Case Report

Uncommon *EGFR* mutations: state-of-the-art and case reports

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Abstract: Limited clinical evidence is available about the activity of *EGFR* tyrosine kinase inhibitors (TKIs) in the setting of uncommon *EGFR* mutations and effective treatment decision making-process is challenging. Lack of prospective clinical evidence in this molecular setting is in this sense critical. The wide spread of genetic changes and the unclear role of clinical features such as smoking status and sex contribute to making more difficult treatment choices. Here we briefly discuss the current state-of-the-art of this molecular setting and report both a case of long response and a case of rapid disease progression in two patients with advanced non-small cell lung cancer (NSCLC) carrying different *EGFR* uncommon mutations and treated with upfront osimertinib. The first case is about a 64 smoker female carrying an exon 20 uncommon mutation (exon 20 D770 N771 insG) who received upfront osimertinib when the disease relapsed after surgery and adjuvant chemotherapy. The second one is about a 65-year-old female with no history of smoking and carrying a rare exon 18 *EGFR* (delE709_T710insD). Both these cases stress the unpredictable clinical outcome of *EGFR* TKIs in patients with NSCLC carrying these uncommon genetic alterations. Large updated databases including these patients are needed in order to guide clinicians in molecular-guided therapeutic paths.

Keywords: Uncommon *EGFR* mutation; osimertinib; afatinib; non-small cell lung cancer (NSCLC); case report

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Introduction

EGFR mutations other than *EGFR* exon 19 deletions and exon 21 L858R substitutions are defined uncommon. They represent a wide group of various molecular changes including exon 20 insertions, exons 18 and 19 point mutations. In up to 25% of all cases of uncommon *EGFR* mutations, two or more different *EGFR* mutations are detected within a single tumor sample. These alterations are defined complex mutations (1). Several clinical data coming from retrospective data collections, reports of clinical cases and few prospective studies showed unpredictable clinical activity of *EGFR*-tyrosine kinase inhibitors (TKIs) in patients carrying these uncommon mutations (2,3).

On a clinical level, patients carrying uncommon *EGFR* mutations often differ from those with classic ones as their incidence is higher in smokers. This may in part explain the inconsistent clinical activity of TKIs in this rare setting as smoking status is a well-known negative predictive clinical driver for *EGFR*-TKIs activity (4,5).

Although robust data coming from large randomized clinical trial showed the efficacy and tolerability benefits of *EGFR* TKIs in patients carrying common *EGFR* mutations, few and heterogeneous prospective data are available in the uncommon mutations setting. Among the *EGFR* TKI phase III randomized trials published to date, only studies testing gefitinib (in the IPASS and NEJ002 studies) and afatinib (in the LUX-Lung 3 and 6) included a small number of patients with uncommon *EGFR* mutations (6,7). In particular, in both a post hoc analysis of the LUX-Lung trials and a recent meta-analysis, afatinib demonstrated clinical activity against the most prevalent exon 18 and exon 21 uncommon mutations (G719X and L861Q) (3,8,9).

Moreover, recent results from a small phase 1/2 clinical trial in previously treated patients with *EGFR* exon 20 insertions led to a breakthrough therapy designation by the U.S. Food and Drug Administration (FDA) for the new small-molecule TKI mobocertinib (10). Also poziotinib and amivantanab showed meaningful activity in the same

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setting of *EGFR* exon 20 mutant non-small cell lung cancer (NSCLC) in recent phase I/II trials (11,12).

Given the lack of robust prospective data, several retrospective analyses have been conducted and results suggested altogether the unpredictability of clinical activity of *EGFR*-TKIs in patients with tumours harbouring uncommon mutations than the common ones (2).

Moreover, osimertinib, a third-line generation *EGFR*-TKI, has been recently approved as new upfront standard treatment option for patients affected by NSCLC with common *EGFR* alterations (13). Also for osimertinib few data are available about the predictive role of uncommon *EGFR* mutations. Phase III trials testing osimertinib enrolled only NSCLC patients with common sensitive mutations (exon 19 deletion or exon 21 L858R) (13,14). However, a small phase II trial where 36 NSCLC patients with uncommon *EGFR* mutations were treated with upfront osimertinib showed encouraging response rates with manageable toxicities (15).

Overall, effective clinical decision of the best upfront treatment in the setting of uncommon *EGFR* mutation is challenging as it is supported by limited evidence coming from small subgroups of prospective trials and outcomes of clinicians' choice are unpredictable.

Here, we report both a case report of partial disease response in a smoker patient with advanced NSCLC harbouring an exon 20 *EGFR* mutation treated with upfront osimertinib and a case of third generation *EGFR*-TKI failure upfront treatment in a never-smoker patient carrying an exon 18 mutation.

We present the following cases in accordance with the CARE reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-20/rc).

Case presentation

Case 1—a good partial disease response to osimertinib in EGFR exon 20 uncommon mutation

A smoking (30 pack-years) 64-year-old housewife received diagnosis of stage IIb (cT2a cN1) lung adenocarcinoma in January 2016. She had no other relevant morbidities, nor family history of cancer. She underwent right upper lobectomy in February 2016. Subsequent adjuvant chemotherapy with cisplatin and vinorelbine for 4 cycles was administered. During follow-up, a computed tomography (CT) scan performed in November 2018 and a positron emission tomography CT (PET-CT) scan in December 2018 showed disease recurrence in mediastinal para-aortic with concomitant new lung nodes. A molecular analysis of *EGFR* (exons 18, 19, 20 and 21), *ALK* and *ROS-1* genes were conducted on the primary tumor and showed an uncommon *EGFR* mutation (exon 20 D770 N771 insG). DAKO *ALK* and *ROS-1* D4D6 ICH were negative. DAKO *PDL-1* ICH 22 C3 was also negative (tumor proportion score 0%).

Treatment options were discussed with the patient. In particular, upfront chemotherapy versus second/third generation TKI were proposed. The patient asked for receiving the treatment option with the lower risk of adverse events and started first-line osimertinib 80 mg/day on the 18th of February 2019. No adverse events occurred. On the 1st of May 2019, a restaging PET-CT scan demonstrated an almost complete disease response to osimertinib (*Figure 1*). The patient is still receiving treatment at full dose (last follow-up was on the 24th May 2021) with no signs of radiological progression of the disease.

Case 2—a disease progression to upfront osimertinib in EGFR exon 18 uncommon mutation

A Caucasian 65-year-old retired teacher with no history of smoking nor significant environmental exposures received diagnosis of stage IIIa (cT4 intralobar nodes, cN0) lung adenocarcinoma in September 2018. She had multiple relevant cardiovascular morbidities such as blood hypertension and atrial fibrillation but no restrictive lung disease nor family history of cancer. She underwent left lower lobectomy in February 2015 and received subsequent adjuvant chemotherapy with cisplatin and vinorelbine for 3 cycles. During the adjuvant treatment the patient experienced a common terminology criteria for adverse events (CTCAE) grade 2 diarrhea and a grade 3 febrile neutropenia. A subsequent follow-up program was conducted during which pleural progression occurred at a CT scan in October 2019. A Next Generation Sequencing FoundationOne®CDx analysis was conducted on the primary tumor. The *EGFR* delE709_T710insD exon 18 mutation with no other alterations in disease relevant gene was reported. DAKO PDL-1 ICH 22 C3 was negative (tumor proportion score 0%).

After discussion with the patient about treatment options with second-generation afatinib and third-generation osimertinib, upfront treatment with osimertinib 80 mg/day was started day on the 2nd of February 2020 due to mainly worries of gastrointestinal toxicity of afatinib. The

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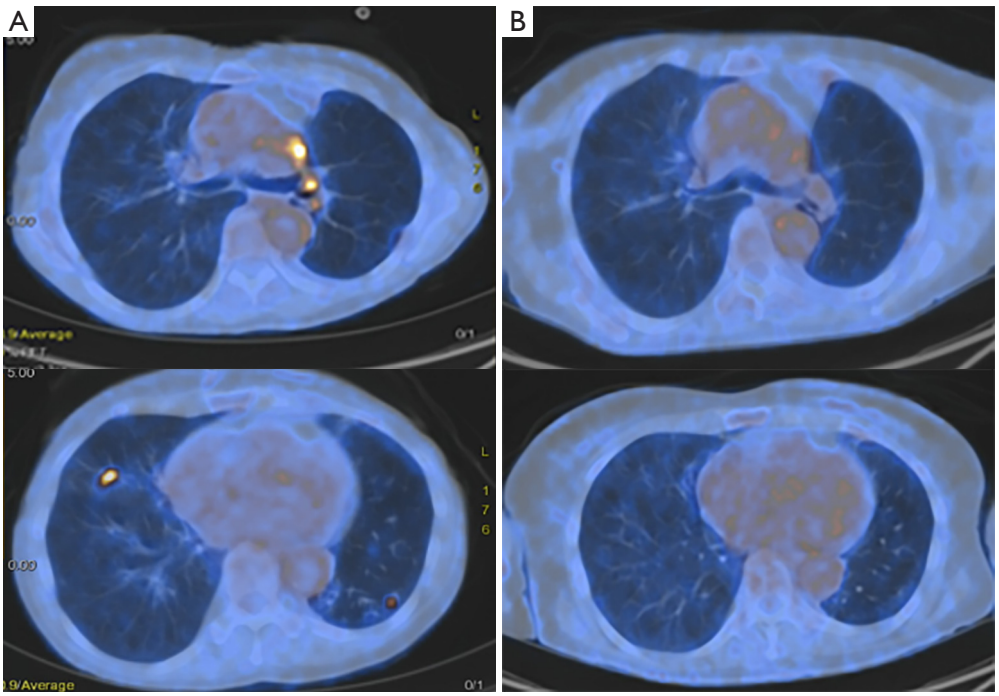

Figure 1 Case 1 PET-CT scan of the chest-mediastinal window. Neoplastic mediastinal lymph nodes and lung nodes. (A) Baseline disease. (B) Complete disease response after 12 weeks of therapy with osimertinib. PET, positron emission tomography; CT, computed tomography.

treatment was quite well tolerated with only CTCAE grade 1 diarrhea after the first month of treatment. At the first disease restaging with a CT scan at the end of April 2020 (after 12 weeks of continuative treatment) further pleural disease progression was described and treatment with osimertinib was interrupted (*Figure 2*). A second line chemo-immunotherapy with carboplatin paclitaxel bevacizumab and atezolizumab was started with initial partial response at a restaging CT scan in June 2020 but subsequent pleural progression occurred in November 2020. A third line treatment with pemetrexed (January 2021–March 2021) did not provide clinical or radiological benefit. The patient is still alive (last follow-up on the 4th of June 2021) but she is now receiving only best supportive care.

For both cases, all procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consents were obtained from the patients for publication of this case report and accompanying images. Copy of written consents are available for review by the editorial office of this journal.

Discussion

Limited clinical data are available about the efficacy of *EGFR*-TKIs in patients with NSCLC carrying uncommon *EGFR* mutations. Few prospective data and large retrospective analyses suggested that second generation *EGFR*-TKIs may play a role in patients with tumours driven by these uncommon mutations (2). In particular, a post-hoc analysis of 3 prospective clinical trials testing afatinib suggested promising clinical activity in NSCLC carrying certain subtypes of uncommon *EGFR* mutations, including complex mutations with exon 18 and exon 21 (3).

Moreover, first clinical data suggest promising activity with better tolerance of third generation osimertinib, which is now considered a standard of therapy for NSCLC carrying classical mutations. Regarding uncommon mutations, in a small phase II trial osimertinib showed promising antitumor activity against uncommon *EGFR* mutations including 19 cases of exon 18 G719X and 8 cases of exon 20 S768I (15).

Here we reported two cases of upfront medical treatment with osimertinib in the setting of uncommon *EGFR* mutations with opposite clinical outcomes. This underlines the challenges in making effective treatment decisions in

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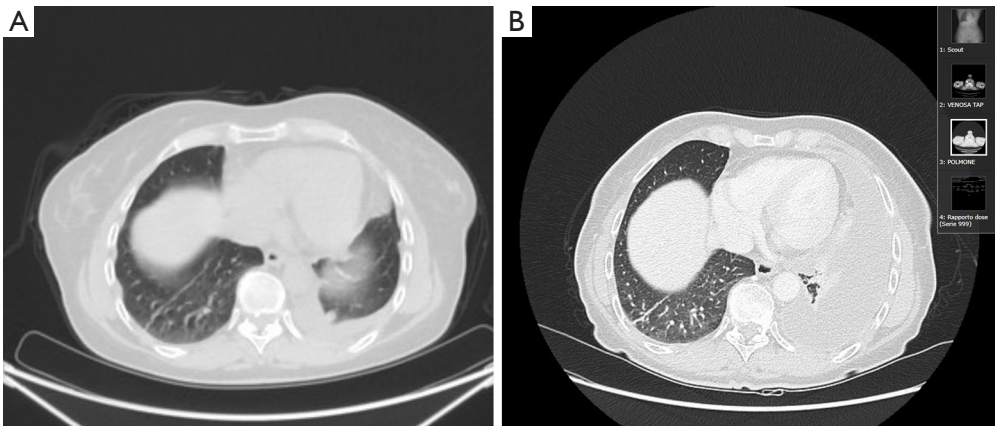

Figure 2 Case 2 CT scan of the chest. Pleural progression during front-line treatment with osimertinib. (A) Baseline disease. (B) Disease progression after 12 weeks of therapy. CT, computed tomography.

the setting of uncommon *EGFR* mutations and the clinical need of periodically updated and easily accessible database including clinical data on predictive role of uncommon *EGFR* mutations.

Conclusions

Treatment decision process of NSCLC harbouring uncommon *EGFR* mutations is challenging and both second generation afatinib and third generation osimertinib may play a therapeutic role, irrespectively to smoking status. Effective clinical decision still lacks of sufficient evidence to define the best treatment strategy. In this sense, there is a clinical need of literature report of these rare molecular alterations and their predictive role for response to *EGFR*-TKIs in large updated databases in order to guide clinicians to personalize therapeutic strategies for NSCLC patients.

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