Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in the Treatment of Epidermal Growth Factor Receptor–Mutant Non–Small Cell Lung Cancer Metastatic to the Brain

Mariam Jamal-Hanjani and James Spicer

Abstract

Brain metastases are a common and devastating consequence of disease progression in patients with non–small cell lung cancer (NSCLC). The epidermal growth factor receptor (EGFR) inhibitors erlotinib and gefitinib have shown efficacy in patients with NSCLC and brain metastases. The cerebrospinal fluid (CSF) exposure to these drugs is a small fraction of the plasma levels achieved with standard doses, but disruption of the blood–brain barrier in the presence of central nervous system metastases is likely to lead to locally increased drug concentration, and dose escalation to boost CSF exposure has documented clinical efficacy. The use of gefitinib and erlotinib in this setting is reviewed here, including evidence from case reports, case series, and single-arm phase II trials. High response rates in the brain are seen in patients with EGFR mutation, or in populations in which this genotype is expected. By contrast, activity in the context of documented wild-type EGFR in disease metastatic to the brain is not common. These drugs may potentiate the effectiveness of radiotherapy to the brain, and their use may also delay development of disease within the brain. Clin Cancer Res; 18(4); 938–44. ©2011 AACR.

Management of Brain Metastases

Surgery

Surgery is a treatment option for patients with oligometastatic disease. Surgery followed by WBRT can significantly reduce the recurrence of brain metastases and improve median survival compared with WBRT alone; this has been shown in prospective randomized clinical trials (6, 7). In patients with multiple brain metastases, there is no evidence to suggest benefit from surgery.

Radiotherapy and stereotactic radiosurgery

The survival of patients treated with WBRT ranges from 4 to 6 months but can be longer depending on several prognostic variables, including functional status, age, sites of disease outside of the brain, and epidermal growth factor receptor (EGFR) mutation status (8–10). Brain metastases often result in significant clinical deterioration in neurologic and neurocognitive function, and approximately half of these patients die as a direct result of progression within the brain (11). WBRT improves symptoms and improves or at least stabilizes neurocognitive function (12), but nonetheless overall survival remains poor (13). WBRT has potential short-term sequelae including headache, erythema, nausea, and vomiting, as well as long-term complications including somnolence, fatigue, memory loss, and rarely dementia (14, 15).

SRS uses high doses of targeted radiation and is particularly useful in patients with single lesions, those who are
unable to tolerate surgery, and for those with surgically inaccessible lesions (1). In patients with single brain metastases, surgery or SRS combined with WBRT improves overall survival compared with WBRT alone. In patients with 4 or fewer brain metastases, SRS results in equivalent overall survival but worse local control compared with SRS plus WBRT (2, 6, 16, 17). The maximum number of brain metastases for which SRS is considered suitable is controversial, but it is generally used in patients with 1 to 4 brain metastases, less than 4 cm in diameter (14), on the basis of earlier studies showing that patients with 1 to 2 metastases treated with SRS had significantly longer median survival compared with patients with 3 or more metastases (18). More recently, comparable survival has been shown in the 2 groups (19), and there is some evidence that total treatment volume, rather than the number of metastases, is a significant predictor of survival. Treatment volume may thus be useful in selecting appropriate patients for SRS. However, some evidence suggests SRS also provides a survival benefit in patients with 4 or more metastases (20).

**Systemic therapy including tyrosine kinase inhibitors**

Compared with brain metastases from small cell lung cancer, germ cell tumors, and lymphomas, NSCLC in the same site is less sensitive to chemotherapy (21). An intracranial response to first-line chemotherapy in NSCLC correlates with a similar response in the extracranial sites (22, 23), but in heavily pretreated patients chemotherapy has played a limited role. This is thought to be due to several factors, including existence of the blood–brain barrier (BBB) and inherent chemotherapy resistance of brain metastases (2). The efficacy of chemotherapy is more evident in treatment-naïve patients. Single-agent chemotherapy drugs, such as temozolomide and topotecan, and drugs in combination, such as paclitaxel, cisplatin, gemcitabine, and vinorelbine, have shown some activity in brain metastases (1). Radiotherapy and chemotherapy in combination has been shown to improve the response rate within the brain and/or progression-free survival (PFS) in some studies but not overall survival (24–26).

The BBB is formed by tight junctions between brain endothelial cells and acts as a selective barrier between the systemic circulation and cerebrospinal fluid (Fig. 1; ref. 27). Transport systems on the luminal and abluminal endothelial cell membranes regulate the passage of small hydrophilic molecules. Large hydrophilic molecules such as chemotherapeutic and molecular-targeted drugs can only be transported across the membrane by receptor-mediated mechanisms (2). The BBB also expresses high levels of drug efflux proteins of the ATP-binding cassette (ABC) transporter family at the brain endothelial cells, for example, P-glycoprotein (PgP), which actively removes certain drugs from the brain (28). The integrity of the BBB is directly related to the size of a brain metastasis; a growing tumor may disrupt the BBB as well as increase blood vessel permeability and result in a reduction in PgP expression (29, 30). A clinical positron emission tomography study using $[^{11}C]$-erlotinib has shown effective erlotinib distribution to CNS metastases but not normal brain (31). The failure of some patients to benefit from erlotinib may be explained by the expression of efflux proteins both in the BBB and in the tumor cell membrane. The active metabolite of erlotinib, OSI-420, is a substrate of PgP, providing a route for drug efflux that may contribute to failed CNS penetration (32). By contrast, gefitinib in any form is not a PgP substrate and is known to inhibit PgP activity (33). In a pharmacokinetic study of CNS exposure to gefitinib, NSCLC patients metastatic to the CNS, and with either an EGF mutation or demographics predictive of clinical benefit from an EGFR tyrosine kinase inhibitor (TKI), the drug was given concurrently with WBRT to 6 patients, and plasma and cerebrospinal fluid (CSF) levels of gefitinib were

![Image](https://example.com/image.png)

**Figure 1.** Influences of the BBB on TKI concentration in the CSF. Endothelial cells in the CNS are connected by tight junctions that form a barrier to the free transport of macromolecules between blood and CSF. In the intact BBB (center), active transport mechanics allow entry for limited concentrations of TKI, counteracted by efflux pumps. These mechanisms may be disrupted by metastatic tumor deposits, allowing freer influx of drugs (right). ABCG2, breast cancer resistant protein; MRP, multidrug resistant proteins.
measured (34). The gefitinib CSF exposure was 2.4% that of plasma, similar to previous reports (35). The CSF levels in such studies are likely to underestimate drug exposure within the tumor in the context of a disrupted BBB (31).

**EGFR Mutation in Brain Metastases**

Somatic mutations of the tyrosine kinase domain of the *EGFR* gene are associated with significant sensitivity and improved outcome in patients with extracranial NSCLC treated with *EGFR* TKIs (36–39). In a cohort of 19 patients with available tissue from CNS metastases, *EGFR* mutations were found in 12 metastatic lung adenocarcinomas to the brain, and in 6 cases the same *EGFR* mutation was found in the corresponding primary lung tumors (40). This finding implies that *EGFR* mutation is often an early event in disease evolution. An analysis of *EGFR* mutation status and survival in 93 patients with NSCLC and brain metastases revealed 44% with an *EGFR* mutation (10). Median survival was longer in those with an *EGFR* mutation [14.5 vs. 7.6 months; hazard ratio 0.5; 95% confidence interval (CI), 0.30–0.82; *P* = 0.09]. This analysis suggested that *EGFR* mutation status is associated with improved survival independent of age, functional status, extracranial disease status, and the number of brain metastases. There is some evidence that the presence of *EGFR* mutation predisposes to CNS metastases. Li and colleagues looked at the *EGFR* mutation status of 110 patients with NSCLC, in whom 14 patients developed brain metastases either at diagnosis (1 out of 14) or during follow-up (41). The *EGFR* mutation rates were 64% (9 out of 14) and 31% (30 out of 96) in the patients with and without brain metastases, respectively (*P* < 0.05). Although this study was retrospective, *EGFR* mutation status was assessed using tissue from diagnostic procedures, allowing an interpretation of the mutation rate at diagnosis.

**Activity of EGFR Inhibitors in Brain Metastases**

Preclinical evidence for the efficacy of gefitinib exists in mouse models of NSCLC brain metastases with an *EGFR* mutation (42), and this drug acts as a radiation sensitizer in various cancer cell lines including NSCLC (43). Several case reports have reported complete and sustained responses following treatment of brain metastases with erlotinib and gefitinib (44–47). Small case series have shown response to gefitinib after failure of standard therapy, including complete response in the brain (48–50). In a prospective study of 41 unselected patients with brain metastases treated with gefitinib, a partial response was seen in 4 patients (10%), with an overall disease control rate (partial response plus stable disease) of 27% (51). The median duration of response was 13.5 months. Gefitinib proved effective in both WBRT-pretreated and WBRT-naive patients. In another prospective study, Wu and colleagues looked at the efficacy of gefitinib in 40 unselected patients previously treated with chemotherapy (52). The response rate was 32% with median PFS and overall survival durations of 9.0 and 15.0 months, respectively. In general, the results in patients selected for activating *EGFR* mutation or surrogate demographic features, discussed below, have been superior to these series in cases in which mutation status is unknown. The prevalence of *EGFR* mutation is higher in patients with East Asian ethnicity. In a retrospective series of unselected (*EGFR* status not defined) Japanese patients treated with gefitinib, 6 out of 14 with brain metastases had an objective response (43%), and 8 had stable disease (53). In a retrospective study of 69 patients with NSCLC and brain metastases treated with erlotinib, 17 of whom had an *EGFR* mutation (54), the objective response rate in those with an *EGFR* mutation was 82.4%, with no responses observed in the others. The median time to progression within the brain for patients with *EGFR*-mutated cancers was 11.7 months (95% CI, 7.9–15.5) compared with 5.8 months (95% CI, 5.2–6.4) for wild-type or unknown *EGFR* status (*P* < 0.05). Overall survival was 12.9 versus 3.1 months, respectively (*P* < 0.001). This study suggests that the clinical benefit seen with an *EGFR* TKI in these patients is associated with the presence of an *EGFR* mutation. More recently, 23 adenocarcinoma patients with CNS metastases and a known *EGFR* mutation were treated with erlotinib or gefitinib (55). No prior therapy for existing brain metastases had been given. None of the patients had received an *EGFR* TKI previously, and 17 patients were treated as second-line therapy. The response rate was 70% with a median PFS and overall survival of 6.6 (95% CI, 0.0–14.7) and 19.8 months (95% CI, 14.1–25.6), respectively. There is some evidence that CNS disease also responds to newer *EGFR*-targeted TKIs. A single patient with *EGFR*-mutated NSCLC developed CNS metastases while receiving afatinib in a phase I trial (56). Dose escalation of afatinib led to a response in both brain and thoracic disease.

A phase II study of 48 East Asian patients evaluated the use of second-line erlotinib in NSCLC patients with asymptomatic brain metastases after 2 to 6 cycles of first-line platinum-doublet chemotherapy without extracranial progressive disease (57). Eligible patients had an activating *EGFR* mutation and/or adenocarcinoma and received erlotinib until they developed radiologic intracranial disease progression or asymptomatic brain metastases. The overall response rate, both intra- and extracranial, was 56%, which compares favorably with response rates of 27% and 42% in patients with an *EGFR* mutation in the pivotal second-line studies (58, 59). PFS was 23.2 months in those with an *EGFR* mutation and 8.2 months in those without (*P* = 0.06). In the 29 patients who progressed, 26 progressed within the brain and 5 progressed in extracranial sites. A retrospective analysis has been done of 23 chemotherapy-naive Asian never-smokers with lung adenocarcinoma and asymptomatic synchronous brain metastases treated with either first-line erlotinib or gefitinib (60). These patients had not received prior radiotherapy or SRS. The intracranial response rate was 74% with a median PFS and overall survival of 7.1 and 18.8 months, respectively. These studies in patients with *EGFR* mutation, or histology and demographics associated with this genotype, support the use of first-line *EGFR* TKI therapy in the context of asymptomatic...
Thus, at this dose, the concentrations of 3,730 nmol/L and 39.4 nmol/L, respectively. With repeated episodes of CNS progression, gefitinib was further increased to a maximum dose of 1,250 mg/day, corresponding to a CSF concentration of 6.2 nmol/L. Three cycles of WBRT were independent positive predictors of response to gefitinib when given concurrently with WBRT (34). The higher serum concentration of erlotinib compared with gefitinib is thought to lead to higher CSF concentration and, therefore, a response in CNS disease. Escalating doses of erlotinib have also been shown to achieve significant BBB penetration. This increase may be achieved either by switching drugs (e.g., gefitinib to erlotinib) or by escalating dose.

**EGFR inhibitors combined with radiotherapy**

In a phase I study, radiotherapy with concurrent erlotinib was well tolerated in patients with brain metastases from NSCLC, with no treatment-related neurotoxicity (66). The addition of an EGFR TKI to radiotherapy may improve the response to radiotherapy. In a retrospective series of 63 patients with brain metastases from lung adenocarcinoma, both EGFR mutation and the addition of an EGFR TKI to WBRT were independent positive predictors of response (67). Xu and colleagues showed that patients respond to the combination of WBRT and gefitinib, but it is difficult to assess in this single-arm study the contribution made by gefitinib when given concurrently with WBRT (34). The recently conducted randomized phase II TACTIC trial compared the efficacy of WBRT plus erlotinib with WBRT alone (68), and the results of this trial are awaited. Subsequently, exploration of alternative schedules and sequencing of EGFR TKI combined with radiotherapy may be warranted.

**Prophylaxis of central nervous system metastases in EGFR-mutated non–small cell lung cancer**

A recent retrospective study looked at the impact of gefitinib or erlotinib compared with chemotherapy on the brain metastases. Table 1 summarizes the studies of EGFR inhibitors done in selected and unselected patients with CNS metastases from NSCLC.

### Table 1. Trials studying the efficacy of EGFR tyrosine kinase inhibitors in non–small cell lung cancer with central nervous system metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Selection</th>
<th>Phase</th>
<th>N</th>
<th>RR (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unselected patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceresoli et al. (61)</td>
<td>Gefitinib</td>
<td>European</td>
<td>II</td>
<td>41</td>
<td>27</td>
<td>PFS 3 mo</td>
</tr>
<tr>
<td>Wu et al. (52)</td>
<td>Gefitinib</td>
<td>East Asian, adenocarcinoma</td>
<td>II</td>
<td>40</td>
<td>32</td>
<td>PFS 9 mo</td>
</tr>
<tr>
<td><strong>Selected patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hotta et al. (53)</td>
<td>Gefitinib</td>
<td>East Asian</td>
<td>II</td>
<td>57</td>
<td>43</td>
<td>OS 12.9 mo</td>
</tr>
<tr>
<td>Porta et al. (54)</td>
<td>Erlotinib</td>
<td>EGFR mutation</td>
<td>II</td>
<td>69</td>
<td>82</td>
<td>OS 12.9 mo</td>
</tr>
<tr>
<td>Kim et al. (55)</td>
<td>Gefitinib</td>
<td>EGFR mutation, East Asian, adenocarcinoma</td>
<td>II</td>
<td>23</td>
<td>70</td>
<td>PFS 6.6 mo, OS 19.8 mo</td>
</tr>
<tr>
<td>Li et al. (41)</td>
<td>Gefitinib</td>
<td>EGFR mutation, East Asian, adenocarcinoma</td>
<td>II</td>
<td>110</td>
<td>89</td>
<td>PFS 23.2 mo</td>
</tr>
<tr>
<td>Wu et al. (57)</td>
<td>Erlotinib</td>
<td>East Asian, EGFR mutation, and/or adenocarcinoma</td>
<td>II</td>
<td>48</td>
<td>56</td>
<td>PFS 7.1 mo, OS 18.8 mo</td>
</tr>
<tr>
<td>Kim et al. (60)</td>
<td>Gefitinib</td>
<td>East Asian, never-smoker, adenocarcinoma</td>
<td>II</td>
<td>23</td>
<td>74</td>
<td>PFS 7.1 mo, OS 18.8 mo</td>
</tr>
</tbody>
</table>

Abbreviations: mo, months; OS, overall survival; PR, partial response; RR, response rate; TTP, time to progression.

Dose escalation

Some cases of brain metastases refractory or resistant to standard-dose EGFR inhibitors respond to dose escalation or switching to a different TKI. In a case report, Jackman and colleagues present a patient with EGFR-mutant metastatic NSCLC receiving gefitinib (61). In vitro gefitinib drug testing on a tumor cell line derived from a pleural effusion in this patient showed an IC50 of 10 to 50 nmol/L. The patient showed an IC50 of 10 to 50 nmol/L. The patient's tumor was almost achieved in CSF. With each increase in gefitinib dose, the patient responded radiologically, cytologically, and symptomatically.

Katayama and colleagues showed that erlotinib could be an effective treatment option in patients who develop CNS disease after a good initial response of extracranial disease to gefitinib (62). Trough serum concentration of erlotinib administered at 150 mg/day is 3.5 μmol/L, which is 9 times higher than that of gefitinib administered at 250 mg/day (0.4 μmol/L). The higher serum concentration of erlotinib compared with gefitinib is thought to lead to higher CSF concentration and, therefore, a response in CNS disease. Escalating doses of erlotinib have also been shown to be effective in patients with relapsed CNS disease. Hata and colleagues report a case in which erlotinib given as 300 mg/day on alternating days led to a symptomatic and radiologic CNS response in a patient having had prior treatment with gefitinib, chemotherapy, WBRT, and standard-dose erlotinib (63). Pulsatile high-dose weekly erlotinib therapy has also been shown to achieve higher therapeutic CSF concentrations, resulting in disease response after the failure of standard daily dosing (64, 65). These cases suggest that brain metastases may remain sensitive to EGFR TKIs after progression on TKI therapy, but require a higher CSF concentration to achieve significant BBB penetration. This increase may be achieved either by switching drugs (e.g., gefitinib to erlotinib) or by escalating dose.

EGFR inhibitors in lung cancer with brain metastases

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emergence of CNS metastases in patients with EGFR-mutant tumors (69). Ninety-nine patients received an EGFR TKI, and 30 patients received chemotherapy. Thirty out of 129 patients had brain metastases at diagnosis, and 28 of these patients received CNS therapy such as radiotherapy. The risk of CNS progression was significantly higher in the chemotherapy group, with 1- and 2-year cumulative risks of CNS progression of 5% and 21% in the TKI group, compared with 24% and 31% in the chemotherapy group, respectively. The authors argue that treatment with an EGFR TKI in EGFR-mutant patients might have a prophylactic effect against CNS progression, although it is clear that these drugs delay progression at any site when compared with chemotherapy (38).

Conclusions

Standard treatment for NSCLC metastatic to the brain is associated with poor outcome, and more effective agents are needed to prolong survival and to maintain and prevent deterioration of neurologic and neurocognitive function. Erlotinib and gefitinib have been shown to be active in this setting. Unsurprisingly, there is evidence that these drugs are most effective in patients with EGFR-mutated NSCLC or in the presence of demographics associated with this genotype (East Asian ethnicity, adenocarcinoma, nonsmoking status). Treatment with these drugs should be considered as a valid option before radiotherapy in these patient groups in the context of asymptomatic brain metastases. However, in patients for whom surgery or SRS is indicated in oligometastatic disease, these treatment modalities are preferred in the first instance because they result in effective long-term local control with significantly reduced risk of CNS recurrence and prolonged median survival compared with other treatment options.

There is some evidence that a TKI may potentiate the effectiveness of radiotherapy. Patients with EGFR mutation receiving TKIs for systemic disease may have a lower risk of developing CNS metastases than do those treated with chemotherapy, raising the possibility of a prophylactic effect of TKIs against CNS progression (69). In cases in which there is isolated CNS progression, TKI dose escalation may be of benefit, and even a switch from one type of TKI to another may result in an intracranial response following earlier clinical benefit from an EGFR TKI (62). These responses are mostly attributed to achieving higher TKI serum and, therefore, CSF concentrations. Accurately recording the pattern of treatment failure (CNS versus systemic) in this context is important in clinical trials because of the wide divergence of plasma and CSF concentrations.

These generally well-tolerated EGFR TKIs should be considered as a treatment option for NSCLC patients with brain metastases in the presence of EGFR mutation, or when associated demographics are present in the case of unknown EGFR mutation status. These drugs may also contribute to treatment response when administered concurrently with radiotherapy, although more evidence for this is needed. Overall, the preclinical evidence, the correlation between EGFR mutation status in the primary lung tumor and brain metastasis, and the superior survival of these patients support the clinical evidence reviewed here for efficacy of EGFR TKIs in the treatment of patients with EGFR-mutated NSCLC and brain metastases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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