Metabolic complete tumor response in a patient with epidermal growth factor receptor mutant non-small cell lung cancer treated with a reduced dose of afatinib

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Abstract
Tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (EGFR) are the first-line treatment for EGFR-mutant non-small cell lung cancer. Toxicities related to EGFR-TKIs include skin rash, paronychia, and diarrhea, which in some cases can lead to dose reductions or treatment interruptions. Herein, we report the case of a 51-year-old woman affected by advanced adenocarcinoma harboring an exon 19 deletion in the EGFR gene, who was treated with second-generation EGFR-TKI following a scheduled gradual dose reduction to better manage toxicities. Following prescription labeling, treatment was initiated at a dose of 40 mg daily. After a few months, the dose was reduced to 30 mg daily owing to grade 3 skin toxicity. A metabolic complete tumor response was observed after 1 year of treatment, then therapy was continued at 20 mg daily, enabling disease stabilization. In conclusion, low dose afatinib was effective in an EGFR-mutant non-small cell lung cancer patient who required dose reductions to better manage toxicities.
Introduction

Lung cancer is one of the most common cancer types and a leading cause of cancer-related deaths worldwide.\textsuperscript{1,2} Lung tumors are generally classified as non-small cell lung cancer (NSCLC) and small cell lung cancer according to their histological features, and each subtype shows a characteristic molecular heterogeneity.\textsuperscript{3} Among NSCLC cases is a subset in which members of the \textit{ErbB} family, including epidermal growth factor receptor (\textit{EGFR}/\textit{ErbB1}), \textit{HER2}/\textit{ErbB2}, \textit{HER3}/\textit{ErbB3}, and \textit{HER4}/\textit{ErbB4} are often mutated; these transmembrane proteins are involved in various cellular pathways, and it has been observed that alterations in some of them are crucial for tumorigenesis.\textsuperscript{3}

The most common \textit{EGFR} mutations occur in exons 18 through 21, which encode the intracellular tyrosine kinase (TK) domain. The classical oncogenic \textit{EGFR} mutations are exon 19 deletion (Ex19Del) and exon 21 point mutations, which account for approximately 85\% of all \textit{EGFR} mutations.\textsuperscript{4} \textit{EGFR} Ex19Del mutations are the most prevalent, representing approximately 60\% of all NSCLC-associated \textit{EGFR} mutations.\textsuperscript{4} These deletions include several molecular variants, including in-frame deletions, substitutions, and insertions.

Because \textit{EGFR} somatic activating mutations are common drivers of cancer, \textit{EGFR} protein has become a molecular target for personalized therapy over the past decade; several reversible and irreversible tyrosine kinase inhibitors (TKIs), i.e., gefitinib, erlotinib, afatinib, dacotinib, and osimertinib, have been developed and approved as first-line treatments for patients with somatic \textit{EGFR} mutations.\textsuperscript{5–9}

Clinical application of the second-generation TKI afatinib has been spreading because of its efficacy;\textsuperscript{10–15} nevertheless, it can cause adverse events (AEs) including cutaneous (rash or acne) and gastrointestinal (diarrhea or stomatitis) toxicities that necessitate treatment interruptions or dose reductions.\textsuperscript{11}

Herein, we report the case of a patient with advanced adenocarcinoma harboring a common \textit{EGFR} Ex19Del mutation that is known to confer afatinib sensitivity. The patient was effectively treated with a gradually decreasing afatinib dose. Dose reduction from 40mg to 20mg allowed disease stabilization as well as better toxicity management. In our experience, afatinib at a reduced dose remains effective while allowing better tolerability than at higher doses.

Case report

This study was compliant with all relevant ethical regulations involving human participants and was approved by the Istituto Oncologico del Mediterraneo Institutional Review Board (project ID code: n_1 of 24.09.2015). Signed informed consent was obtained from the patient. A 51-year-old woman with no smoking history presented at our hospital referring a 4-month history of cough and exertional dyspnea.
The patient also had a medical history of hypertension, celiac disease, and dyslipidemia. Computed tomography (CT) imaging of the chest revealed a total consolidation of the middle lobe of the right lung, with ground glass effect and pleural diffusion (M1a) (Figure 1a).

Positron emission tomography (PET) imaging (Figure 2a) confirmed the same lesions and hilar homolateral adenopathy; no evidence of distant metastases to other sites was noted. The patient underwent bronchoscopy with biopsy and brushing, and the diagnoses was NSCLC adenocarcinoma. EGFR gene sequencing showed the presence of an Ex19Del, activating E746-A750del mutation, and ALK negative. The patient was diagnosed as Stage IV (cT4 N0 M1a), according to the American Joint Committee on Cancer staging system, 7th edition. On the basis of on histotype, tumor biology, and the patient’s good performance status, first-line therapy with afatinib (40 mg oral-daily) was initiated in September 2015.

After 3 months of TKI therapy, a CT scan showed a good response to afatinib with partial reduction of the middle lobe lesion, with no more definable ground glass area (Figure 1b) and good tolerability. In April 2016, a CT scan revealed further reduction of the middle lobe lesion (not shown). Despite the good tumor response,
the patient reported grade 3 skin rash and grade 1 diarrhea. As a consequence of the grade 3 skin toxicity, afatinib was interrupted, with gradual regression to grade 2 toxicity in 5 days. The patient started oral and topical antibiotic treatment according to dermatologic consultation. Six days after treatment interruption, the patient restarted afatinib at 30 mg daily. In October 2016, a CT scan revealed further reduction of middle lobe lesion and absence of hilar lymphadenopathy (Figure 1c). Aside from resolution of respiratory symptoms, the patient presented with improved cutaneous toxicity, with persistence of a grade 1 cutaneous rash and grade 1 paronychia requiring treatment with 2% sulfosalicylic cream, astringent gel, and polyethylene glycols ointment. Considering the good clinical response to treatment and limited extension of disease, the patient underwent a PET scan, which showed complete metabolic tumor response (Figure 2b).

After radiotherapy consultation, afatinib was interrupted and the patient was admitted for radiation treatment between 12 December 2016 and 20 January 2017. Intensity modulated radiation therapy consisting of a total dose of 6020 cGy was focused on the right hemi-mediastinum plus homolateral lung lesion with a boost on the right pulmonary hilum. As a consequence of radiotherapy, the patient presented with post actinic pneumonia (Figure 1d), which was treated with corticosteroids, and then afatinib was restarted at 30 mg daily. In September 2017, a CT scan showed resolution of pneumonia and an additional tumor response (Figure 1e). Because the grade 2 cutaneous toxicity reemerged in October 2017, the afatinib dosage was further reduced to 20 mg daily. The patient continued therapy with afatinib at 20 mg daily until May 2019 with good disease control and tolerability.

Discussion

Historically, platinum-based chemotherapy was the standard first-line treatment for NSCLC. In patients harboring EGFR mutations, EGFR-TKIs are now the standard of care and provide improved progression-free survival and overall response rates. In fact, several studies have demonstrated the improved effectiveness of EGFR-TKIs versus chemotherapy as a first-line therapy for metastatic NSCLCs harboring certain activating EGFR mutations, with fewer AEs than standard chemotherapy. EGFR mutation status is the most important determining factor for clinical response to EGFR-TKI. EGFR Ex19Del mutations account for approximately 60% of lung cancer-associated EGFR mutations and include a heterogeneous group of mutations. The most frequently observed EGFR Ex19Del is E746-A750, which is between the third $\beta$-strand of the EGFR tyrosine kinase domain and its key regulatory $\alpha$C helix, whereas many other EGFR Ex19Dels are complex insertion-deletions starting at leucine 747, in which the deleted amino acids are replaced with non-native residues (such as the L747-A750 > P and L747-P753 > S variants). Although it is known that EGFR Ex19Dels can constructively impact the sensitivity of TKI treatment by activating the TK region, potential differences in TKI sensitivity between individual EGFR Ex19Dels is not well established.

Afatinib is an irreversible, second-generation EGFR-TKI that has been proven to provide significantly longer overall survival compared with platinum-based chemotherapy when used in lung cancer patients with EGFR Ex19Del mutations. Second-generation TKIs have also demonstrated superior outcomes versus the first-generation TKIs, erlotinib and gefitinib. Recent studies have investigated
potential differences in the TKI sensitivity of common and uncommon EGFR Ex19Dels. Good clinical response to first-line afatinib monotherapy has been observed in each EGFR Ex19Del molecular variant.30 However, patients harboring EGFR Ex19Dels starting at codon E746 had a better median progression-free survival (14.2 months) than those harboring Ex19Dels starting at codon L747 (6.5 months).26 The recommended starting dose of afatinib is 40 mg daily for patients whose lung cancers harbor EGFR mutations, although this dose is often accompanied by side effects, with diarrhea and rash/ acne being the most frequently reported AEs. In fact, more severe AEs were observed in patients who received the standard 40 mg afatinib daily compared with those who received a first-generation EGFR-TKI, such as gefitinib or erlotinib.31 Therefore, in clinical practice, many clinicians prescribe a lower starting dose of afatinib32,33 or perform dose modifications34,35 to improve patient outcomes and adherence,31 without compromising its beneficial effect.

In our case, the patient was treated with 40 mg afatinib daily owing to its ability to irreversibly block EGFR, which is different than first-generation EGFR-TKIs. After 6 months of treatment, the dose was reduced to 30 mg because of cutaneous toxicity; dose reduction to 30 mg daily resulted in a complete metabolic tumor response after another 5 months of therapy. A previous case report36 and several clinical trials37,38 have reported the effectiveness and safety of the treatment strategy involving reduced doses of afatinib in patients with NSCLC harboring the EGFR Ex19Del mutation E746-A750del who developed unacceptable side effects at higher doses. Furthermore, a recent clinical trial that enrolled patients with metastatic lung adenocarcinoma who were treated with either 30 mg or 40 mg afatinib daily as first-line treatment demonstrated that patients who received an initial afatinib dose of 40 mg daily required dose reduction (or discontinuation) more frequently than those who initially received 30 mg daily (40% vs. 8%); however, this study did not discriminate between patients with Ex19Dels and those with exon 21 L858R point mutations.31

In our case, a lower afatinib dose still allowed the patient to achieve a complete metabolic tumor response and then stable disease with a long lasting response (47 administrations from September 2015 to May 2019). Reducing the afatinib dose helps better manage AEs, including cutaneous toxicity. In our experience, afatinib at a reduced dose retains its efficacy with a better toxicity profile compared with higher doses.

**Conclusion**

This case demonstrated that low-dose afatinib was effective for disease control in a patient diagnosed with NSCLC harboring the EGFR Ex19Del mutation E746-A750del who developed unacceptable side effects at higher doses. However, more clinical trial and/or real-life data are required to find a reliable strategy for:

(i) effectively treating patients harboring common and uncommon EGFR mutations, discriminating the use of different TKIs to reach the best clinical outcomes, while also reducing AEs;
(ii) reducing AEs associated with afatinib, while maintaining its clinical efficacy by...
using lower starting doses or dose reduction for the management of lung cancer.

The reporting of this study conforms with the CARE guidelines.39

Acknowledgement
The authors would like to thank the patient involved the study.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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