Rapid Intracranial Response to Osimertinib in a Patient with Epidermal Growth Factor Receptor T790M-Positive Adenocarcinoma of the Lung

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Introduction

The T790M status in an individual patient can be spatiotemporally heterogeneous because of selective pressure from epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Our case report shows that re-biopsy in EGFR-mutated non-small cell lung cancer (NSCLC) patients with acquired TKI resistance should be performed.

Case Report

A 39-year-old female smoker (20 pack-years, ECOG 0) presented with multiple asymptomatic brain metastases. Analysis revealed a lung adenocarcinoma with an epidermal growth factor receptor (EGFR) exon 19 deletion (p.E746_A750del; c.2232_2249delins18). She achieved a partial remission on gefitinib in July 2012.

Keywords

• AZD9291 · Osimertinib · Intracranial · Lung cancer · Response · EGFR mutation · T790M

Established Facts

• Osimertinib (AZD9291, Tagrisso) is a potent, irreversible third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) selective for sensitizing EGFR and T790M resistance mutations (acquired after therapy with gefitinib).
• Currently approved TKIs have poor properties for penetrating blood-brain barrier.

Novel Insights

• Our report demonstrates that osimertinib is able to inhibit the growth of a radiotherapy- and surgery-refractory EGFR T790M-positive brain metastasis in a patient with lung adenocarcinoma.
• To our knowledge this is the first report of a patient with radiotherapy- and surgery-refractory brain disease who could be salvaged with the third-generation EGFR inhibitor osimertinib.

Summary

Background: Osimertinib (AZD9291, Tagrisso) is a potent, irreversible third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Case Report: Our report demonstrates that osimertinib is able to inhibit the growth of a radiotherapy- and surgery-refractory EGFR T790M-positive brain metastasis in a patient with lung adenocarcinoma. Conclusion: These data show that re-biopsy in EGFR-mutated non-small cell lung cancer patients with acquired TKI resistance should be performed.

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After 6 months, a growing right parietal metastasis was treated with gamma-knife radiosurgery (18 Gy). Due to rapid recurrence, the lesion was resected and whole brain radiation (26 Gy) was administered followed by pemetrexed/bevacizumab until May 2015. The patient suffered from chronic steroid treatment due to peritumoral edema of the brain metastasis. Therefore, bevacizumab was successfully used to reduce edema and steroids could be reduced. A second resection of the parietal metastasis was performed due to progressive unilateral neurological deficits. At this time, molecular analysis detected the EGFR p.T790M (c.2369C>T) mutation in addition to the EGFR p.E746_A750del mutation (fig. 1). The tumor re-grew within 2 months after resection (fig. 2A). She was started on osimertinib (80 mg daily) and restaging after 4 weeks of therapy demonstrated a significant partial remission of the brain metastasis (fig. 2B) and a partial remission of the lung disease (in the absence of further organ involvement). Currently, the patient is doing well without any side effects and continues on osimertinib.

Our patient underwent multiple local treatments for the brain metastases due to the prior unavailability of osimertinib.

**Discussion**

Acquired resistance to gefitinib is caused by a T790M gatekeeper mutation in > 50% of patients [1]. Several third-generation EGFR TKIs are being developed to selectively target mutant EGFR and T790M, including rociletinib, osimertinib, HM61713, EGF816X and ASP8273 [2–4]. Both osimertinib and rociletinib have demonstrated response rates of 60% and progression-free survival of 9–10 months [5, 6].

Progression in the central nervous system (CNS) in patients with asymptomatic brain metastases treated with gefitinib occurs in up to 50% of cases [7]. Given the side effects of radiotherapy to the brain, activity in the CNS of systemic therapy is clinically essential. In a preclinical study by Ballard et al. [8], osimertinib demonstrated high distribution into mouse and cynomolgus monkey brain, while gefitinib (mouse), rociletinib (mouse, cynomolgus), and afatinib (mouse) had poor or no measurable brain concentrations. Furthermore, osimertinib led to tumor regression in a mouse xenograft model with EGFR-mutated brain metastases. Consistent with these preclinical data, our report demonstrates that osimertinib was able to inhibit the growth of a radiotherapy- and surgery-refractory EGFR T790M-positive brain metastasis in a patient with lung adenocarcinoma.

The T790M status in an individual patient can be spatiotemporally heterogeneous because of selective pressure from EGFR TKI. There is a large variety of T790M occurrence (30–83%) after first-generation EGFR TKI treatment [9]. Kuiper et al. [10] showed that the incidence of T790M mutation in first post-TKI biopsy in his cohort of EGFR-mutated NSCLC patients was 52%. Hata et al. [11] found an incidence of 28% for a T790M mutation in leptomeningeal metastases after acquired resistance to EGFR TKI. In a review, Ohashi [12] demonstrated an overall survival benefit for patients with EGFR-mutated lung adenocarcinoma.
These data show that re-biopsy in EGFR-mutated NSCLC patients with acquired TKI resistance should be performed. Furthermore, in patients with acquired resistance to first- or second-generation TKIs, consideration should be given to whether radiotherapy/surgery should be delayed until no further effect of osimertinib or other third-generation TKI is established.

In conclusion, this case demonstrates the good efficacy of the third-generation TKI osimertinib in leptomeningeal metastases. Based on the data from Hata et al., a T790M mutation in leptomeningeal metastases can be found in approximately 28% of cases after acquired resistance to EGFR TKI. In patients with EGFR T790M-positive brain metastases, delaying radiotherapy/surgery until no further effect of osimertinib or other third-generation TKI should be considered.

**Disclosure Statement**

All authors declare no conflicts of interest.

**References**