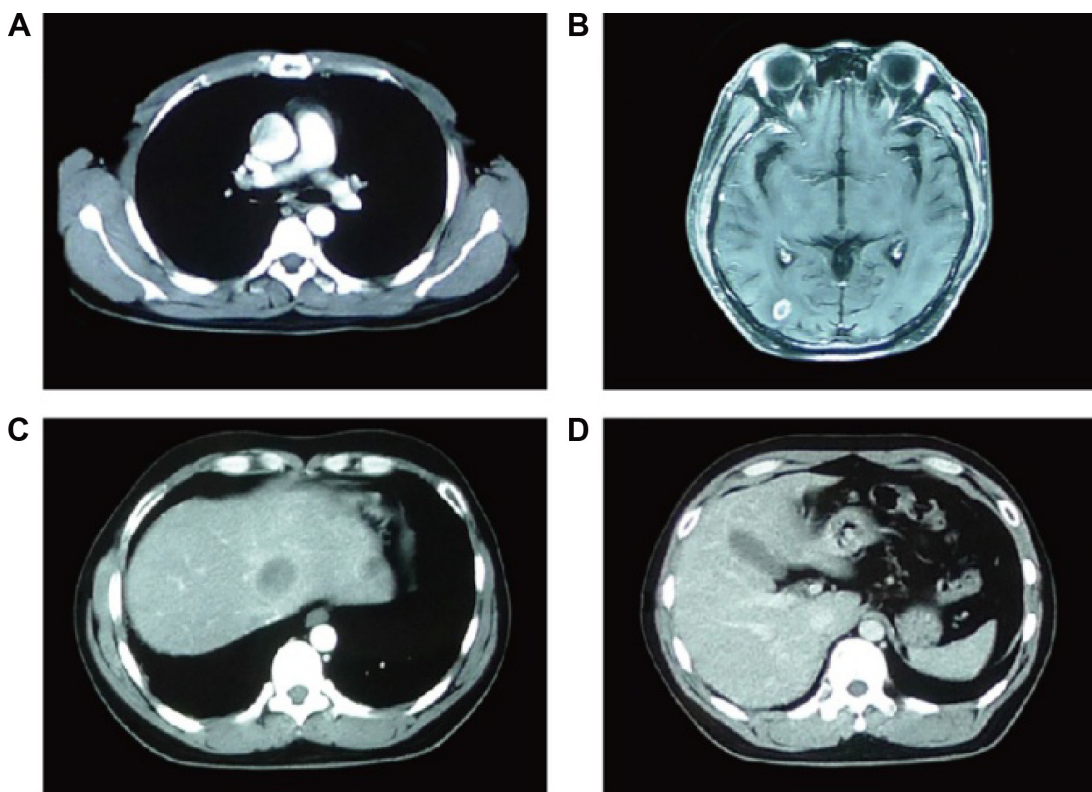


**Figure 3** Enhanced brain computed tomography scan showing that erlotinib treatment combined with whole-brain radiation therapy was effective for the patient.

**Notes:** Enhanced brain computed tomography scan revealing metastasis in the right occipital lobe (**A**). This metastasis significantly shrank after erlotinib treatment combined with whole-brain radiation therapy until September 2009 (**B**).

have demonstrated the promising efficacy of erlotinib as a second-line or third-line treatment for patients with advanced NSCLC.<sup>10,25</sup> As shown in the Iressa Pan-Asia Study (IPASS), a multicenter, Phase III, randomized study that examined the combination of gefitinib, carboplatin and paclitaxel as a first-line treatment for clinically selected patients in East Asia,<sup>2</sup> EGFR-mutant lung cancer patients form a distinct subgroup exhibiting a superior clinical outcome in response to EGFR TKI treatment. Subsequently, two Japanese trials comparing first-line gefitinib therapy with chemotherapy for exclusively

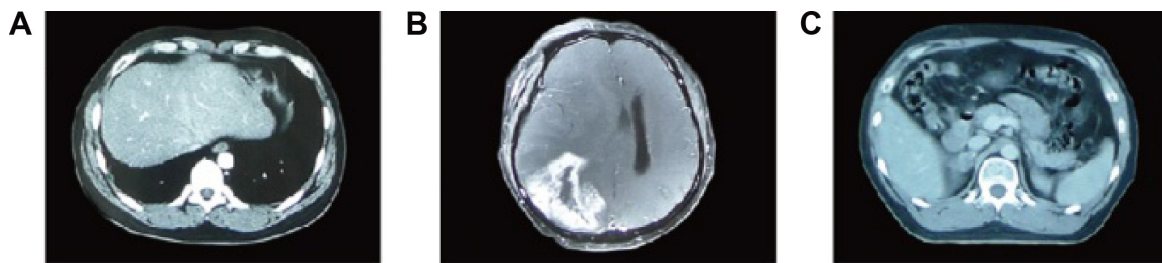
EGFR-mutant lung cancers confirmed the conclusion of the IPASS.<sup>5,6</sup> However, no related studies on sequential intercalated combination regimens of chemotherapy and erlotinib have been reported. Importantly, activating EGFR mutations was found in only 30%–40% of Chinese patients with adenocarcinoma, and EGFR mutation testing was performed in only 10% of these patients; thus, the EGFR mutation status is unknown in most Chinese patients when decisions are made regarding the first-line treatment regimen.<sup>26</sup> For these patients, a combination of chemotherapy and EGFR TKIs



**Figure 4** Abdominal computed tomography scan showed liver and adrenal metastases, and other lesions did not change significantly.

**Notes:** Enhanced abdominal computed tomography scan showing liver and adrenal metastases (**A, D**). A brain magnetic resonance image revealed abnormal enhancement in nodules of the right occipital lobe with a history of suspected metastases and a right cerebellar lesion without abnormal enhancement (**B**). An enhanced chest computed tomography scan showed no significant change compared to the original film (**C**).





**Figure 5** A brain magnetic resonance image and an enhanced abdominal computed tomography showed no significant change from the previous month.

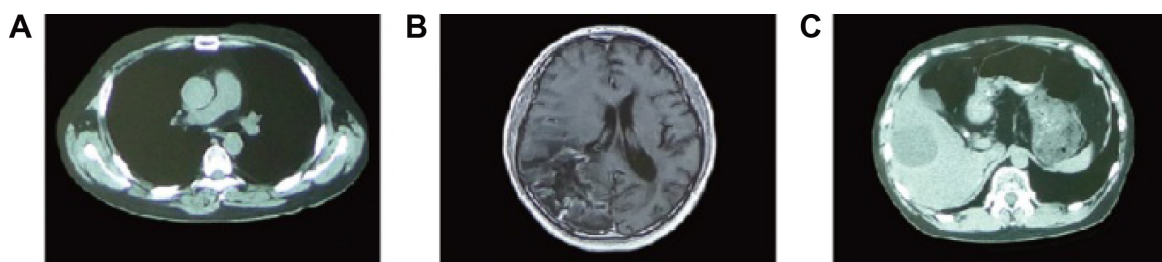
**Notes:** An enhanced abdominal computed tomography scan revealing multiple liver lesions and right adrenal metastases (A, C). A brain magnetic resonance image showed no significant change from the previous month (B).

might be optimal. Although previous Phase III studies in unselected populations showed that the combination of chemotherapy and erlotinib did not improve survival compared with chemotherapy alone,<sup>23,24</sup> sequential intercalated combination regimens of chemotherapy and erlotinib (the First-line Asian Sequential Tarceva and Chemotherapy Trial) significantly improved response and progression-free survival rates, especially in patients with adenocarcinoma.<sup>27</sup>

Our patient with untreated stage IIIB NSCLC received six cycles of paclitaxel and dicycloplatin. During the subsequent follow-up, the patient attained disease control, defined as a CR or a PR according to the response evaluation criteria in solid tumors (RECIST).<sup>28</sup> Pemetrexed disodium and cisplatin therapy was administered after the confirmation of PD according to the RECIST guidelines.<sup>28</sup> This regimen was supplemented with WBRT and shrinking field cranial irradiation. Maintenance therapy with erlotinib was initiated immediately after attaining disease control using the appropriate traditional first-line chemotherapy. In the subsequent follow-up period, the emergence of new metastases and significant growth of the primary lesion indicated PD according to the RECIST guidelines.<sup>28</sup> At that time, the patient was treated with traditional docetaxel and carboplatin chemotherapy. Thus, a sequential intercalated combination regimen of chemotherapy and erlotinib is a treatment option for patients with advanced NSCLC. When a patient experiences rapid

NSCLC progression, such as PD according to the RECIST guidelines,<sup>28</sup> we recommend first-line chemotherapy. When a patient is stable (CR, PR, or SD according to the RECIST guidelines<sup>28</sup>) or is experiencing slow progression (some cases of PD), we propose that erlotinib maintenance therapy should be administered.

Most studies of EGFR TKIs have focused on patients with specific characteristics (eg, sex, smoking status, and histology) and activating EGFR mutations. Therefore, many studies have focused on patients with characteristics associated with the presence of activating EGFR mutations, especially those patients with histological evidence of adenocarcinoma. We did not perform EGFR mutation testing in this study because the majority of each biopsy specimen was used for pathologic testing and because of the associated cost and patient intolerance of this testing. However, some patients with lung SCC derive a clinical benefit from EGFR TKIs. In 2006, Achille et al reported a case of a white male former smoker with advanced lung SCC who responded to erlotinib.<sup>29</sup> No EGFR mutations were found in that patient's tumor tissue. The frequency of EGFR mutations is much lower in lung SCC patients and is reported to be between 0% and 5%.<sup>30-34</sup> The largest lung SCC study to date was conducted by Miyamae et al;<sup>31</sup> EGFR mutations were detected in 3.4% of the 87 lung SCC specimens by using SmartAmp2 and peptide nucleic acid-enriched sequencing methods. The



**Figure 6** Imaging findings after the patient received maintenance therapy with oral gefitinib.

**Notes:** A brain magnetic resonance image and an enhanced abdominal computed tomography scan shown in a stable disease (B, C). An enhanced chest computed tomography scan showed no significant change compared to the original film (A).

current case did not appear to meet any of the suggested criteria for EGFR TKI therapy. EGFR mutation is a powerful predictor of the treatment response to EGFR TKIs.<sup>2,3,35–38</sup> In the BR.21 study,<sup>39</sup> patients harboring an EGFR mutation had a 23% reduced risk of death following erlotinib treatment compared with placebo (hazard ratio [HR]: 0.77). As stated in the review by Sun et al, 25% of lung cancers are not attributable to smoking, and a high proportion of Asian women are never-smokers but still develop lung cancer.<sup>39</sup> In the Japanese cohort examined by Kawaguchi et al, 36.2% of the female lung SCC patients were never-smokers (n=991).<sup>40</sup> Several risk factors such as environmental tobacco smoke, cooking oil vapors, and wood or coal burning are associated with lung cancer in never-smokers, and exposure to these risk factors is also common among Chinese men. Due to the retrospective nature of the present study, evaluating whether these factors contributed to our patient's disease is difficult.<sup>41,42</sup>

Although the mechanisms by which gefitinib and erlotinib inhibit EGFR function are similar, whether they possess comparative efficacy as a salvage therapy for NSCLC remains controversial.<sup>43</sup> A series of case studies reported objective responses or SD in certain patients who received erlotinib after failing treatment with gefitinib for advanced NSCLC.<sup>44–47</sup> However, two Phase II studies of erlotinib in such patients reported overall response rates of only 4%–10%.<sup>48,49</sup> Erlotinib exhibited remarkable efficacy in combination with chemotherapy in NSCLC patients with brain metastases.<sup>49–51</sup> EGFR TKIs exhibit excellent penetration of the blood–brain barrier because of their chemical structure and low molecular weight. In 2003, Cappuzzo et al<sup>49</sup> first reported one CR and three PRs after 3 months of single-agent gefitinib treatment in four NSCLC patients with pretreated brain metastases. Furthermore, a multi-institutional Phase II study demonstrated that the overall survival of patients receiving WBRT with concurrent erlotinib therapy for the treatment of NSCLC was longer than that observed in historical controls and that this therapy particularly benefitted patients with EGFR mutations.<sup>21</sup> Moreover, in our case, a significantly different response to gefitinib therapy was observed after attaining SD in response to erlotinib therapy and chemotherapy. However, we could not ascertain the mechanisms underlying the effectiveness of gefitinib in this case. In vitro studies indicated that the common mechanisms underlying TKI resistance (T790M and mesenchymal to epithelial transition factor [MET] amplification) were not inhibited by clinically achievable doses of gefitinib or erlotinib.<sup>52,53</sup> Secondary T790M mutation and MET amplification have been commonly described as the mechanisms underlying acquired resistance to EGFR

TKIs.<sup>52,53</sup> If tumor progression occurs in patients with erlotinib-responsive NSCLC harboring EGFR mutations, the tumor cells have a high probability of becoming cross-resistant to gefitinib. However, other secondary mutations such as L747S and E884K have also been described; these mutations may result in differential responses to gefitinib and erlotinib.<sup>54</sup> According to experimental studies, some irreversible and second-generation EGFR inhibitors can overcome the resistance induced by secondary T790M mutations.<sup>52,55,56</sup> Currently, irreversible EGFR inhibitors and anti-MET therapeutics are being developed for the treatment of NSCLC. The results of clinical trials will determine whether these agents can be used to treat patients with acquired resistance to EGFR TKIs.<sup>57,58</sup>

## Conclusion

For patients with advanced NSCLC, sequential intercalated combination regimens of chemotherapy and erlotinib could be considered. An assessment of concurrent erlotinib and radiation therapy for the initial treatment of brain metastases from NSCLC demonstrated that this combination was safe and well tolerated. However, these findings must be interpreted cautiously because they were only observed in one case and because a randomized, controlled trial has yet to be performed. Larger prospective, randomized clinical trials are needed to validate our findings and confirm these hypotheses.

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## Disclosure

The authors report no conflicts of interest in this work.

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