Perspective

Current progress and outcomes of clinical trials on using epidermal growth factor receptor-tyrosine kinase inhibitor therapy in non-small cell lung cancer patients with brain metastases

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Received 1 September 2017
Available online 12 December 2017

Abstract

Non-small cell lung cancer (NSCLC) continues to be one of the major causes of cancer-related deaths worldwide, and brain metastases are the major cause of death in NSCLC patients. With recent advances in understanding the underlying molecular mechanism of NSCLC development and progression, mutations in epidermal growth factor receptor (EGFR) have been recognized as a key predictor of therapeutic sensitivity to EGFR tyrosine kinase inhibitors (TKIs). Using EGFR-TKI alone or in combination with standard treatments such as whole-brain radiotherapy and surgery has been an effective strategy for the management of brain metastasis. Particularly, a newer generation of EGFR-TKIs, including osimertinib and AZD3759, has been developed. These new EGFR-TKIs can cross the blood—brain barrier and potentially treat EGFR-TKI resistance and improve prognosis. In this article, current progress and outcomes of clinical trials on the use of EGFR-TKIs for treating NSCLC patients with brain metastasis will be reviewed.

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Keywords: Non-small cell lung cancer; Brain metastases; Epidermal growth factor receptor mutation; Tyrosine kinase inhibitors; Therapeutic outcomes

Introduction

Non-small cell lung cancer (NSCLC) is one of the major causes of cancer-related deaths in the world. As the disease has an insidious onset, many NSCLC patients were diagnosed during stage III–IV with lymph node or distal metastases.1,2 Brain metastasis refers to cancer cells spreading to the brain parenchyma, meninges, cranial nerves, and intracranial vessels, which leads to acute deterioration of the health status and impairment of the quality of life of the patients. In
NSCLC patients, approximately 25%—40% of patients will eventually develop brain metastases, which usually occur 2 years after diagnosis of the primary tumor. Even in non-metastatic primary NSCLC patients, approximately 9% will develop brain metastases.

Clinical studies have shown that after the occurrence of brain metastases in NSCLC patients, their survival time will be significantly shortened, and if no corresponding treatment is given, the median survival period is 1—2 months. Epidermal growth factor receptor (EGFR) mutations are believed to be factors independent of age, physical status, and extracranial disease; additionally, EGFR mutations are an independent risk factor affecting the survival time of NSCLC patients with brain metastases. When compared to patients with wild-type EGFR, those with EGFR mutations have a significantly longer median survival time. However, another study showed no statistical differences in the incidence of brain metastases between patients with EGFR mutations and wild-type EGFR, and the brain metastases had no significant effect on the median survival time.

Currently, the treatment methods for NSCLC with brain metastases mainly include surgery, radiotherapy (such as whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS)), and chemotherapy. Surgical resection of brain metastases alone can effectively alleviate tumor compression, but with relatively higher postoperative local intracranial recurrence rate. Qin et al. analyzed that the mean median survival time of the patients was 12.7 months in surgery group and 14.85 months in SRS group, respectively. The 1-, 2- and 5-year overall survival (OS) rates of the patients were 59%, 33% and 19% in surgery group, and 62%, 33% and 14% in SRS group, respectively. WBRT or SRS can significantly increase the survival time; however, patients cannot usually tolerate the related complications and adverse reactions. Furthermore, the majority of chemotherapy drugs cannot penetrate the blood—brain barrier (BBB) to enter into tumor tissues, which limits the therapeutic outcomes of systemic chemotherapy in treating NSCLC patients with brain metastases. Epidermal growth factor receptor-tyrosine kinase inhibitors (TKIs) have small molecules used in targeted therapy, and a certain proportion can penetrate the BBB, showing therapeutic effects in patients with NSCLC brain metastases with EGFR mutations. Considering that NSCLC patients with EGFR-sensitive mutations are more prone to brain metastases compared with those with wild-type EGFR, TKI treatment for the former should be a good option. This article describes the current treatment progress of TKI treatment for NSCLC patients with brain metastases.

Theoretical foundation of TKI treatment for NSCLC brain metastases

The BBB is composed of endothelial cells, astrocytes, pericytes, and multiple carrier proteins and is one of the internal barriers participating in the innate immunity of the body. The BBB can block pathogens and other macromolecules from entering into the brain tissues and ventricles from the bloodstream. It is generally believed that only lipophilic small molecules (Mr < 400 Da) can penetrate the normal BBB through diffusion and other transport mechanisms. The majority of chemotherapeutic drugs are hydrophilic macromolecules that cannot penetrate the BBB without the carrier proteins. Furthermore, many multiple drug-resistant efflux pumps exist on the capillary surface of the BBB, such as P-glycoprotein and multidrug-resistant-associated proteins, which can further limit the entry of drugs into the brain tissues.

Drugs used in TKI-targeted therapy have characteristically small molecules, such as gefitinib (446.9 Da) and erlotinib (394 Da). Experiments with the multidrug-resistant PC-6/PTX lung cancer cells showed that gefitinib can directly interact with over-expressed P-glycoprotein and inhibit its drug-efflux function. Therefore, some proportion of TKIs can penetrate the BBB. Clinical studies also found that the BBB penetration rate of erlotinib in NSCLC patients with brain metastases is (4.4 ± 3.2)%. With increasing doses of TKIs used, their corresponding concentrations in the cerebrospinal fluid (CSF) also increase. Therefore, in patients with brain metastases who do not respond to low concentrations of TKIs, increasing drug concentrations can result in effective disease control. In addition, experiments using animal models also showed that when the integrity of the BBB is disrupted, such as when the diameter of the brain metastases is >0.25 mm, its permeability will increase. Wang et al. analyzed the CSF of 22 NSCLC patients treated with gefitinib and found that its penetration rate was significantly higher in patients with brain metastases than in patients without brain metastases (1.5% vs. 0.9%, P = 0.010). This shows that the occurrence of brain metastases may affect the structure of the BBB and increase drug permeability, increasing the concentrations of TKIs in the CSF,
thereby becoming more effective in preventing the growth of intracranial tumors.

TKIs are enriched in tumor tissues. McKillop et al found in mouse xenograft models that gefitinib concentrations were mainly higher in tumor and skin tissues and lower in the CSF and blood. Pharmacokinetic analysis of mouse models with lung cancer with brain metastases showed that gefitinib concentrations in the brain tissues were dose-dependent. Approximately 5 hours after administering gefitinib, an absorption peak was reached and the concentration in the brain tissues was far higher than that in CSF (200 mg/kg dose, area under curve (AUC)total brain/AUCtotal blood = 0.7; AUCCSF/AUCfree blood = 0.18). This shows that gefitinib has some specificity toward tumors, and therefore, may inhibit the incidence of drug-related adverse reactions. This may also further suggest the possible mechanisms by which gefitinib may be an effective treatment for NSCLC brain metastases.

**TKI monotherapy in NSCLC brain metastases**

*First-generation EGFR-TKIs*

First-generation EGFR-TKIs such as gefitinib, erlotinib, and other monotherapies are mainly used to treat asymptomatic NSCLC brain metastases and are therapeutically effective. In 2003, Villano et al reported the first case of successful treatment using gefitinib. After treating with routine doses of gefitinib for 5 months, the size of brain metastasis was significantly decreased. Hotta et al conducted a retrospective analysis of 57 NSCLC patients who underwent gefitinib treatment and found that in 14 patients with brain metastases, 1 had complete response, 5 had partial response, and 8 had stable condition. In 2009, Kim et al reported the therapeutic efficacy of gefitinib or erlotinib monotherapy as the first-line therapy. In this study, 23 NSCLC patients with asymptomatic brain metastases were treated with gefitinib or erlotinib, and results showed that the partial systemic response rate was 69.6%, 13.0% had stable condition, and 17.4% had progressive disease. Intracranial tumor responses were observed in 17 patients (73.9%). The median progression-free survival (PFS) and OS time of the patients were 7.1 and 18.8 months, respectively.

Clinical research data show that the therapeutic efficacy of first-generation EGFR-TKIs is higher in NSCLC patients with brain metastases who have EGFR-sensitive mutations. In analyzing multiple case reports, these patients who were treated with gefitinib (250 mg/day) obtained complete responses within 1–5 months. Results of a phase II clinical trial also found that compared with patients with wild-type EGFR, these patients had higher response rates after treating with gefitinib or erlotinib. Park et al conducted a study on 23 NSCLC patients with brain metastases who had exon 19 or 21 EGFR mutations as study subjects. A prospective analysis revealed that the partial response rate of patients to gefitinib or erlotinib monotherapy was 82%, and 11% of patients had stable condition, while only 7% had progressive disease. The median PFS and OS of the patients were 6.6 and 15.9 months, respectively. Porta et al conducted a retrospective analysis of 69 NSCLC patients with brain metastases who had undergone erlotinib treatment; 17 of them had EGFR exon 19 or 21 mutation. The objective response rate was 82.4%, median time to progression was 11.7 months, and median OS was 12.9 months. In 52 patients with unknown EGFR status or wild-type EGFR, the objective response rate was 0, median time to progression was 5.8 months, and median OS was 3.1 months. A prospective phase III clinical trial conducted in Japan obtained similar results: NSCLC patients with brain metastases who had EGFR mutations showed an overall response rate of 87.8% to gefitinib monotherapy; 9.8% of patients had stable condition and 2.4% had progressive disease. This study also found that patients with EGFR exon 19 deletion or exon 21 L858R mutation had different prognosis status. Among these patients, the median PFS (17.5 vs. 10.2 months) and OS (30.3 vs. 19.8 months) in patients with exon 19 mutation were significantly longer than in patients with exon 21 mutation. However, another study found that the disease control rates in patients with exon 19 deletion and exon 21 L858R mutations were 88.89% (32/36) and 89.74% (35/39), respectively, and the median PFS was 10.4 and 8.6 months, respectively, but these differences were not statistically significant.

The CSF penetration rate and concentrations of erlotinib are higher than that of gefitinib; however, current research data showed no differences in the prognosis of the two drugs. The results of a study by Togashi et al showed that CSF penetration rates of gefitinib and erlotinib were (1.13 ± 0.36) % and (2.77 ± 0.45) %, respectively, and CSF concentrations were (3.7 ± 1.9) ng/ml and (28.7 ± 16.8) ng/ml, respectively. The CSF penetration rate and concentrations of erlotinib were significantly higher than those of gefitinib; however, the difference in central nervous system response rates between the two groups of NSCLC patients with brain metastases who were
positive for EGFR mutations was insignificant (1/3 vs. 4/7). Similarly, Zhang et al. conducted a retrospective study comparing the therapeutic efficacy of gefitinib and erlotinib in treating NSCLC patients with brain metastases who were positive for EGFR mutations. The results of the study showed that among the 39 patients treated with gefitinib, the disease control rate was 89.74% (35/39; 6 had complete responses, 12 partial responses, 17 stable condition), and the median PFS was 9.5 months. Among the 42 patients treated with erlotinib, the disease control rate was 90.48% (38/42; 4 had complete responses, 15 partial responses, and 19 stable condition), and the median PFS was 9.0 months. Differences between the two drugs in treating NSCLC patients with brain metastases who had EGFR mutations were insignificant. This may be due to the fact that gefitinib has significantly higher concentrations in the brain tissues than in the CSF. Considering that gefitinib is more tolerable than erlotinib, it is therefore the recommended treatment for NSCLC patients with brain metastases who have EGFR mutations.

Icotinib is a highly selective EGFR-TKI and the first new anti-cancer small molecule drug for targeted therapy that had completely independent intellectual property rights in China. Icotinib shows similar chemical structure, molecular effector mechanisms, and therapeutic efficacy as gefitinib and erlotinib, but is safer and more suitable in treating late-stage NSCLC patients. In 2016, the World Conference on Lung Cancer reported a comparative study of icotinib or whole-brain irradiation (WBI) to treat late-stage NSCLC patients with brain metastases who have EGFR mutations. This study enrolled a total of 176 NSCLC patients. Among these patients, 16.5% had symptomatic brain metastases. The patients were randomized into a WBI + chemotherapy group (n = 91) or icotinib group (n = 85). Compared with WBI + chemotherapy, icotinib significantly improved the median intracranial PFS [hazard ratio (HR) = 0.56], which were 4.8 and 10.0 months, respectively. Icotinib also showed better PFS compared with WBI + chemotherapy, which was 6.8 vs. 3.4 months. However, no significant difference in OS between the two groups (18.0 vs. 20.5 months) was observed. Compared with WBI + chemotherapy, the intracranial objective response rate of icotinib significantly improved, which was 40.9% and 67.1%, respectively. The overall response rates were 11.1% and 55.0%, respectively. With regard to safety, the incidence of Grade ≥3 adverse events assessed by the investigator was 8.2% (n = 7), while that of the WBI + chemotherapy group was 26.2% (n = 28). The commonly observed adverse events in the icotinib group were elevated liver transaminase and rashes, while that of the WBI + chemotherapy group was hematologic toxicity. These results suggest that icotinib can be a treatment option for late-stage NSCLC patients with accompanying brain metastases who have EGFR mutations.

**Second-generation EGFR-TKIs**

Generally, NSCLC patients who show therapeutic effectiveness with first-generation EGFR-TKIs will develop secondary drug resistance after 9–12 months. The T790M mutation is the major mechanism that causes drug resistance to first-generation EGFR-TKIs. Second-generation EGFR-TKIs such as afatinib are effective against the T790M drug-resistant mutation and in treating NSCLC patients with brain metastases. Hoffknecht et al. conducted a study on late-stage NSCLC patients who experienced treatment failure with gefitinib or erlotinib and were given afatinib. In 100 patients with accompanying brain metastases, the median time to treatment failure was 3.6 months, and differences between patients with and without brain metastases were insignificant. In 31 patients with evaluable therapeutic efficacy, the disease control rate was 81% (25/31, no patient had a complete response, 13 partial responses, and 12 stable condition). Therefore, the majority of NSCLC patients with brain metastases who experienced treatment failure with first-generation EGFR-TKIs can benefit from afatinib treatment.

**Newer-generation EGFR-TKIs**

**Osimertinib**

Osimertinib (Tagrisso) is an irreversible inhibitor against EGFRs and is clearly effective in treating patients with T790M drug-resistant mutations. Previous clinical studies showed that osimertinib can effectively penetrate the BBB of the mouse and cynomolgus monkey as compared with gefitinib, afatinib, and other EGFR-TKIs. The concentration of osimertinib in mouse brain tissues is 5–25 times as high as that in the plasma, with the same levels of active AZ5104 metabolite. Treatment with 5 mg·kg⁻¹·d⁻¹ of osimertinib significantly inhibits the growth of brain tumors. These results show that osimertinib can potentially treat NSCLC brain metastases. Reichegger et al. reported a NSCLC patient with brain metastases who experienced treatment failure with radiotherapy...
and surgery and was positive for the \textit{EGFR} T790M mutation. After treating the patient with osimertinib, the intracrani al lesions rapidly responded. The results of a phase I clinical trial showed that when 20–240 mg of osimertinib was given to patients with \textit{EGFR}-sensitive and \textit{EGFR} T790M drug-resistant mutations, the overall response and disease-control rates were 64\% and 96\%, respectively. The major adverse reactions included diarrhea (30\%), rash (24\%), and nausea (17\%). The majority of adverse reactions were Common Terminology Criteria Adverse Events (CTCAE) Grade 1, and 16\% of patients showed Grade 3/4 adverse reactions without dose-dependent toxicity.\textsuperscript{40} The pooled phase II study of AURA and AURA 2 enrolled 411 \textit{EGFR}-positive NSCLC patients; 39\% of them had brain metastases. The results of the study revealed that the systemic response rate of all enrolled patients treated with osimertinib was 61\%. The overall systemic response rate in patients with brain metastases was 56.0\%.\textsuperscript{41}

Vallée et al.\textsuperscript{12} conducted a study on a late-stage NSCLC patient who was given AZD9291 after the treatment failure with cisplatin-pemetrexed or gefitinib. The results of the study revealed that CT scan and clinical evaluation confirmed a stable disease after 5 months of treatment with AZD9291. Mok et al.\textsuperscript{43} reported the therapeutic efficacy of osimertinib as the first-line therapy. In this study, 144 patients with T790M-positive advanced NSCLC (those with CNS metastases) were enrolled, and the results showed that the median duration of PFS was longer among patients receiving osimertinib than among those receiving platinum therapy plus pemetrexed [8.5 months vs. 4.2 months; \textit{HR}, 0.32; 95\% confidence interval (CI), 0.21 to 0.49].

AZD3579

AZD3579 is an \textit{EGFR} inhibitor designed to effectively penetrate the BBB to treat brain metastases. AZD3579 has high passive permeability (29.5 $\times$ 10$^{-6}$ cm/sec) and can effectively penetrate the BBB.\textsuperscript{44} In animal tumor models, AZD3579 was found to block tumor progression and increase the survival rate. In four NSCLC patients with brain metastases treated with 50/100 mg of AZD3579 twice a day, one had partial response and one had stable condition. Their CSF concentrations were 7.7 nmol/L and 6 nmol/L, respectively.

In 2017, the results of a phase I clinical trial on the latest use of AZD3579 to treat NSCLC brain metastases and leptomeningeal metastases were reported.\textsuperscript{45} A total of 67 patients were enrolled and 29 to the dose-escalation phase and 38 to the dose-expansion phase. In the dose-escalation phase, of 21 patients with brain metastases, 11 (52\%) had tumor shrinkage, with 3 (14\%) showing confirmed partial responses. In the dose-expansion phase, of 18 patients with brain metastases who had never been treated with \textit{EGFR}-TKIs, about 15 (83\%) of patients had a confirmed objective responses, and 16 (89\%) had confirmed diseases control. These results suggest that AZD3579 is clearly effective in treating NSCLC patients with brain metastases. Currently, phase II studies on patients with brain and leptomeningeal metastases are still ongoing.

Using TKIs combined with chemoradiotherapy in treating NSCLC brain metastases

Currently, the majority of researchers believed that local radiotherapy or WBRT will result in increased permeability of the BBB,\textsuperscript{46–49} and TKIs are known to decrease the resistance of wild-type \textit{EGFR} NSCLC cells to radiotherapy and increase the sensitivity of \textit{EGFR}-mutant cells to radiotherapy.\textsuperscript{50} Gow et al.\textsuperscript{51} conducted a study on 63 lung adenocarcinoma patients with brain metastases who had undergone WBRT and found that \textit{EGFR} mutations [odds ratio (OR) = 4.46, \textit{P} = 0.029] and use of TKIs (\textit{OR} = 3.8, \textit{P} = 0.034) are independent factors affecting WBRT response rates, which were higher in patients with \textit{EGFR} mutations than those with wild-type \textit{EGFR} (54\% vs. 24\%, \textit{P} = 0.045). Patients who simultaneously used EGFR-TKI had a higher WBRT response rates than those who did not (67\% vs. 39\%, \textit{P} = 0.038). A retrospective study on 282 NSCLC patients with brain metastases showed that patients who used combined TKI treatment (\textit{n} = 104) had a significantly longer OS (31.9 vs. 17 months, \textit{P} < 0.0001) and PFS for intracranial disease (19.8 vs. 12 months, \textit{P} < 0.0001) than those who had undergone conventional treatment (WBRT, SRS, or surgery, or a combination of these) (\textit{n} = 178) alone.\textsuperscript{52} Therefore, many researchers believed that radiotherapy and TKI therapy have a synergistic effect on the cell lines with \textit{EGFR} mutations and proposed that the two treatments can be used as a combined treatment for NSCLC patients with brain metastases who have \textit{EGFR} mutations.\textsuperscript{53,54} Currently, many clinical studies combined the use of erlotinib and radiotherapy. Results of a phase II clinical trial showed that when \textit{EGFR} status is not considered, 40 patients who had undergone WBRT and erlotinib had...
a median survival time of 11.8 months. Among the 17 patients with known \textit{EGFR} status, consisting of 8 with wild-type \textit{EGFR} and 9 with \textit{EGFR} mutations, the median survival time was 9.3 and 19.1 months, respectively. In another phase II clinical trial on 54 NSCLC patients with brain metastases, the WBRT and erlotinib group \((n = 23, 11 \text{ with } \textit{EGFR} \text{ mutations})\) had longer PFS and OS compared with the WBRT group \((n = 31, \text{ \textit{EGFR} status unknown})\). However, in a phase III clinical trial comparing erlotinib and temozolomide combined with WBRT and SRS against WBRT and SRS alone, the survival time of patients in the combination therapy group was shorter. In addition, Grades 3–5 toxicity induced by the combined treatment was more severe. In another study on 80 NSCLC patients with brain metastases (wild-type \textit{EGFR}), PFS and OS were unimproved in the group treated with WBRT and erlotinib when compared with the group treated with WBRT and placebo.

In a phase II clinical trial on a Chinese population, 21 NSCLC patients with brain metastases had undergone WBRT and gefitinib treatment. It was found that four (19%) patients had complete responses, 13 (62%) had partial responses, 3 had stable condition, and only 1 had progressive disease. The PFS and OS were 10 and 13 months, respectively. Zeng et al conducted a retrospective study including 90 NSCLC patients with brain metastases. Among these patients, 45 were given gefitinib (250 mg/d) and 45 gefitinib in combination with WBRT (40 Gy/20 f/4 w), with a median interval of 15 days between gefitinib treatment and WBRT. The results showed significant differences in the objective response rate of brain metastases (64.4% vs. 26.7%, \(P < 0.001\)), disease control rate (71.1% vs. 42.2%, \(P = 0.006\)), median time to progression of brain metastases (10.6 vs. 6.6 months, \(P < 0.001\)), and OS (23.4 vs. 14.8 months, \(P = 0.002\)) between the combination treatment and the gefitinib monotherapy groups. A few studies also showed that NSCLC patients with brain metastases who underwent radiotherapy in combination with TKI had poor treatment outcomes and did not significantly affect the prognosis of the patients. In a phase II clinical trial, 59 NSCLC patients with brain metastases were randomizd to WBRT and gefitinib group or WBRT and temozolomide group. Results showed that even though patients had good tolerability toward gefitinib, the median survival time of the two groups were 6.3 and 4.9 months, respectively. Byeon et al conducted a retrospective study and found no significant differences in intracranial PFS (16.6 vs. 21.0 months, \(P = 0.492\)), extracranial PFS (12.9 vs. 15.0 months, \(P = 0.770\)) and 3-year survival rates (71.9 vs. 68.2%, \(P = 0.675\)), when radiotherapy was used with EGFR-TKIs in treating NSCLC patients with brain metastases compared with radiotherapy alone. However, results of a meta-analysis study on radiotherapy with TKIs in treating NSCLC patients with brain metastases found that those who underwent combination treatment had better response rates [risk ratio (RR) = 1.48, 95% CI: 1.12–1.96, \(P = 0.005\)] and disease control rates (\(RR = 1.29, 95\% CI: 1.02–1.60, P = 0.035\)) compared with those treated with radiotherapy alone. Patients in the former group also experienced benefits in time to central nervous system progression (\(HR = 0.56, 95\% CI: 0.33–0.80, P < 0.001\)) and median OS (\(HR = 0.58, 95\% CI: 0.42–0.74, P < 0.001\)).

**Treatment options after a failed brain metastasis therapy**

NSCLC patients with brain metastases may also experience extracranial metastases during TKI treatment, and brain metastases that were effectively controlled may progress again; therefore, these two scenarios can be considered as failure of TKI treatment. Current research indicates that the major causes of TKI treatment failure in brain metastases are as follows: low concentrations of TKIs in the CSF, resulting in inability to elicit its therapeutic effects, and development of TKI drug resistance.

After a failed treatment, Jackman et al used large doses of gefitinib on a NSCLC patient with brain metastases to increase gefitinib concentrations in the brain tissues. The gefitinib dose was increased from 500 mg/d to 750 mg/d and then to 1000 mg/d over a period of 10 weeks. The carcinomatous meningitis improved both radiographically and cytophotologically. However, the gefitinib dose was decreased to 500 mg due to somnolence and rising hepatic transaminases. Two months later, cytology from a repeat lumbar puncture documented recurrent leptomeningeal metastases and the gefitinib dosage was then increased to 1250 mg daily for 2 weeks. Despite these changes, the patient’s condition continued to deteriorate. Grommes et al retrospectively studied patients with \textit{EGFR} mutant lung cancer treated with pulsatile erlotinib for CNS metastases that developed or worsened following prior therapy with an EGFR-TKI at standard dosing. Erlotinib was administered as monotherapy to all patients at a median dose of 1500 mg once per week. Best CNS radiographic response was partial in 67% (6/9, including 2 with isolated leptomeningeal metastases), stable disease in 11% (1/9), and progressive disease in 22% (2/9). Median time to CNS progression was 2.7
months and median OS was 12 months. Shukuya et al. reported 17 NSCLC patients who developed isolated brain metastases after obtaining benefits from EGFR-TKI treatment. They subsequently terminated TKI treatment and treated these patients with WBRT or SRS; TKI treatment was continued after the radiotherapy. Results showed that overall response and disease control rates were 41% and 76%, respectively. The median PFS, extracranial PFS and the median OS were 80, 171, and 403 days, respectively. Therefore, they believed that this method is more effective in treating patients with isolated metastatic lesions.

**Conclusion and future prospects**

With the emergence of EGFR-TKIs, the survival rate of NSCLC patients with brain metastases has improved considerably, especially of those with *EGFR* mutations. The new-generation EGFR-TKIs such as osimertinib can better overcome the limitations of the BBB to targeted macromolecular drugs and are therefore highly effective in treating intracranial tumors. The therapeutic efficacy of these drugs on patients with the T790M drug-resistant mutation is clear. In addition, the combination of EGFR-TKI and brain radiotherapy may be one of the strategies with the greatest potential in treating intracranial metastases in NSCLC patients.

**Conflicts of interest**

The authors declare that they have no conflicts of interest.

**References**

1. Kocher F, Lunger F, Seeber A, et al. Incidental diagnosis of asymptomatic non-small-cell lung cancer: a registry-based analysis. *Clin Lung Cancer*. 2016;17:62–67. e1.
2. Walters S, Marine C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004–2007. *Thorax*. 2013;68:551–564.
3. Dempke WC, Edvardsen K, Lu S, Reinmuth N, Reck M, Inoue A. Brain metastases in NSCLC — are TKIs changing the treatment strategy? *Anticancer Res*. 2015;35:5797–5806.
4. Goncalves PH, Peterson SL, Vigneau FD, et al. Risk of brain metastases in patients with nonmetastatic lung cancer: analysis of the metropolitan detroit surveillance, epidemiology, and end results (SEER) data. *Cancer*. 2016;122:1921–1927.
5. Noronha V, Joshi A, Gokarn A, et al. The importance of brain metastasis in EGFR mutation positive NSCLC patients. *Chemother Res Pract*. 2014;2014:856156.
6. Zimm S, Wampler GL, Stablein D, Hazra T, Young HF. Intra-cerebral metastases in solid-tumor patients: natural history and results of treatment. *Cancer*. 1981;48:384–394.
7. Eichler AF, Kahle KT, Wang DL, et al. EGFR mutation status and survival after diagnosis of brain metastasis in non-small cell lung cancer. *Neuro Oncol*. 2010;12:1193–1199.
8. Hendriks LE, Smit EF, Vosse BA, et al. EGFR mutated non-small cell lung cancer patients: more prone to development of bone and brain metastases? *Lung Cancer*. 2014;84:86–91.
9. Qin H, Wang C, Jiang Y, Zhang X, Zhang Y, 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. Park SJ, Kim HT, Lee DH, 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*. 2012;77:556–560.
11. Porta R, Sánchez-Torre JM, Paz-Ares L, et al. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. *Eur Respir J*. 2011;37:624–631.
12. Hsu F, De Caluwe A, Anderson D, Nichol A, Toriumi T, Ho C. EGFR mutation status on brain metastases from non-small cell lung cancer. *Lung Cancer*. 2016;96:101–107.
13. Tajes M, Ramos-Fernández E, Weng-Jiang X, et al. The blood-brain barrier: structure, function and therapeutic approaches to cross it. *Mol Membr Biol*. 2014;31:152–167.
14. Wilhelm I, Molnár J, Fazakas C, Haskó J, Krizbai IA. Role of the blood-brain barrier in the formation of brain metastases. *Int J Mol Sci*. 2013;14:1383–1411.
15. Demeule M, Régina A, Jodoïn J, et al. Drug transport to the brain: key roles for the eflux pump P-glycoprotein in the blood-brain barrier. *Vasc Pharmacol*. 2002;38:339–348.
16. Kitazaki T, Oka M, Nakamura Y, et al. Gefitinib, an EGFR tyrosine kinase inhibitor, directly inhibits the function of P-glycoprotein in multidrug resistant cancer cells. *Lung Cancer*. 2005;49:337–343.
17. Deng Y, Feng W, Wu J, et al. The concentration of erlotinib in the cerebrospinal fluid of patients with brain metastasis from non-small-cell lung cancer. *Mol Clin Oncol*. 2014;2:116–120.
18. Masuda T, Hattori N, Hamada A, et al. Erlotinib efficacy and cerebrospinal fluid concentration in patients with lung adenocarcinoma developing leptomeningeal metastases during gefitinib therapy. *Cancer Chemother Pharmacol*. 2011;67:1465–1469.
19. Togashi Y, Masago K, Fukudo M, et al. Efficacy of increased-dose erlotinib for central nervous system metastases in non-small cell lung cancer patients with epidermal growth factor receptor mutation. *Cancer Chemother Pharmacol*. 2011;68:1089–1092.
20. Clarke JL, Pao W, Wu N, Miller VA, 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.
21. Grommes C, Oxnard GR, Kris MG, et al. “Pulsatile” high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. *Neuro Oncol*. 2011;13:1364–1369.
22. Fidler IJ, Yano S, Zhang RD, Fujimaki T, Bucana CD. The seed and soil hypothesis: vascularisation and brain metastases. *Eur Respir J*. 2011;37:624–631.
23. Wang M, Jing Z, Minjiang C. Cerebral penetration of gefitinib in patients with lung adenocarcinoma. In: *ASCO Annual Meeting Proceedings*. 2011;7608.
24. Chen Y, Wang M, Zhong W, Zhao J. Pharmacokinetic and pharmacodynamic study of Gefitinib in a mouse model of non-
small-cell lung carcinoma with brain metastasis. Lung Cancer. 2013;82:313–318.
25. McKillop D, Partridge EA, Kemp JV, et al. Tumor penetration of gefitinib (Iressa), an epidermal growth factor receptor tyrosine kinase inhibitor. Mol Cancer Ther. 2005;4:641–649.
26. Villano JL, Maurer AM, Vokes EE. A case study documenting the anticancer activity of ZD1839 (Iressa) in the brain. Ann Oncol. 2003;14:656–658.
27. Hotta K, Kiu K, Ueoka H, et al. Effect of gefitinib (‘Iressa’, ZD1839) on brain metastases in patients with advanced non-small-cell lung cancer. Lung Cancer. 2004;46:255–261.
28. Kim JE, Lee DH, Choi Y, et al. Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. Lung Cancer. 2009;65:351–354.
29. Chonan M, Narita N, Tominaga T. Total regression of brain metastases in non-small cell lung cancer patients harboring EGFR mutations treated with gefitinib without radiotherapy: two case reports. BMC Res Notes. 2016;9:2.
30. Jung YH, Han CW, Jung YD, Cho YY, Han DJ. Complete remission of brain metastases in non-small cell lung cancer patients harboring an EGFR mutation treated with tyrosine kinase inhibitor without radiotherapy: a report of 3 cases. Case Rep Oncol. 2014;7:149–154.
31. Iuchi T, Shingyoi M, Sakaïda T, et al. 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.
32. Zhang JX, Cai D, Li SY, et al. Clinical comparison of erlotinib and gefitinib in non-small cell lung cancer with brain metastases. Chin J Cancer Prev Treat. 2015;22:285–288.
33. Togashi Y, Masago K, Masuda S, et al. Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. Cancer Chemother Pharmacol. 2012;70:399–405.
34. Zhao Q, Shentu J, Xu N, et al. Phase I study of icotinib hydrochloride (BPI-2009H), an oral EGFR tyrosine kinase inhibitor, in patients with advanced NSCLC and other solid tumors. Lung Cancer. 2011;73:195–202.
35. Wu YL, Yang JJ, Zhou CC, et al. phase III trial comparing WBI and chemotheraphy with icotinib in NSCLC with brain metastases harboring EGFR mutations (CTONG 1201). J Thorac Oncol. 2017;12:S6.
36. Hoffknecht P, Tufman A, Behler T, 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.
37. Ballard P, Yates JW, Yang Z, et al. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. Clin Cancer Res. 2016;22:5130–5140.
38. Kim D, Yang J, Cross D, et al. Preclinical evidence and clinical cases of AZD9291 activity in EGFR-mutant non-small cell lung cancer (NSCLC) brain metastases (BM). Ann Oncol. 2014;25(suppl_4):i152.
39. Reichegger H, Jochum W, Förbs D, Hader C, Früh M. Rapid intracranial response to osimertinib in a patient with epidermal growth factor receptor T790M-positive adenocarcinoma of the lung. Oncol Res Treat. 2016;39:461–463.
40. Janne PA, Ramalingam SS, Yang JCH, et al. Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor-resistant non-small cell lung cancer (NSCLC). J Clin Oncol. 2014;32(15 suppl):8009.
41. Ahn M, Tsai C, Yang J, et al. 3083 AZD9291 activity in patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC) and brain metastases: data from Phase II studies. Eur J Cancer. 2015;51:S625–S626.
42. Vallée A, Audigier-Valette C, Herbreteau G, et al. Rapid clearance of circulating tumor DNA during treatment with AZD9291 of a lung cancer patient presenting the resistance EGFR T790M mutation. Lung Cancer. 2016;91:73–74.
43. Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2017;376:629–640.
44. Kim DW, Yang JCH, Chen K, et al. AZD3759, an EGFR inhibitor with blood brain barrier (BBB) penetration for the treatment of non-small cell lung cancer (NSCLC) with brain metastasis (BM): preclinical evidence and clinical cases. J Clin Oncol. 2015;33(15 suppl):S016.
45. Ahn MJ, Kim DW, Cho BC, et al. Activity and safety of AZD3759 in EGFR-mutant non-small-cell lung cancer with CNS metastases (BLOOM): a phase 1, open-label, dose-escalation and dose-expansion study. Lancet Respir Med. 2017;5:891–902.
46. d’Avella D, Cicciarello R, Albiero F, et al. Quantitative study of blood-brain barrier permeability changes after experimental whole-brain radiation. Neurosurgery. 1992;30:30–34.
47. Qin D, Ma J, Xiao J, Tang Z. Effect of brain irradiation on blood-CSF barrier permeability of chemotherapeutic agents. Ann J Clin Oncol. 1997;20:263–265.
48. Khatri A, Gaber MW, Brundage RC, et al. Effect of radiation on the penetration of irinotecan in rat cerebrospinal fluid. Cancer Chemother Pharmacol. 2011;68:721–731.
49. Zeng YD, Liao H, Qin T, et al. Blood-brain barrier permeability of gefitinib in patients with brain metastases from non-small-cell lung cancer before and during whole brain radiation therapy. Oncotarget. 2015;6:8366–8376.
50. Khalifa J, Amini A, Popat S, Gaspar LE, Fairevé-Finn C. International association for the study of lung cancer advanced radiation technology committee. Brain metastases from NSCLC: radiation therapy in the era of targeted therapies. J Thorac Oncol. 2016;11:1627–1643.
51. Gow CH, Chien CR, Chang YL, et al. Radiotherapy in lung adenocarcinoma with brain metastases: effects of activating epidermal growth factor receptor mutations on clinical response. Clin Cancer Res. 2008;14:162–168.
52. Cai L, Zhu JF, Zhang XW, et al. A comparative analysis of EGFR mutation status in association with the efficacy of TKI in combination with WBRT/SRS/surgery plus chemotherapy in brain metastasis from non-small cell lung cancer. J Neurooncol. 2014;120:423–430.
53. Bokobza SM, Jiang Y, Weber AM, Devery AM, Ryan AJ. Short-course treatment with gefitinib enhances curative potential of radiation therapy in a mouse model of human non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2014;88:947–954.
54. Zhang S, Zheng X, Huang H, et al. Afatinib increases sensitivity to radiation in non-small cell lung cancer cells with acquired EGFR T790M mutation. Oncotarget. 2015;6:5832–5845.
55. Welsh JW, Komaki R, Amini A, 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.
56. Zhuang H, Yuan Z, Wang J, Zhao L, Pang Q, Wang P. Phase II study of whole brain radiotherapy with or without erlotinib in patients with multiple brain metastases from lung adenocarcinoma. Drug Des Devel Ther. 2013;7:1179–1186.

57. Sperduto PW, Wang M, Robins HI, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: radiation Therapy Oncology Group 0320. Int J Radiat Oncol Biol Phys. 2013;85:1312–1318.

58. Lee SM, Lewanski CR, Counsell N, et al. Randomized trial of erlotinib plus whole-brain radiotherapy for NSCLC patients with multiple brain metastases. J Natl Cancer Inst. 2014;106. pii: dju151.

59. Ma S, Xu Y, Deng Q, Yu X. Treatment of brain metastasis from non-small cell lung cancer with whole brain radiotherapy and Gefitinib in a Chinese population. Lung Cancer. 2009;65:198–203.

60. Zeng YD, Zhang L, Liao H, et al. Gefitinib alone or with concomitant whole brain radiotherapy for patients with brain metastasis from non-small-cell lung cancer: a retrospective study. Asian Pac J Cancer Prev. 2012;13:909–914.

61. Pesce GA, Klingbiel D, Ribi K, et al. Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03). Eur J Cancer. 2012;48:377–384.

62. Byeon S, Ham JS, Sun JM, et al. Analysis of the benefit of sequential cranial radiotherapy in patients with EGFR mutant non-small cell lung cancer and brain metastasis. Med Oncol. 2016;33:97.

63. Jiang T, Min W, Li Y, Yue Z, Wu C, Zhou C. Radiotherapy plus EGFR TKIs in non-small cell lung cancer patients with brain metastases: an update meta-analysis. Cancer Med. 2016;5:1055–1065.

64. Jackman DM, Holmes AJ, Lindeman N, 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. 2006;24:4517–4520.

65. Shukuya T, Takahashi T, Naito T, et al. Continuous EGFR-TKIs administration following radiotherapy for non-small cell lung cancer patients with isolated CNS failure. Lung Cancer. 2011;74:457–461.

Edited by Pei-Fang Wei