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Case Report

Osimertinib for Uncommon Endothelial Growth Factor Receptor-Mutant Non-Small Cell Lung Carcinoma: A Case Report

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Keywords
Non-small cell lung cancer · Uncommon epidermal growth factor receptor mutation · Osimertinib · Case report

Abstract
Background: Non-small cell lung cancer (NSCLC) accounts for 84% of all lung cancers and continues to remain the leading cause of cancer-related mortality worldwide. The advent of gene targeted therapies has changed the landscape of NSCLC management. Osimertinib is a third-generation tyrosine kinase inhibitor (TKI) that has activity against exon 19, exon 21 (L858R) mutations. It is also active against T790M mutation which is the most common resistant mechanism to earlier generation TKIs. Activity of osimertinib against rare EGFR mutations is largely unknown. We report the case of a 64-year-old woman with metastatic NSCLC carrying an exceedingly rare deletion-insertion exon 19 EGFR mutation (p.E746_S752delinsV) who demonstrated sustained disease control with osimertinib, achieving a progression-free survival of 26 months. ***Case Presentation:*** A 64-year-old nonsmoker female presented with back pain for 1 month. Magnetic resonance imaging spine showed pathological fracture secondary to multiple lytic lesions. She underwent FDG PET/CT that showed large left lower lobe mass, bilateral pulmonary nodules, widespread osteolytic lesions. She underwent iliac lytic lesion biopsy that was consistent with adenocarcinoma (TTF1- and CK7-positive). Tumor tissue next-generation sequencing showed EGFR exon 19 mutation (DNA change: c.2237_2255delinsT, amino acid change: p.E746_S752delinsV [Glu 746_Ser752delinsval]). She was started on osimertinib and showed clinical response within 2 weeks of starting therapy. She was able to maintain a response for 26 months since starting treatment. ***Conclusion:*** In summary, there are limited prospective data to guide therapy in patients with rare EGFR mutations. Prospective

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studies are required to evaluate the response to endothelial growth factor receptor-tyrosine kinase inhibitors in patients with rare EGFR mutations in order to ensure patient safety and response to treatment in this patient population.

Introduction

Non-small cell lung cancer (NSCLC) accounts for 84% of lung cancers and continues to be the leading cause of cancer-related mortality worldwide [1]. The advent of targeted therapies has revolutionized the landscape of NSCLC management. Osimertinib is an irreversible third-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) that is selective for patients with mutant EGFR and has activity against the T790M point mutation that results in resistance to first- and second-generation EGFR-TKIs [2]. The FLAURA trial was a landmark study that demonstrated superiority of osimertinib compared to first-generation EGFR-TKIs in terms of both progression-free survival (PFS) and overall survival in previously untreated advanced NSCLC patients harboring specific EGFR sensitizing mutations such as exon 19 deletions or L858R exon 21-point mutation [3]. Exon 19 deletions and L858R exon 21-point mutations are common, accounting for approximately 80% of EGFR mutations. The remaining 10–20% EGFR mutations are comprised rare genomic alterations within exon 18–25 of the *EGFR* gene, and the role of osimertinib in patients harboring these uncommon mutations remains largely unknown [4]. Here, we report the case of a 64-year-old woman with metastatic NSCLC carrying an exceedingly rare deletion-insertion exon 19 EGFR mutation (p.E746_S752delinsV) who demonstrated sustained disease control with osimertinib, achieving a PFS of 26 months.

Case

A 64-year-old woman, never-smoker, presented with back pain for 1 month which led her to be wheelchair-dependent. Magnetic resonance imaging lumbar spine revealed pathological fracture due to metastatic bony lesions in the fourth lumbar vertebrae and concern for metastatic disease involving the left side of the upper sacrum.

^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography revealed a large left lower lobe mass with mild non-focal activity (standardized uptake value 3.8), innumerable bilateral small pulmonary nodules without significant FDG uptake, as well as widespread osteolytic metastases (standardized uptake value 4.6). CT-guided core-needle biopsy of a lytic right-iliac lesion revealed adenocarcinoma with positive immunohistochemical staining for cytokeratin-7 and thyroid transcription factor-1 consistent with lung origin. Due to lumbar spinal instability, she underwent L2-S1 posterior spinal fixation. She was soon readmitted with worsening shortness of breath and became oxygen (O_2)-dependent due to increased cancer burden in her lungs and bilateral pleural effusions. Next-generation sequencing from original biopsy was positive for an uncommon deletion-insertion EGFR exon 19 mutation (DNA change: c.2237_2255delinsT, amino acid change: p.E746_S752delinsV [Glu 746_Ser752delinsval]). Programmed death-ligand 1 expression was 0%. Due to a clinical picture consistent with mutant EGFR driven NSCLC (never-smoker woman with NSCLC), the patient was started on palliative therapy with osimertinib 80 mg daily. Within 2 weeks, her shortness of breath improved, and she was not dependent on O_2

anymore. After several months on osimertinib, she experienced severe nausea, vomiting, and fatigue, and her dose was reduced to 40 mg daily which she tolerated well. During treatment with osimertinib, serial scans demonstrated response to therapy with no clear evidence of disease progression for 26 months (Fig. 1). Thereafter, a CT chest revealed worsening pulmonary metastases, and a CT abdomen-pelvis revealed mixed sclerotic and lucent lesions throughout the osseous spine and sternum suspicious for osseous metastases. Due to disease progression, the patient was started on palliative chemotherapy with carboplatin and pemetrexed (Fig. 2).

Discussion

Patients with advanced NSCLC without oncogenic driver mutations are treated with chemoimmunotherapy or immunotherapy alone based on programmed death-ligand 1 assessment and disease characteristics [5]. NSCLC patients with EGFR mutations account for 10–20% of all lung cancer patients in the USA [6]. Targeted therapies for EGFR-mutant NSCLC have emerged as first-line treatment for patients with advanced NSCLC harboring sensitizing mutations; however, it is important to note that majority of the landmark studies for EGFR targeted therapies only included patients with classical EGFR mutations; exon 19 deletions and L858R exon 21-point mutations [3, 7, 8]. In 2018, Food and Drug Administration approved afatinib, a second-generation EGFR-TKI, as first-line treatment for patients with metastatic NSCLC harboring nonresistant EGFR mutations (S768I, L861Q, and/or G719X) other than exon 19 deletions or exon 21 L858R substitutions.

Uncommon mutations comprise a heterogeneous group of genomic alterations within exons 18–25 of the *EGFR* gene [4, 9, 10]. Frequently occurring uncommon mutations include G719X, S768I, L861Q, complex mutations, and exon 20 insertions [11]. Although there has been a recent increase in the detection of these uncommon mutations owing to the widespread use of next-generation sequencing, little is known about the efficacy of EGFR-TKIs in this population.

The UNICORN study is a multicenter retrospective study in a cohort of 60 patients with uncommon EGFR-mutant NSCLC treated with osimertinib as first-line therapy [12]. This study included patients with atypical exon 19 deletions (i.e., deletion-insertions as seen in our patient). The results of this study reported an overall response rate of 60% and a PFS of 8.6 months in patients harboring uncommon mutations treated with first-line osimertinib. The UNICORN phase 2 trial included 40 patients with previously untreated NSCLC harboring uncommon EGFR mutations. Patients in this trial were treated with 80 mg osimertinib daily, and the study found that osimertinib showed clinical activity in these patients with an ORR of 55% and a PFS of 9.4 months [11]. A Korean multicenter phase-II trial (KCSG-LU15-09) that included patients with uncommon EGFR mutations treated with osimertinib reported a median PFS of 8.2 months [13].

Deletion-insertion mutations as seen in our patient represent an exon 19 deletion subtype and are rare among the uncommon EGFR mutations. One retrospective study by Chen et al. [14] attempted to delineate the clinical features and prognosis associated with different subtypes of EGFR exon 19 deletion-insertions. This study analyzed 69 patients with exon 19 deletion-insertions, out of which 5 patients (7.2%) harbored the mutation seen in our patient (E746_S752delinsV). The study concluded that patients with EGFR deletion-insertion mutations exhibited limited sensitivity to 3rd generation EGFR-TKIs with a median PFS of 7 months compared to 16.6 months with first-generation tyrosine kinase inhibitor (TKI) and 13.6 months with second-generation TKI. However, our patient achieved sustained disease control with osimertinib with a PFS of 26 months. Similarly, Wang et al. [15] reported 41

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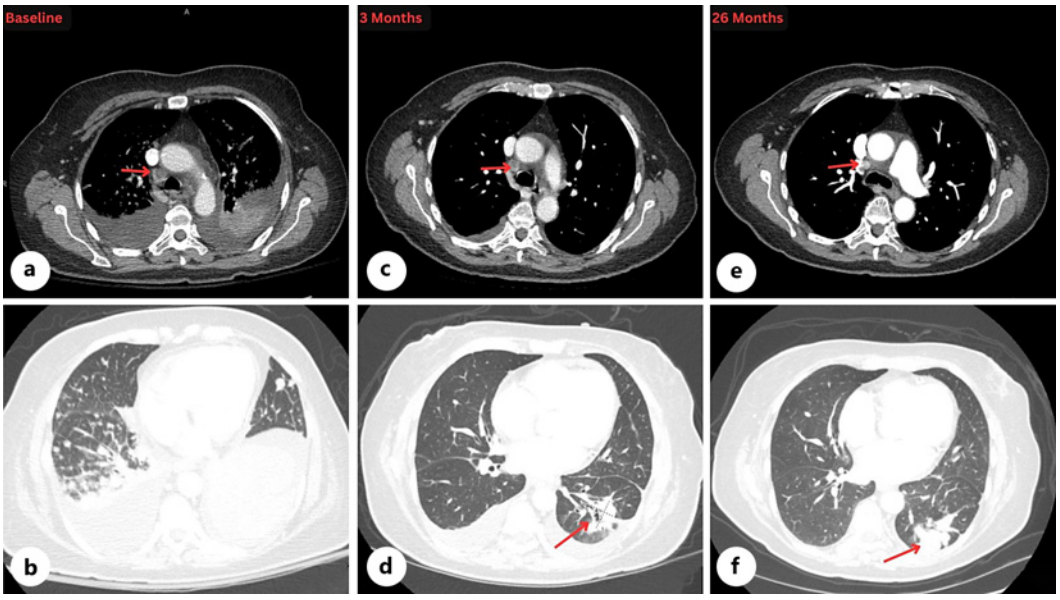

Fig. 1. Baseline: CT chest with contrast revealing a right paratracheal lymph node measuring 1.5 × 1.4 cm (**a**) and innumerable bilateral pulmonary nodules with left lung collapse (**b**). Three months after initiation of osimertinib: CT chest with contrast revealing decrease in the size of the right paratracheal lymph node, now measuring 1.2 × 1.2 cm (**c**). A rounded nodular opacity with central cavitation (2.9 × 2.5 cm) previously not seen due to left lung collapse is now visible (**d**). 26 months after initiation of osimertinib: The right paratracheal lymph node appears stable compared to previous scans measuring 0.9 × 0.8 cm (**e**). Worsening disease in the left lower lobe is noted, with the nodular opacity now measuring 2.4 × 1.6 cm (**f**) (2.1 × 1.4 cm on preceding scan).

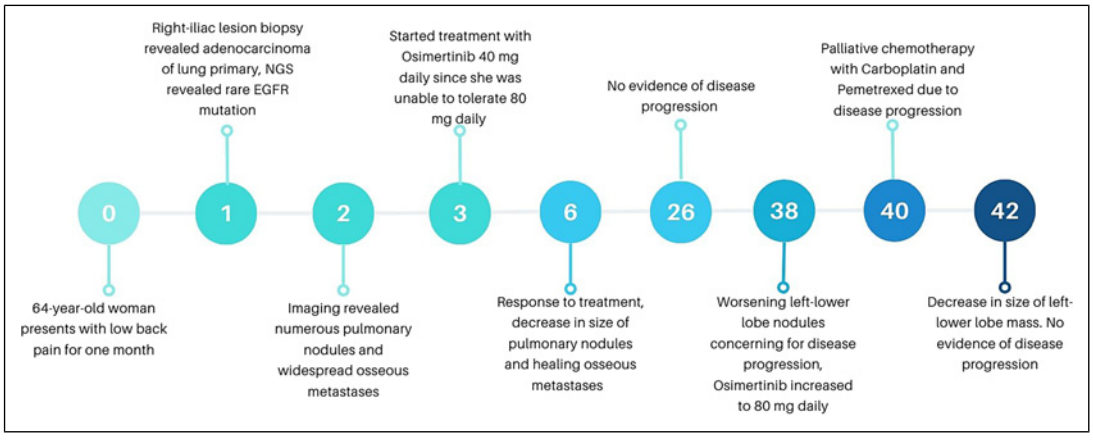

Fig. 2. Timeline diagram of significant events with numbers representing time in months from diagnosis.

patients with exon 19 deletion-insertions who had similar outcomes when compared to patients with EGFR exon 19 deletion when treated with first-generation EGFR-TKIs. Due to the heterogeneity and rarity of uncommon EGFR mutations, it is unlikely that we would ever have reliable results by conducting randomized controlled trials in this patient population. Hence, registry-based studies, retrospective review of large clinic genomic databases, and reporting rare cases (like ours) will help build the evidence to determine the best treatment approach. Preference of one EGFR-TKI over another is not justified currently due to conflicting

retrospective reports of clinical benefit derived from different agents. Although evidence is limited, this case highlights the potential benefit osimertinib provides in treating patients harboring EGFR exon 19 deletion-insertion.

Conclusion

Third-generation EGFR-TKIs are now recognized as first-line treatment for patients with previously untreated NSCLC harboring EGFR mutations. Most studies that led to this landmark introduction excluded patients with uncommon EGFR mutations, and hence, there are limited prospective data to guide management in these patients. While further prospective studies are required to determine the best management strategies, continued reporting of response to different EGFR-TKIs among patients with uncommon EGFR mutations is strongly encouraged to help guide management in this population.

Statement of Ethics

Ethical approval is not required for this case report in accordance with national guidelines. Written informed consent was obtained from patient for publication of the details of their medical case and any accompanying images (available upon request). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000542201).

Conflict of Interest Statement

Niveditha Popuri, MD, Vishnu Nagalapuram, MD, Unaiza Zaman, MD, and Raid Aljumaily, MD, have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership or other equity interest; and expert testimony or patent-licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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Author Contributions

All authors had access to the data and participated in the writing of the manuscript. Conceptualization, resources, visualization, and supervision: Dr. Raid Aljumaily. Methodology and writing – original draft: Dr. Niveditha Popuri. Software, formal analysis, investigation, data curation, and funding acquisition: N/A. Validation: Dr. Vishnu Nagalapuram. Writing – review and editing: Dr. Vishnu Nagalapuram, Dr. Raid Aljumaily, and Dr. Unaiza Zaman. Project administration: Dr. Vishnu Nagalapuram and Dr. Unaiza Zaman.

Data Availability Statement

All data underlying the results are available as part of the article, and no additional source data are required. Further inquiries can be directed to the corresponding author.

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