TREATMENT OF ISOLATED INTRACRANIAL PROGRESSION OF LUNG CANCER DURING TREATMENT WITH SYSTEMIC EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS (EGFR-TKIs)

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ABSTRACT

Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are an effective treatment for non-small-cell lung cancer (NSCLC) harbouring *EGFR* mutations. The development of isolated central nervous system (CNS) metastases is a relevant clinical problem in patients who respond well to EGFR-TKIs.
Methods: We present a patient with isolated progression of brain metastases during treatment of *EGFR*-mutated NSCLC with an EGFR-TKI and review the treatment options in this setting, including the evidence for and toxicity of treatment with high-dose TKIs.
Results: Oligometastatic CNS progression during TKI therapy may be treated locally. Both whole brain radiotherapy (WBRT) and stereotactic brain irradiation are well tolerated and effective in this setting. The use of high-dose pulsed TKIs is intended to increase the concentration of TKI in the brain and has been reported to be effective and without significant toxicity in case reports and small case series. These therapeutic options are illustrated in the case of a 44-year-old NSCLC patient who developed CNS progression after WBRT during second-line erlotinib and was treated locally with stereotactic radiosurgery (SRS) and, upon further CNS progression, with high-dose pulsed erlotinib. This resulted in intracerebral response; however, significant haemorrhage also occurred. Severe haemorrhage has not previously been described as a complication of high-dose pulsed erlotinib.
Conclusion: Possible explanations for isolated CNS progression during TKI treatment include inadequate dosing across the blood—brain barrier and longer survival on TKIs. The efficacy and tolerability of high-dose pulsed TKIs for CNS metastases has been previously reported. None of the cases reported showed the severe haemorrhage and cerebral oedema that developed in our patient. Simultaneous anticoagulation as well as previous SRS may have predisposed our patient to haemorrhage and may prove to be relative contraindications to high-dose pulsed erlotinib. Most centres only see a few patients in this clinical situation, and co-operative efforts are needed to collect and analyse similar cases and to develop appropriate treatment strategies.

Keywords: Lung cancer, targeted therapy, tyrosine kinase inhibitor, brain metastases.

BACKGROUND

Advanced-stage lung cancer carries a very limited prognosis. Although many patients benefit from palliative systemic chemotherapy, resistance to chemotherapy generally develops within several months. Tyrosine kinase inhibitors (TKIs) that target mutations of the gene encoding epidermal growth factor receptor (EGFR) have become an established treatment option and can improve both progression-free survival (PFS)[1] and overall survival (OS),[2] in particular in patients whose tumours harbour deletions in exon 19 of the *EGFR* gene.[3] Nevertheless, resistance to EGFR-TKIs continues to cause disease progression.[4] The approach to progression during EGFR-TKI treatment varies depending on the rate and clinical significance of the progression, as well as the number and localisation of active metastases.[5] For patients with oligometastatic progression, local treatments with continuation of EGFR-TKIs may lead to an additional progression-free interval.[6,7]

Isolated central nervous system (CNS) progression presents a particular challenge and is a relevant clinical problem in patients who respond well to EGFR-TKIs. However, it is unclear whether the *EGFR* mutation itself predisposes to CNS metastases, to what degree incomplete CNS penetration of EGFR-TKIs plays a role, or whether the longer survival of patients responding to EGFR-TKIs exposes late steps in the natural history of the disease. There is evidence that *EGFR* mutations may predispose patients to CNS metastases. A Japanese case series[8] suggested higher rates of *EGFR* mutation in patients with brain metastases than in unselected patients; and a study of Korean patients with resected non-small-cell lung cancer (NSCLC) found a trend of increased rates of brain relapse in patients with *EGFR* mutation.[9] An association between *EGFR* mutation and risk of brain metastases was also reported by Shin et al.[10] in a recent analysis of 314 Korean patients with lung adenocarcinoma. In addition, in 629 European patients with lung adenocarcinomas tested for *EGFR* mutation, there was a trend to more brain metastases at first diagnosis in those with *EGFR*-mutated compared with wild-type (WT) tumours (19% versus 13%, p=0.078).[11]

Patients treated with EGFR-TKIs seem to develop CNS metastases more often than otherwise seen in advanced lung cancer. Omuro and colleagues[12] reported that the CNS was the initial site of recurrence in 7 of 21 patients with adenocarcinoma of the lung who had responded to gefitinib. Four of these seven patients did not have systemic disease progression.[12] An analysis of 287 Korean patients treated with erlotinib or gefitinib showed that 16% had progression in the CNS, and 7% had isolated CNS progression. Those patients who had responded well to EGFR-TKIs were at higher risk of developing isolated CNS progression (26% versus 4%, p<0.001).[13] CNS metastases are an important cause of death in patients with *EGFR*-mutation-positive lung cancer. A retrospective analysis of Chinese patients tested for *EGFR* mutation and treated with first or second-line EGFR-TKIs showed that patients who died of CNS metastases had undergone EGFR-TKI treatment for longer than patients who died of other causes (median time on EGFR-TKIs: 8 versus 1.9 months; p<0.0003). More patients with EGFR mutations (44.8%) died of CNS metastases than did *EGFR* WT patients (8.3%) (p<0.001).[14] It has been suggested that some *EGFR*-mutated patients with asymptomatic brain metastases can be initially treated with a systemic TKI alone.[15]

Further strategies for the treatment of CNS metastases include whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), conventional chemotherapy, and alternate dosing of EGFR-TKIs including high-dosepulsed administration. Here we present a patient with isolated intracranial progression of an *EGFR*-mutated lung adenocarcinoma who was treated with WBRT, three courses of SRS and, finally, high-dose pulsed erlotinib, and discuss the relevant evidence in this setting.

METHODS

We analysed the course of a patient treated at our centre who developed isolated intracranial progression of CNS metastases during treatment of *EGFR*-mutated NSCLC with an EGFR-TKI. We reviewed the treatment options in this setting, including the evidence for and toxicity of treatment with WBRT and SRS during EGFR-TKI treatment and the use of high-dose pulsed EGFR-TKIs.

RESULTS

Clinical Case Presentation Part 1

A 44-year-old Caucasian female never-smoker presented with left arm weakness. Computed tomography revealed several brain lesions and a mass in the right lung. Positron emission

tomography showed metastases in the liver and right kidney. Following bronchoscopic biopsy, adenocarcinoma of the lung in clinical Stage 4 was diagnosed. Whole brain irradiation (2.5 Gy on weekdays to 35 Gy) and the first three cycles of chemotherapy (cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 1 day every 3 weeks) led to a partial response; however, during the fifth cycle of chemotherapy the patient presented with pulmonary embolus, which was treated with tinzaparin, and progression of both the intrathoracic primary tumour and the abdominal metastases. Molecular analyses showed an exon 19 deletion in *EGFR*, and second-line treatment with erlotinib at 150 mg/day was initiated. This led to regression of all tumour sites. After 13 months of erlotinib, magnetic resonance imaging (MRI) showed isolated progression of two cerebral metastases with continued response of the systemic disease.

Review of the Literature

EGFR-TKIs in patients with brain metastases

EGFR-TKIs are able to cross the blood—brain barrier to some degree and their activity in CNS metastases from lung cancer was reported more than ten years ago.[16] Since then TKIs have been used widely in this setting, and complete responses of CNS metastases under TKI treatment have been reported.[17] Leptomeningeal metastases may also be treated with EGFR-TKIs in patients with *EGFR* mutations.[18] A retrospective analysis of patients with brain metastases treated initially with either a TKI or chemotherapy showed lower risk of CNS progression in those treated with TKIs compared with chemotherapy.[19] Gefitinib, erlotinib, and afatinib have all been reported to have activity against CNS metastases. While there has not been a direct comparison of the efficacy of these agents in this setting, individual case reports and small case series have suggested that some patients experiencing progression under gefitinib or erlotinib may benefit from a switch to another TKI.[20-22]

A recently published analysis of patients with CNS metastases treated with afatinib during a pre-market compassionate use programme showed significant rates of response to treatment with afatinib.[23] Patients included in this analysis were heavily pre-treated, receiving afatinib as a salvage treatment following progression after at least one course of platinum-based chemotherapy and at least one TKI. 35% of patients had a cerebral response, and 66% had cerebral disease control on afatinib. Further studies describing the treatment of CNS metastases with EGFR-TKIs are summarised in recent reviews.[24-26] Based on the available evidence, patients with *EGFR*-mutated NSCLC and asymptomatic CNS metastases should be treated with an EGFR-TKI. Progressive or symptomatic CNS disease may require additional treatment. The efficacy of third-generation EGFR inhibitors, such as AZD929127 and CO-168628, in patients with brain metastases and evidence of resistance mutations has yet to be determined.

Safety and efficacy of whole brain radiotherapy during treatment with EGFR-TKIs

Several studies and case series have investigated EGFR-TKI treatment during WBRT. Ma and colleagues[29] administered WBRT during gefitinib treatment. There was no unexpected toxicity and quality of life was found to improve during the course of treatment. The safety and efficacy of gefitinib with WBRT was also reported by Gow and colleagues[30] who found a trend towards improved OS in patients treated with simultaneous TKI+WBRT (OS: 22.3 months) versus WBRT alone (OS: 11.7 months, p=0.121). The safety of erlotinib and WBRT was reported by Lind and colleagues[31] in a Phase I dose-finding study combining erlotinib 100 mg/day and erlotinib 150 mg/day with WBRT. Expected rates of systemic erlotinib side-effects were observed. In contrast to the relatively good tolerability described by the previous authors, Olmez and colleagues[32] describe a small case series in which 3 of 8 patients treated with WBRT and EGFR-TKIs experienced unexpected clinical deterioration including altered mental status, hyponatraemia, and liver toxicity. The authors hypothesise that this may have been due to the poor general state of health and high tumour burden of these patients.

Several medium-sized trials have investigated WBRT+EGFR-TKI in patients not selected for *EGFR*-mutation status in an attempt to exploit the radiosensitising effects of EGFR-TKIs. Welsch and colleagues treated 40 patients with WBRT during treatment with erlotinib 150 mg/day. EGFR status was tested in 17 patients and found to be positive in 9. The authors describe good tolerability, with no significant neurotoxicity and no Grade 4-5 toxicity. The overall response rate was 86%.[33] Lee et al.[34] conducted a similar randomised trial of WBRT +/- erlotinib in predominantly *EGFR* WT lung cancer patients with brain metastases.

A PFS or OS advantage for concurrent erlotinib during WBRT was not observed, and patients treated with erlotinib during WBRT had more rash and fatigue but no decrease in quality of life compared with those receiving placebo.[34]

WBRT plus sequential focal radiation boost with image-guided intensity-modulated radiotherapy has also been investigated as a treatment strategy for NSCLC patients with brain metastases. Zhou and colleagues[35] describe 29 patients treated in this setting and report a 1-year intracranial control rate of 63%. Patients previously treated with EGFR-TKIs (11 of the 29 patients studied) had better survival; however, these patients also showed a higher incidence of Grade 2-3 cognitive impairment and Grade 2 leukoencephalopathy on follow-up MRI.

Safety and efficacy of stereotactic radiosurgery during TKI treatment

The combination of SRS with erlotinib was investigated by the Radiation Therapy Oncology Group (RTOG). The RTOG 0320 trial compared WBRT and SRS alone with WBRT and SRS with temozolomide or erlotinib in NSCLC patients with 1-3 brain metastases,[36] using erlotinib as a radiosensitising agent independent of *EGFR* mutation status. A total of 126 patients were enrolled and 41 were randomised to erlotinib plus WBRT and SRS. In this predominantly *EGFR* WT population OS was numerically higher in patients who did not receive erlotinib or temozolomide (13.4 months versus 6.1 months), although without statistical significance. Also, more Grade 3-5 toxicity was seen in patients treated with either temozolomide (41%) or erlotinib (49%) during WBRT and SRS compared with WBRT and SRS alone (11%) ($p<0.001$). In the erlotinib plus WBRT and SRS arm one patient had Grade 4 brain necrosis and Grade 5 haemorrhagic stroke.[36] A recent analysis of 282 Chinese patients treated with WBRT, SRS, and/or surgery combined with EGFR-TKIs showed that the simultaneous administration of EGFR-TKIs during WBRT and SRS was associated with improved OS, freedom from intracranial disease progression, and freedom from extracranial disease progression. This population included a high proportion of *EGFR* mutations (55 of 109 tested). Toxicity was not explicitly reported; however, the investigators conclude that combining EGFR-TKIs with local therapies is beneficial to this patient group.[37]

In conclusion, EGFR-TKIs combined with WBRT or WBRT+SRS in patients without *EGFR* mutations are not beneficial to unselected patients and may in fact be harmful. The combination may be beneficial to patients with *EGFR*-mutated tumours. There is no evidence that EGFR-TKIs should be stopped during WBRT or SRS in patients with *EGFR*-mutation-positive NSCLC showing good clinical response to TKIs.

Clinical Case Presentation Part 2

Our patient had already received WBRT at the time of first diagnosis, and so the decision was made to perform SRS of the two brain metastases with 18 Gy. This was well tolerated without significant toxicity. Four months later one further brain metastasis appeared and was also irradiated with 18 Gy. Unfortunately, 3 months later multifocal CNS progression developed. A neurosurgical biopsy confirmed the presence of the same exon 19 deletion as in the primary tumour, with no evidence of known resistance mutations, in particular T790M.

Review of the Literature

High-dose and pulsed EGFR-TKIs

Standard doses of erlotinib (150 mg/day) may result in clinically relevant cerebrospinal fluid (CSF) concentrations of both erlotinib and its active metabolite OSI-420, with a CSF penetration rate of approximately 5%.[38] Other authors have reported CSF penetration of approximately 1% (Jackman et al., 2006).[39] The pharmacokinetics and CSF concentration of EGFR-TKIs appear to be influenced by patient genetics. Fukudo and colleagues[40] measured the concentration of erlotinib in the serum and CSF of patients with leptomeningeal metastases and found the germline *ABCG2 421A* allele to be associated with increased CSF penetration of erlotinib and its active metabolite OSI-420. There is evidence that the administration of high-dose pulsed EGFR—TKIs results in improved penetration of the blood-brain barrier and increased concentrations of TKI in the CSF.

Increasing the dose of erlotinib from 75 mg/day to 150 mg/day results in an increase in serum concentration and a corresponding increase in CSF concentration.[41] Further increases in EGFR-TKI dose, as applied in pulsed high-dose TKI treatments, result in increases in both serum and CSF concentration.[39,42] These concentrations appear sufficient to treat CNS metastases

progressing under standard doses of EGFR-TKI. The safety of high-dose weekly erlotinib was reported by a Phase I/II study that treated NSCLC patients with chemotherapy resistance with 1,200 mg, 1,600 mg, or 2,000 mg erlotinib weekly.[43] The response rate was low, likely due to the inclusion of WT tumours; however, there was no Grade 4 or 5 toxicity and only one case each of Grade 3 fatigue, dehydration, and pneumonitis.

The use of high-dose pulsed EGFR-TKIs in *EGFR*-mutated tumours with CNS metastases has been reported in case studies and series. A case series published in 2011[44] reported on 9 patients with *EGFR*-mutant lung cancer treated with 1,500 mg erlotinib once a week for CNS metastases. There was a partial response in 4 of 9 patients (44%), disease stabilisation in 3 patients, and progressive disease in 2 patients with no Grade 3-5 toxicity. A second case series describes 10 patients with lung adenocarcinoma treated with 1,000-1,500 mg erlotinib once weekly.[45] The authors describe CNS response in 1 of 10 patients, with stabilisation of cerebral disease in a further 2 patients. These case series and case reports describing the use of high-dose and/or pulsed TKIs are summarised in Table 1.[45-49]

Clinical Case Presentation Part 3

Faced with multifocal CNS progression, our patient consented to a trial of high-dose pulsed erlotinib.

Table 1: Clinical response and toxicity during high-dose pulsed tyrosine kinase inhibitors: summary of case reports and case series.

Publication	n	*EGFR* mutation	Drug and dose	Disease control rate	Duration of treatment effect	Toxicity >Grade 3	Toxicity Grade 1-2	Haem-orrhage
Grommes et al.[44]	9	Exon 19 deletion (n=3), exon 19 insertion (n=1), exon 21 L858R substitution (n=4), exon 18 G719S/exon 21 L861Q substitutions (n=1)	Erlotinib 1,500 mg once weekly	7/9 (78%)	Mean time to CNS progression 2.7 months	None	Grade 1-2 rash, Grade 1 fatigue, diarrhoea, nausea, hair thinning, intratumoural CNS haemorrhage	Grade 1 in 3/9 (33%)
Jackman et al.[45]	10	Exon 19 deletion (n=6), exon 21 L858R substitution (n=3), exon 21 L858R substitution + *T790M* (n=1)	Erlotinib 1,000-1,500 mg once weekly	3/10 (30%)	Mean time to CNS progression 2.5 months	NR	NR	NR
Santhosh-Kumar et. al.[46]	1	Exon 19 deletion, no *T790M* mutation	Erlotinib 600-750 mg daily for 3 days on and 2 days off. Total dose 2,550 mg/week	1/1 (100%)	>12 months	None	Grade 1 rash and diarrhoea	None
Dhruva and Socinski[47]	1	NR	Erlotinib 600 mg every 4 days plus bevacizumab	1/1 (100%)	Treatment for 10 months	None	Skin and gastrointestinal toxicity	None
Clarke et al.[42]	1	*L858R* mutation and *T790M* mutation	1,000-1,500 mg/week	1/1 (100%)	Survival after CNS metastases 14 months	Hydrocephalus treated with VP shunt	NR	None
Hata et al.[48]	1	Exon 18 G719A	Erlotinib 300 mg/day on alternate days	1/1 (100%)	>6 months to CNS progression	None	Rash	None

Table 1 continued.

Publication	n	*EGFR* mutation	Drug and dose	Disease control rate	Duration of treatment effect	Toxicity >Grade 3	Toxicity Grade 1-2	Haem-orrhage
Yi et al.[49] Patient #1*	1	*EGFR*-mutation positive, details NR	Gefitinib 750 mg/day	1/1 (100%)	Survival after CNS metastases >18.6+ months	NR	NR	NR
Yi et al.[49] Patient #11*	1	EGFR-mutation positive, details NR	Gefitinib 500 mg/day	1/1 (100%)	Survival after CNS metasta-ses >8.6 months	NR	NR	NR
Jackman et al.[3]	1	Deletion exon 19	Gefitinib daily 500-1,000 mg	1/1 (100%)	Survival after high-dose gefitinib 4 months	Somno-lence, elevated hepatic transami-nases		None

* Yi et al.[49] describe various approaches to CNS metastases in 11 individual patients. Patient #1 and Patient #11 are presented separately within the paper and for that reason are presented as individual case reports in the table.
NR: not reported; EGFR: epidermal growth factor receptor; CNS: central nervous system.

Erlotinib pulses (600 mg every 4 days) were added to the daily treatment with erlotinib 150 mg. This resulted in a weekly erlotinib dose of 2,100 mg. After 2 weeks the patient developed increasing headache and arm weakness. MRI showed haemorrhage into three brain metastases and partial response of the other brain metastases (Figure 1). Erlotinib and anticoagulants were stopped, and due to a 6 mm midline shift the largest haematoma was evacuated surgically. After a period of post-operative recovery the patient resumed erlotinib pulses with a 25% dose reduction (450 mg every 4 days). There was no further haemorrhage; however, 24 days later cerebral oedema and subdural hygroma (Figure 2) developed and the patient died, 24 months after the initial diagnosis of brain metastasis.

DISCUSSION

We describe a patient with *EGFR*-mutation-positive lung adenocarcinoma and isolated intracranial progression during second-line treatment with erlotinib. If she had presented today, this patient would likely be treated with a first-line EGFR-TKI rather than chemotherapy. Large randomised Phase III trials of EGFR-TKIs have consistently shown higher response rates and longer PFS in *EGFR*-mutated tumours treated with TKIs compared with platinum-based chemotherapy.[1,4,50,51] An OS benefit for first-line EGFR-TKIs versus TKIs after progression on chemotherapy is less clear, as most clinical trials have addressed only the type and not the sequence of systemic therapy. It was recently shown that patients with exon 19 deletions show a clinically relevant survival benefit on first-line afatinib compared with first-line platinum-based chemotherapy.[2] Systemic therapy is the standard of care for most patients with Stage 4 NSCLC; however, patients presenting with oligometastatic disease, in particular with isolated CNS or adrenal metastases, may benefit from combined systemic and local therapies[53] including surgery[54] or stereotactic irradiation.[55]

While a neurologically asymptomatic patient may not have required specific treatment of the brain metastases during TKI therapy, our patient presented with arm weakness and would have been a candidate for WBRT during TKI treatment. The available literature shows the combination of WBRT and EGFR-TKI to be well tolerated. There is evidence that adding SRS to WBRT is beneficial to patients with 1-3 brain metastases,[56] and that SRS without WBRT may limit toxicity in these patients;[57] however, these studies

did not include patients treated concurrently with EGFR-TKIs.

Isolated progression of CNS metastases poses a challenge to the treating physician. Inadequate dosing of EGFR-TKIs across the blood—brain barrier is one explanation, and has led to attempts to increase the CNS dose of TKIs through the administration of high-dose pulsed TKIs.[52]

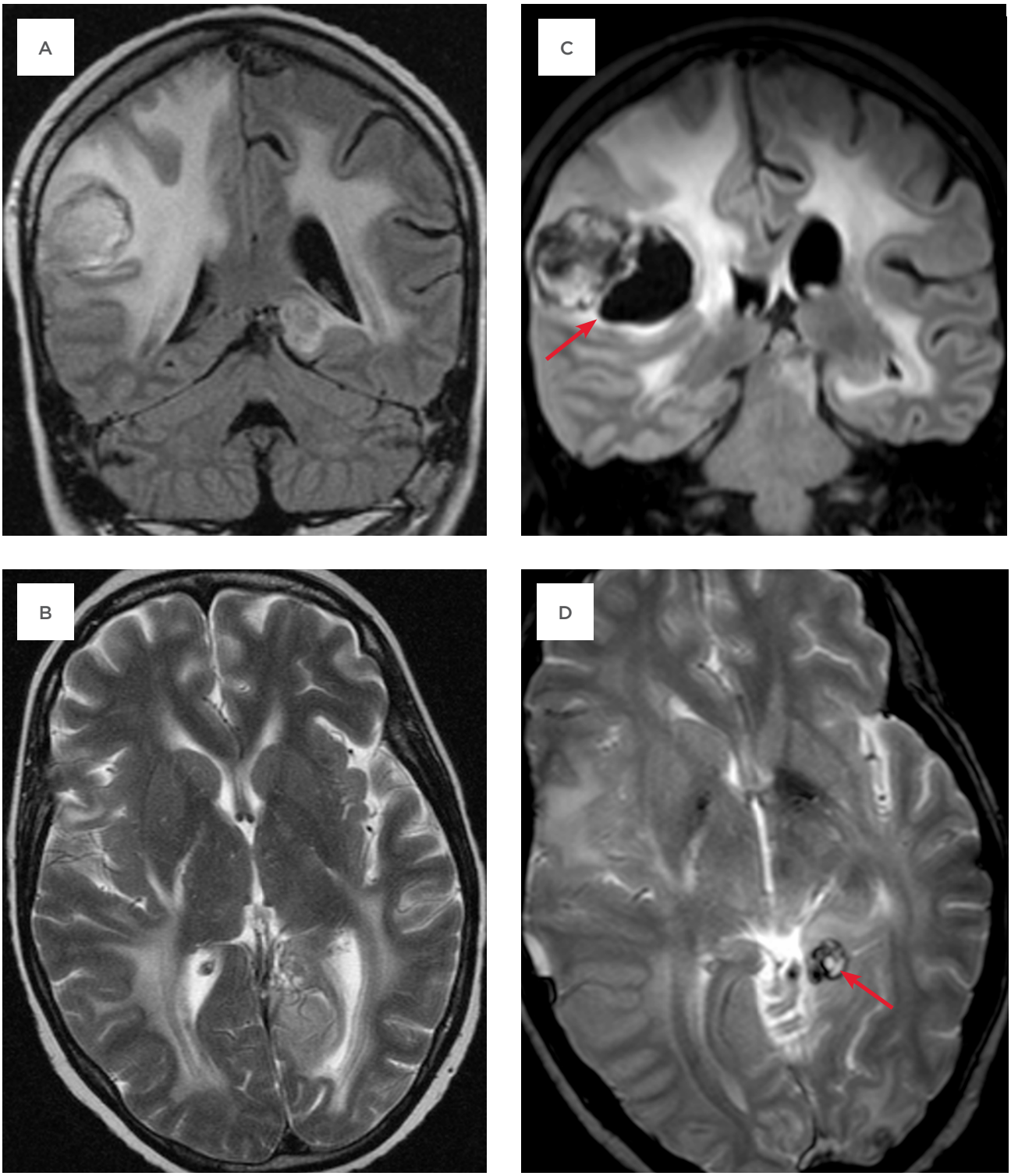

Figure 1: MRI scans showing brain metastases before and during treatment.
A: MRI image (FLAIR) before beginning high-dose pulsed erlotinib. B: MRI image (T2W) before beginning high-dose pulsed erlotinib. C: MRI image (FLAIR) showing haemorrhage (arrow) during high-dose pulsed erlotinib. D: MRI image (T2W) showing haemorrhage (arrow) during high-dose pulsed erlotinib. MRI: magnetic resonance imaging; FLAIR: fluid attenuation inversion recovery.

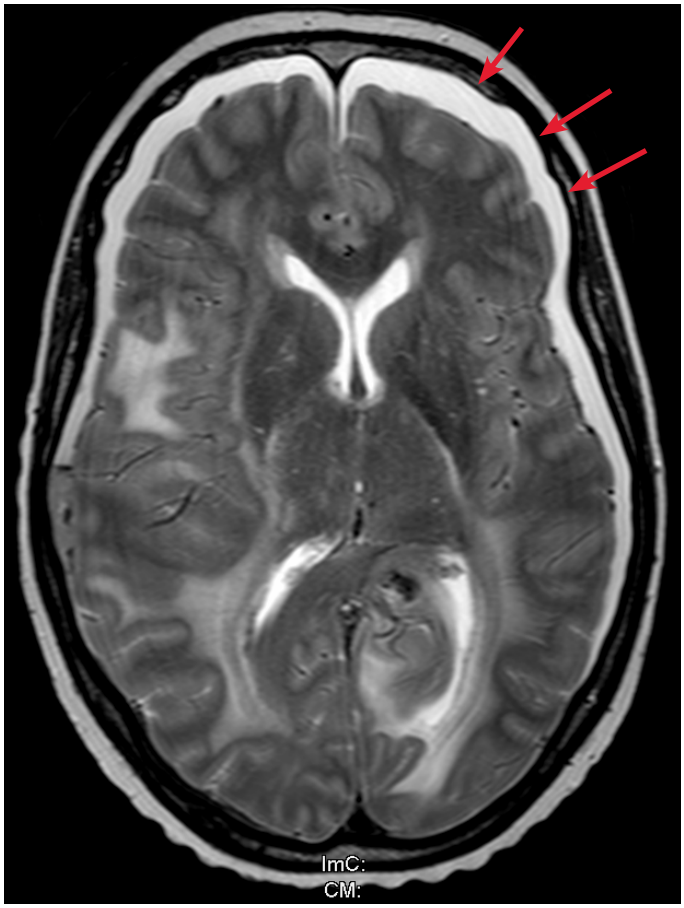

Figure 2: MRI image (T2W) showing hygroma development (arrows) following high-dose pulsed erlotinib.
MRI: magnetic resonance imaging.

This treatment strategy has not been evaluated in structured trials; however, evidence from published cases suggests that it may be effective and well tolerated. The absence of resistance mutations in biopsy material from our patient's brain metastases suggests that inadequate dosing, and not molecular resistance, may have been responsible for her disease progression. Had a *T790M* mutation been present our patient may have been a candidate for treatment with a third-generation TKI; however, to our knowledge none of the current trials of these drug candidates allow for the recruitment of patients with clinically unstable brain metastases.

Our patient responded to high-dose pulsed erlotinib but suffered significant haemorrhage. Simultaneous anticoagulation for pulmonary embolus as well as previous SRS may have predisposed her to haemorrhage, and may therefore be relative contraindications to high-dose pulsed EGFR-TKIs. Because most centres only see a few patients in this situation, co-operative efforts are needed to collect and analyse these cases, and to develop appropriate treatment strategies.

CONCLUSION

Patients with *EGFR* mutations presenting with asymptomatic brain metastases may be treated with a first-line EGFR-TKI. There has not yet been a direct comparison of the EGFR-TKIs in this setting; however, responses to one TKI after failure of another have been reported. Symptomatic brain metastases in patients with *EGFR* mutations may be treated with WBRT parallel to EGFR-TKI treatment. There is no significant evidence that the EGFR-TKI erlotinib has clinical utility as a radiosensitising agent during WBRT or SRS in patients with WT tumours. SRS combined with EGFR-TKIs and high-dose pulsed EGFR-TKIs may be considered in individual patients with isolated CNS progression; however, these treatments have yet to be adequately studied in clinical trials, and severe toxicity including haemorrhage is possible. Efforts should be made to include patients in

clinical trials. If clinical trials are not available, cases should be collected in regional registries in order to allow for a better understanding of toxicities and outcomes and to avoid the publication bias inherent with the publication of single cases of good treatment effect and low toxicity.

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