Systemic and Intracranial Efficacy of Osimertinib in EGFR L747P-Mutant NSCLC: Case Report

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ABSTRACT

Introduction: EGFR L747P mutations occur rarely, with limited preclinical research and case reports suggesting resistance to osimertinib.

Main Concerns, Important Clinical Findings, Primary Diagnoses, Interventions, Outcomes: An 84-year-old white male with remote smoking history presented with bilateral pulmonary nodules and multiple subcentimeter enhancing brain lesions 2 years after receiving stereotactic radiation therapy for a left upper lobe lung adenocarcinoma. After two computed tomography-guided biopsies yielded inadequate tissue and cell-free DNA analysis identified no actionable alterations, surgical biopsy results revealed an EGFR L747P mutation. Limited case reports and preclinical data suggested that this rare mutation may be resistant to the third-generation EGFR inhibitor osimertinib and recommended use of second-generation EGFR inhibitors. Because the patient had low disease burden and there were concerns on tolerability of second-generation EGFR inhibitors, the patient was initiated on osimertinib. Treatment was well-tolerated and follow-up imaging results revealed thoracic and intracranial response to therapy, which has been sustained 6 months after treatment initiation.

Conclusion: Despite predicted and previously reported resistance, osimertinib may have durable efficacy against rare EGFR L747P mutations. Persistent attempts to acquire material for tumor genomic analysis may yield results critically important to clinical management.

Keywords: Brain metastases; Epidermal growth factor receptor; Lung cancer; Next generation sequencing; Targeted therapy; Case report

Introduction

Although there is extensive clinical experience with EGFR inhibitors in common activating exon 19 deletions and exon 21 L858R mutations, and more recently with exon 20 insertions, efficacy against rare EGFR mutations is less clear. In such cases, clinicians must rely on preclinical studies, case reports, or small subsets from clinical trials for treatment guidance. Here, we report a rare EGFR L747P mutation, which was generally predicted to be resistant to third-generation EGFR inhibitor osimertinib, but actually

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sustained a durable systemic and intracranial response to osimertinib.

Case Presentation
An 84-year-old white male had previously been treated with stereotactic radiation therapy for an early stage left upper lobe lung adenocarcinoma. After 2 years, he developed bilateral pulmonary nodules (Fig. 1A and C). He had no cardiopulmonary or neurologic symptoms. Result of a computed tomography-guided percutaneous biopsy of a dominant left lung nodule confirmed recurrent lung adenocarcinoma. Magnetic resonance imaging result revealed multiple subcentimeter enhancing brain lesions (Fig. 2A). Performance status was Eastern Cooperative Oncology Group 2.

Relevant history included 10 pack-years smoking more than 50 years before lung cancer diagnosis. Current biopsy archival material yielded insufficient tissue for genomic analysis. Cell-free DNA analysis did not identify any actionable alterations. A second computed tomography-guided biopsy also yielded insufficient tissue. The patient then underwent surgical biopsy. Result of next-generation sequencing revealed EGFR L747P mutation. The tumor also harbored mutations in KDM5C, KALRN, FGF3, ITGA8, DNAJB1, and RRM1 of unknown clinical significance.

On the basis of limited case reports and preclinical studies suggesting resistance to the third-generation EGFR inhibitors, the clinical genomic testing report suggested treatment with second-generation EGFR inhibitors, such as afatinib or dacomitinib. Nevertheless, based on a low disease burden, absence of cancer-associated symptoms, and concerns on potential toxicities, after a detailed risk-benefit discussion of osimertinib, osimertinib (standard dose, 80 mg orally daily) was initiated.

The patient tolerated osimertinib well, complicated only by manageable grade 1 paronychia. Results of repeat thoracic and brain imaging (Figs. 1B and D and 2B) revealed radiographic response, which was ongoing 7 months after treatment initiation.

Discussion
Rare tumor types present clear challenges to clinicians. In place of randomized clinical trials or large population studies, they must rely on far more limited evidence, such as case series, preclinical findings, or even anecdotal experience. EGFR L747P, a missense mutation in exon 19 that results from the conversion from leucine to proline through a double thymine-to-cytosine (TT > CC) transition, seems to represent less than 1% of EGFR mutations. In the published literature, this activating mutation has

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Figure 1. Response of thoracic tumors to osimertinib. Left upper lobe mass (A) at pretreatment baseline and (B) after 6 months of therapy. Left upper lobe nodule (C) at pretreatment baseline and (D) after 6 months of therapy.
generally been associated with intrinsic resistance to first- (e.g., erlotinib, gefitinib) and third-generation (e.g., osimertinib) EGFR inhibitors, with greater sensitivity to second-generation (e.g., afatinib, dacomitinib) EGFR inhibitors. Indeed, a recent structure-function analysis of almost 17,000 patients with EGFR-mutant NSCLC characterized L747P among mutations predicted to be P-loop and αC-helix compressing, a group resistant to first- and third-generation, but sensitive to second-generation, EGFR inhibitors.

Given the available data, why did we elect to administer osimertinib, a therapy predicted to be ineffective against this particular EGFR mutation? Despite the presence of brain metastases, the patient had a low tumor burden, no cancer-related symptoms, and seemed unlikely to clinically deteriorate in the near term if disease progression occurred. In addition, the patient’s advanced age and Eastern Cooperative Oncology Group 2 performance status raised concerns that he may not tolerate second-generation EGFR inhibitors, which have considerably higher rates and severity of mucocutaneous toxicities, including rash, mucositis, paronychia, and rash.

Perhaps most indicative of antitumor efficacy is the intracranial response. Although osimertinib has superior blood-brain barrier penetration than earlier-generation EGFR inhibitors, cerebrospinal fluid analysis suggests that intracranial concentrations of the parent drug and active metabolites are less than 20% those in plasma levels. Whether similar efficacy would have been achieved with a second-generation EGFR inhibitor—hypothetically more pharmacodynamically potent but less able to penetrate the brain—is not known. Furthermore, at the time of future disease progression, the role of second-generation EGFR inhibitor administration is not clear.

This case also serves as a reminder that, when it comes to molecular characterization of advanced nonsquamous NSCLC, persistence and patient education may pay off. Given the difficult anatomical location and small size of the lesions in this patient, only a surgical biopsy—which the patient agreed to despite two recent biopsies and one distant percutaneous biopsy—yielded sufficient material for genomic analysis. With relatively low tumor burden, the lack of actionable alterations on cell-free DNA testing in this case is not unexpected and at the time was interpreted as reflecting assay sensitivity rather than a true absence of targets. Unfortunately, at the time of future disease progression, determination of tumor genotype to evaluate molecular evolution may again require tumor excision.

As for any single case report, this clinical experience cannot be interpreted as a broad recommendation to pursue excisional biopsy for tumor genomic analysis, or to deviate from best available evidence. The other principal limitation of the present report is an unclear explanation for EGFR L747P sensitivity versus resistance to various EGFR inhibitors.
Conclusion

Despite predicted and previously reported resistance, in some instances, osimertinib may have durable efficacy against rare EGFR L747P mutations. Persistent attempts to acquire material for tumor genomic analysis may yield results critically important to clinical management.

CRediT Authorship Contribution Statement

David E. Gerber, Mitchell S. von Itzstein: Conceptualization, Writing - original draft.
David E. Gerber, Melissa Mayer, Jeffrey Gagan, Mitchell S. von Itzstein: Investigation.
David E. Gerber, Melissa Mayer, Mitchell S. von Itzstein: Project administration.
David E. Gerber, Melissa Mayer, Jeffrey Gagan: Writing - review and editing.

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