**Osimertinib in the treatment of leptomeningeal disease in T790M-negative, epidermal growth factor receptor-mutated non-small cell lung cancer: a case report**

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**Abstract:** Leptomeningeal carcinomatosis (LMC) is a terminal event in advanced cancer, its incidence in epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) is increasing due to recent advances in systemic therapy and prolongation of survival. Osimertinib is a third generation EGFR-tyrosine kinase inhibitor (TKI) with preclinical and early clinical studies showing activity against LMC resistant to previous TKI treatments and acquired T790M mutation. We report a case of osimertinib in the treatment of LMC in a T790M-negative, EGFR-mutated NSCLC with significant clinical benefit and no toxicity. Osimertinib is a potentially effective treatment for LMC associated with EGFR-mutated NSCLC regardless of T790M status and a well-tolerated treatment for poor performance status patients.

**Keywords:** Epidermal growth factor receptor (EGFR) mutation; leptomeningeal carcinomatosis (LMC); non-small cell lung cancer (NSCLC); osimertinib; T790M mutation

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**Introduction**

Leptomeningeal carcinomatosis (LMC) in lung cancer carries a poor prognosis with no standard of care treatment. Its incidence has been increasing due to improved survival of patients from advances in systemic therapy (1). Up to 10% of patients with epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) develop LMC (2). Osimertinib is a third generation EGFR-tyrosine kinase inhibitor (TKI) for the treatment of metastatic EGFR-mutant NSCLC in the setting of acquired T790M mutation (3). It has also been shown to be effective in T790M-negative disease (4). Evidence for the effectiveness of this drug in LMC however is very limited. We report a case of LMC in a patient with T790M-negative EGFR-mutated NSCLC treated with osimertinib, having had previous exposure to erlotinib.

**Case presentation**

A 74-year-old male with previous history of carcinoembryonic antigen (CEA)-sensitive recurrent NSCLC presented with asymptomatic rise in CEA level. He was diagnosed with stage IB lung adenocarcinoma (AC) 10 years ago treated with right lobectomy. He was then found to have asymptomatic localised paratracheal recurrence 2 years later, discovered incidentally from investigations of an asymptomatic elevation of CEA level. He received concurrent chemoradiation (60 Gy in 30 fractions) with cisplatin/docetaxel as radio-sensitiser. Due to his non-smoking history and Chinese ethnicity, EGFR mutation testing was recommended at the time but declined by the patient due to cost. Positron emission tomography (PET) scan post treatment showed residual soft tissue mass in the right hilar region. Despite unknown EGFR status, he received 5 years of maintenance erlotinib.
post chemoradiation and was on regular surveillance. He remained well throughout.

He represented twelve months ago again with asymptomatic rise in CEA level (two years after completion of maintenance erlotinib). Computed tomography (CT) chest and PET scan showed stable disease with mild uptake at the right hilar region which was unchanged from previous imaging. Over the next six months, patient remained asymptomatic but CEA continued to rise. Further investigations of repeat imaging including PET scan and CT brain did not reveal a cause. Gastroscopy and colonoscopy showed no evidence of another malignancy. He then complained of new onset headache and intermittent dizziness. General physical and neurological examinations were unremarkable. A magnetic resonance imaging (MRI) of the brain revealed diffuse streaky enhancement within the cerebellar sulci highly suggestive of LMC (Figure 1A). Lumbar punctures showed elevated protein and reduced glucose which would be consistent with LMC but cytology failed to demonstrate any malignant cells. No evidence of

Figure 1 Brain MRIs (T1-weighted post contrast images). (A) MRI pre-treatment showing diffuse streaky enhancement within cerebellar sulci; (B,C,D) MRIs at 8, 12 and 16 weeks post initiation of treatment showing stable left frontal lesion. MRI, magnetic resonance imaging.
disease was found elsewhere on repeat imaging to allow further tissue diagnosis. A presumptive diagnosis of leptomeningeal metastases from recurrent lung AC was made.

Patient received whole brain radiotherapy 30 Gray in 10 fractions with hippocampal sparing technique. In the interim, clinical deterioration was noted with increased hesitant ambulation, poorer speech and anorexia. His performance status dropped from ECOG 0 to 2. EGFR mutation testing was performed on his lobectomy tissue from 10 years ago which demonstrated TKI-sensitive EGFR G719C and EGFR E709A mutations. Plasma T790M testing was negative. Given previous exposure to erlotinib, he was commenced on osimertinib 80 mg daily, which he tolerated well with no toxicity. His systemic and neurological symptoms improved within 3 weeks of commencing osimertinib. His CEA level fell from 349 ug/L pre-treatment to 71 ug/L at 4 months. Three subsequent MRIs over the next 4 months showed stable disease with unaltered mild patchy enhancement in the cerebellar sulci. The first post treatment MRI did show a small area of irregular enhancing lesion in the left frontal pole measuring <10 mm suspicious for leptomeningeal deposit but the size of this has remained stable over next two scans (Figure 1B,C,D). The patient continues to be well and the treatment remains ongoing after 12 months.

Discussion

While EGFR-TKIs are now widely recognised as first line systemic treatment for metastatic EGFR-mutant NSCLC, evidence for the efficacy of these in the treatment of LMC remains limited. Poor penetration of these drugs through the blood-brain barrier remains a significant issue as over 30% of patients who progress during or after treatment with TKIs have intracranial disease (5). Previous small studies and case series have shown some response using first generation TKIs erlotinib and gefitinib in the treatment of LMC (6-11). It has also been demonstrated that a high dose or pulsatile administration of high dose erlotinib may improve the efficacy of these drugs in the setting of failure of standard daily dosing (12-15).

Osimertinib is a third generation TKI developed to target both EGFR-TKI sensitising mutations as well as T790M. It has been shown to be superior over standard platinum-based chemotherapy for the treatment of patients with T790M-positive disease who had progressed after first line TKI (3). It is also superior over first generation TKIs in untreated patients regardless of T790M status (4). In a preclinical study, osimertinib was found to markedly inhibit progression of LMC in in vivo mice model (16). It has also been demonstrated to penetrate the blood brain barrier (BBB) better than gefitinib, afatinib or rociletinib (17). This is supported by sub-analysis of clinical data from the AURA trial, with an overall response rate (ORR) of 70% in patients with brain metastasis treated with osimertinib, compared to 31% in the chemotherapy group (18). The phase 1 BLOOM study is ongoing to assess the activity and safety of osimertinib in the treatment of LMC progressed on prior TKI therapy. Preliminary result on 32 patients at 12 weeks are promising with 23/32 patients achieving a benefit, 10 with radiological response and 13 with stable disease (19). This study included both T790M-positive and unselected patients, it is unknown whether any responders are T790M negative. Several case reports have also demonstrated similar findings (Table 1). However, all except one of these patients had T790M-positive disease.

The other interesting aspect of this case is the sensitivity of CEA as a tumour marker. Some studies have shown positive results using CEA as a prognostic and/or predictive marker in NSCLC, especially in AC, while others were negative (26). It is also suggested that high CEA level may have a role in predicting development of brain metastasis (27). However, its use is limited to individual patients who have demonstrated CEA sensitive disease as current evidence is inadequate to support its routine use in NSCLC. In our case, CEA was initially requested by the patient’s general practitioner as a non-standard follow-up test but has proven to be a useful marker.

Our case suggests that osimertinib may represent an effective therapeutic option for LMC in EGFR-mutant NSCLC, even in T790M-negative disease. Furthermore, our patient has tolerated treatment extremely well, reflecting clinical trial findings that osimertinib is generally well tolerated with less severe adverse events than first generation TKIs (4). This is especially important to patients with LMC who are likely to have poorer performance status. Nevertheless, our case is limited by the lack of tissue to demonstrate malignant cells and mutation status in the cerebrospinal fluid (CSF). There is a possibility that T790M mutation may be present in the CSF if we were able to obtain any malignant cells.

Conclusions

We herein present a case of leptomeningeal disease in a patient with T790M-negative EGFR-mutant NSCLC. This case demonstrates the utility of third generation TKIs in treating leptomeningeal disease, particularly in patients with T790M mutations. Further research is needed to evaluate the role of CEA as a predictive marker in this setting, as well as the optimal treatment strategy for patients with T790M-negative disease.
Table 1 Patient characteristics and outcomes of osimertinib in the treatment of leptomeningeal disease in EGFR-mutant NSCLC

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Type</th>
<th>Patients (n)</th>
<th>Age</th>
<th>Sex</th>
<th>Histologic type</th>
<th>Previous TKI</th>
<th>T790M status</th>
<th>Osimertinib dose (mg/day)</th>
<th>Adverse effects</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. (19)</td>
<td>Phase I trial</td>
<td>32</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>11 positives; 21 unselected</td>
<td>160</td>
<td>(I) Grade 1 skin n=20; (II) At 12 weeks, 10/32 radiological response and 13/32 diarrhoea (12 grade 1, 1 stable disease; (II) 7/8 symptomatic improvement, grade 3; (III) nausea (10 15 remains asymptomatic; (III) mean decrease in grade 1, 1 grade 3; (IV) EGFR-mutant DNA copies was 57% in 22 evaluated patients; (IV) treatment ongoing in 21 patients</td>
<td></td>
</tr>
<tr>
<td>Nanjo et al. (20)</td>
<td>Prospective pilot study</td>
<td>13</td>
<td>Median 67</td>
<td>62%; M: 38%</td>
<td>AC</td>
<td>Median 2 prior TKIs Positive</td>
<td>80</td>
<td>(I) 10≤ grade 2 rash; (II) 6≤ grade 2 paronychia; (III) 1 grade 2 interstitial lung disease</td>
<td>(I) Median PFS 7.2 months; (II) neurological improvement 4/13; (III) CSF cytology clearance 2/5; (IV) CSF penetration rate 2.5±0.3%</td>
<td></td>
</tr>
<tr>
<td>Chalmers et al. (21)</td>
<td>Case report</td>
<td>1</td>
<td>67</td>
<td>F</td>
<td>AC</td>
<td>Erlotinib</td>
<td>Negative</td>
<td>80</td>
<td>(I) Clinical and CSF cytological improvement; (II) maintained CNS response for 1 year with stable systemic disease</td>
<td></td>
</tr>
<tr>
<td>Niu et al. (22)</td>
<td>Case report</td>
<td>1</td>
<td>68</td>
<td>M</td>
<td>AC</td>
<td>Gefitinib</td>
<td>Positive</td>
<td>80</td>
<td>(I) Resolution of clinical symptoms, partial radiologic response; (II) maintained response for 12 months</td>
<td></td>
</tr>
<tr>
<td>Sakai et al. (23)</td>
<td>Case report</td>
<td>1</td>
<td>70</td>
<td>F</td>
<td>AC</td>
<td>Gefitinib &amp; Erlotinib</td>
<td>Positive</td>
<td>80</td>
<td>(I) Symptom relief within days; (II) radiologic improvement on MRI at 7 weeks</td>
<td></td>
</tr>
<tr>
<td>Chan et al. (24)</td>
<td>Case report</td>
<td>1</td>
<td>44</td>
<td>M</td>
<td>AC</td>
<td>Gefitinib</td>
<td>Positive</td>
<td>80</td>
<td>(I) Clinical and radiologic improvement; (II) ongoing stable disease at 10 months</td>
<td></td>
</tr>
<tr>
<td>Takeda et al. (25)</td>
<td>Case report</td>
<td>1</td>
<td>73</td>
<td>F</td>
<td>AC</td>
<td>Gefitinib &amp; Erlotinib</td>
<td>Positive</td>
<td>80</td>
<td>(I) Clinical, CSF and radiologic improvement; (II) progression free at 10 months with ongoing treatment</td>
<td></td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; NR, not reported; AC, adenocarcinoma; PFS, progression-free survival; CSF, cerebrospinal fluid; CNS, central nervous system; MRI, magnetic resonance imaging.
achieving significant clinical response using osimertinib. Further prospective studies are needed to evaluate the efficacy and safety of osimertinib in this setting.

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None.

**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Informed Consent:* Written informed consent was obtained from the patient for publication of this manuscript and any accompanying image.

**References**


