

Long-Term Response to Afatinib in Lung Adenocarcinoma Harboring Compound Uncommon *EGFR* Mutations: Case Report

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ABSTRACT

Lung cancer is the most common cause of cancer-related death worldwide and the prognosis in stage IV is poor with the overall survival not exceeding one year in patients treated with chemotherapy. Molecular disturbances in tumor cells such as *EGFR* gene mutations (exon 19 deletion or L858R substitution in exon 21 *EGFR* gene) are indication to use targeted therapies. We present a case of a 31-year-old female with metastatic adenocarcinoma of the lung with the presence of compound uncommon *EGFR* gene mutations, in which afatinib was used in first line treatment, with a partial response successfully obtained. The treatment was initiated fifteen months ago and is still continued despite acute skin side effects at the beginning of therapy.

Abbreviations: TKIs: Tyrosine Kinase Inhibitors; *EGFR*: Epidermal Growth Factor Receptor; NSCLC: Non-Small Cell Lung Cancer; GGOs: Ground-Glass Opacities; GGNs: Ground-Glass Nodules; BAL: Bronchoalveolar Lavage

Introduction

Lung cancer is the most common cause of cancer-related deaths in the world. The prognosis of patients with advanced or metastatic lung cancer is still poor. The median survival time in patients treated with classic chemotherapy does not exceed 12 months. The presence of specific molecular alterations is a positive predictor of the effectiveness of treatment with tyrosine kinase inhibitors (TKIs). In addition to better effectiveness in this specific population as compared to standard chemotherapy, they show an improvement in the quality of life and a different safety profile. At present, first- (erlotinib and gefitinib) [1,2] second- (afatinib and dacomitinib) [3,4] and third generation (osimertinib) [5] inhibitors can be used in the first-line systemic treatment. Activating epidermal growth factor receptor (*EGFR*) mutations are reported in approximately 10-15% of Caucasian patients with non-small cell lung cancer (NSCLC), mostly in female, younger patients, and in non-smokers or light smokers [6]. The most frequently found *EGFR* gene mutation is a deletion in exon 19, representing 45% of all mutations, followed by L858R substitution in exon 21 (40-

45%) [7,8] So-called uncommon *EGFR* gene mutations are found in 7-23% of patients [9,10]. Compound mutations are identified in up to 25% of uncommon mutations [11]. The prognosis depends strictly on the type of mutation. Patients with the most common rare mutations ("major" uncommon), such as G719X, L861Q and S768I, or patients with compound mutations have a better prognosis, and patients with *EGFR* exon 20 insertion or T790M mutation have a far worse prognosis [12].

Case Report

In July 2019, a 32-year-old non-smoking female reported to her family doctor due to a dry cough lasting for a month. In May 2019, she had a miscarriage in the 10th week of pregnancy. Medical history revealed no comorbidities, and the family history was also not burdened. A chest X-ray showed bilateral shadows of 4 to 6 mm in diameter. The spiral computed tomography of the chest, performed in August 2019, confirmed the presence of multiple disseminated ground-glass opacities (GGOs) up to 15 mm in both lungs and

multiple ground-glass nodules (GGNs) with dimensions up to 9 mm. Additionally, in segment 10 of the right lung, a well-saturated, nodular lesion of 20 mm was visualized. The differential diagnosis included sarcoidosis as well as inflammatory and metastatic lesions. No enlarged lymph nodes in the chest were visualized. The bronchofiberscopy did not reveal any abnormalities. No tumor cells were found in the cytological examination of the bronchoalveolar lavage (BAL) sample. Colonoscopy and gastroscopy as well as gynecological examination were performed, showing no pathology. In September 2019, a PET-CT examination was performed, showing no lesions clearly indicating a malignant process. However, nodular lesions in the lungs were visualized, which, due to the suspicion of bronchoalveolar carcinoma, underwent further diagnosis. During video thoracoscopy, a nodular lesion located in segment 10 of the right lung was sampled for histopathological examination, which confirmed the presence of non-mucous bronchioalveolar carcinoma. The tissue sample was submitted for molecular testing, confirming the presence of two rare *EGFR* gene mutations - G719X substitution in exon 18 and S768I substitution in exon 20.

Detailed results of patient's diagnostic tests are presented in Table 1. The patient was qualified for treatment with afatinib at daily dose of 40 mg and the therapy was initiated in October 2019. After 2 weeks of using the drug, the patient returned for a follow-up visit. The presence of CTCAE G3 acne-like rash accompanied by skin redness and itching was found on the skin of the face and neckline (Picture 1-4, author's own archive). Afatinib treatment was stopped and the oral lymecycline (at a dose of 2 x 300 mg for 10 days) and topical clindamycin were administered. Antipruritic drugs were also introduced with desloratadine and dexamethasone in a dose of 4 mg for 5 days. After a week, the skin lesions began to resolve (to G2), and after 14 days the G1 acneiform rash on the face was present (Picture 5, author's own archive). After a two-week break, treatment with afatinib was resumed at a reduced dose of 30 mg/d. In the first follow-up imaging assessment after 3 months of therapy, a partial response was found according to the RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria which currently retains. The patient continues treatment, there were no other side effects or recurrence of the acne-like rash. The patient is professionally active [13].

Table 1: The results of diagnostic tests.

The Test	Result
Chest X-ray July 2019	single bilateral opacities of 4 to 6 mm in diameter
Chest CT August 2019	multiple disseminated ground-glass opacities up to 15 mm in both lungs, multiple ground-glass nodules with dimensions up to 9 mm, in segment 10 of the right lung, a well-saturated, nodular lesion of 20 mm, lymph nodes not enlarged
Bronchofiberscopy August 2019	to the visible extent without no pathology
Gastroscopy, colonoscopy, gynecological examination August 2019	no pathology
PET-CT September 2019	multiple bilateral ground-glass nodules up to 10 mm, no pathological 18F-FDG uptake, in segment 10 of the right lung nodules with dimension of 11 mm; SUV 2.97, 20 mm SUV 3.98- and 12-mm SUV 4.24
Histopathological examination October 2019	<i>Carcinoma bronchioalveolare non mucinosum</i> G719X substitution in exon 18 S768I substitution in exon 20
Treatment October 2019 - still	afatinib 40 mg/d ---> afatinib 30 mg/d
Response PR	measurable T1-lesion - 20 mm -> 12 mm, reducing the number and size of ground-glass opacities and ground-glass nodules

Discussion

EGFR gene mutation occurs in about 10-15% of Caucasian patients with non-small cell lung cancer⁶. About 90% of these mutations include exon 19 deletion (45%) and exon 21 point mutation (specifically L858R; 40-45%)^{7,8}. Uncommon mutations account for 7-23% of all *EGFR* gene mutations (10% on average) and constitute a heterogeneous group of approximately 600 identified variants of molecular disorders in which the use of *EGFR*

TKIs is associated with different efficacy^{9,10}. The most frequently reported uncommon *EGFR* gene mutations include exon 20 insertions (6% of all *EGFR* gene mutations), mutation G719X (3%), L861Q (1%), S768I (1%) and exon 19 insertions (0.6 %) [14]. It is estimated that approximately 25% of uncommon mutations coexist with another mutation within the same tumor (so called compound mutations)¹¹. Afatinib is an oral small molecule irreversible ErbB family receptor tyrosine kinase. Its efficacy and safety in patients

with *EGFR* mutant (ex19del, L858R) non-small cell lung cancer has been confirmed in multicenter, randomized phase 3 clinical trials LUX-Lung-3 (global study) and LUX-Lung 6 (Asian countries) [15,16]. The LUX-Lung-3 clinical trial showed an increase in median progression-free survival compared to standard first-line platinum-based chemotherapy.

In the total population of patients enrolled in the study, mPFS was 11.1 months and 6.9 months for afatinib and chemotherapy, respectively, and in the subgroup of patients with common mutations (ex19del, L858R), 13.6 months and 6.9 months, respectively (HR 0.47, $P < 0.0001$). In patients with *EGFR* exon 19 deletion treated with afatinib in the LUX-Lung 3 trial, overall survival increased by more than 12 months compared to standard chemotherapy (mOS 33.3 vs 21.1 months) with a reduction in the risk of death by 46% (HR 0.54) [15]. In 2015, an analysis of the efficacy of afatinib was performed in patients with uncommon mutations participated in the LUX-Lung 2, LUX-Lung 3 and LUX-Lung 6 clinical trials (N=100, 75% of them were treated with afatinib). The uncommon mutations were divided into 3 groups: 1 - point mutations or exon 18-21 duplications (n=38), 2 - de novo T790M mutation in exon 20 (as the only mutation or coexisting with another mutation) (n=14) and 3 - exon 20 insertions (n=23). The prognosis of patients in the first group was definitely the best (ORR 71.1%, mPFS 10.7 months, mOS 19.4 months), while the results of afatinib treatment in groups 2 and 3 were much worse: de novo T790M - ORR 14.3%, mPFS 2.9 months, mOS 14.9 months and exon 20 insertion - ORR 8.7%, mPFS 2.7 months and mOS 9.2 months. In addition, in group 1 the results of afatinib treatment were presented according to the presence of 3 most frequent mutations distinguished: G719X, L861G and S768I (alone or co-occurring with other mutations). In patients with G719X mutation, ORR was 77.8%, median PFS was 13.8 months, and median OS was 26.9 months. For the L861G and S768I mutations, the ORR was 56.3% and 100%, respectively, mPFS 8.2 months and 14.7 months, and mOS 17.1 months, and not estimable [17].

In 2019, the pooled results of the analysis of data from 693 patients harboring *EGFR* gene uncommon mutations treated with afatinib within randomized clinical trials, compassionate-use and expanded-access programs, phase IIIb trials, noninterventional trials, case series or case studies were published. The patients were divided into subgroups: 1 - patients with T790M mutation, 2 - patients with exon 20 insertion, 3 - patients with "major" uncommon mutations (G719X, L861Q, S768I), 4 - patients with compound mutations and 5 - patients with other uncommon mutations. The best results of afatinib treatment were reported in patients with major uncommon mutations (median TTF 10.8 months, ORR 60%, mDOR 17.1 months) and compound mutations (mTTF 4.5 months, ORR 65.2%, mDOR 16.6 month). In the presented patient two major uncommon mutations were identified: exon 18 G719X substitution and exon 20 S768I substitution [18]. Treatment started 15 months ago, the patient achieved a partial response according to RECIST

1.1 criteria, which currently retains. One of the most common side effects of afatinib is acneiform rash: it occurred in 89.1% of patients treated with afatinib in the LUX-Lung 3 clinical trial and in 80.8% of Asian patients treated in the LUX-Lung 6 trial. The rash grade ≥ 3 according to the CTCAE criteria was present in 16.2% and 14.2% of patients in the LUX-Lung 3 and LUX-Lung 6 trials, respectively. Acneiform rash was a reason for discontinuing of afatinib therapy in 2.1% of patients in the LUX-Lung 6 study and no patients in the LUX-Lung 3 study. In the presented patient the grade 3 rash resolved after the temporary discontinuation of afatinib therapy, the use of topical and oral antibiotics, and thereafter was successfully resumed at a reduced dose (Figures 1-5).



Figure 1: Acne-like rash (G3) after 2 weeks of afatinib treatment in patient with *EGFR* mutant NSCLC.



Figure 2: Acne-like rash (G3) after 2 weeks of afatinib treatment in patient with *EGFR* mutant NSCLC.



Figure 3: Acne-like rash (G3) after 2 weeks of afatinib treatment in patient with *EGFR* mutant NSCLC.



Figure 4: Acne-like rash (G3) after 2 weeks of afatinib treatment in patient with *EGFR* mutant NSCLC.



Figure 5: Acne-like rash (G2) one week after afatinib discontinuation and introducing antibiotic therapy.

Summary

Afatinib is an effective and safe therapeutic option in lung cancer patients with certain uncommon *EGFR* gene mutations. The presented case is an example of a long-term response to afatinib. In addition, it emphasizes the need for close monitoring of patients in terms of possible side effects, including dermatological complications. Treatment with *EGFR* TKIs maintains a good quality of life, and possible side effects are usually transient and manageable.

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