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Ad hoc afatinib in an eldery lung cancer patient with EGFR exon 19 deletion L747-A750>P

To the Editor

Approximately 10–20% of patients with non–small-cell lung cancer (NSCLC) harbor an epidermal growth factor receptor (EGFR) [1].

Osimertinib has been FDA approved as a first-line option for patients with newly diagnosed EGFR-mutated NSCLC. However, a group of uncommon EGFR mutations showing less benefit from third-generation TKIs, retained instead more pronounced sensitivity to second-generation TKIs.

Here, we describe a patient harboring EGFR exon 19 deletion L746-A750>P, showing exquisite sensitivity to afatinib as first-line option.

In June 2020, an 80-year-old never smoker Caucasic woman with no relevant medical history was admitted to our hospital complaining of chest pain, cough and shortness of breath. On admission, the chest CT scan revealed a 3 x 2 cm tumor in the left lower lobe, with paraortic pleural nodules and massive pleural effusion (Figure 1A). The patient underwent pleural biopsies in videothoracoscopy which led to the diagnosis of lung adenocarcinoma. Total body CT scan confirmed stage IVa lung cancer due to pleural involvement, without any other metastases. Next-generation sequencing (NGS) analysis detected the *EGFR* exon 19 deletion L746-A750>P (Figure 2).

Of interest, few months before patient referral to our center, Truini *et al.* reported results from a preclinical analysis revealing that L747-A750>P mutation shows high sensitivity to afatinib compared to first- and third-generation EGFR tyrosine kinase inhibitors (TKIs) [2]. The patient had a good performance status (Eastern Cooperative Oncology Group 1); she underwent pleurodesis with bleomicine and we decided to start treatment with afatinib, at the reduced dose of 30 mg once daily due to patient age. CT scan after three months showed shrinkage of the pulmonary mass and pleural lesions defining partial response. Treatment was well tolerated and no pause or discontinuation were required. After six months, CT scan revealed disappearance of both pulmonary mass and pleural nodules (Figure 1B). Further CT scan in April 2021 confirmed complete response. The patient is currently free from cancer after 18 months of well-tolerated treatment with afatinib.

Discussion

EGFR exon 19 deletions present several molecular variants, including insertion, substitutions and in frame deletions, the majority enclosing the aminoacids from codons L747 to E749 (LRE fragment). The most frequent *EGFR* exon 19 deletions are del E746-A750 (in 66% of cases) and del L747-P753insS (57% of cases). Among uncommon exon 19-deletions, delL747-A750insP account for about 3–4% in Asiatic population [3, 4] and 2% in

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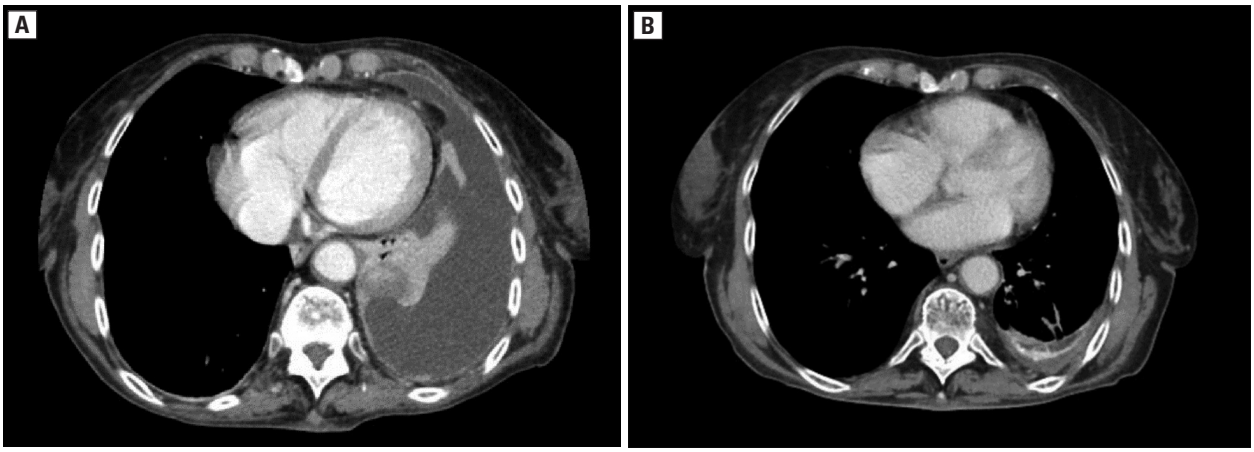

Figure 1. A. Imaging at the time of diagnosis. CT scan showing tumor (3 x 2 cm) in the left lower lobe, with pleural nodules and massive pleural effusion; **B.** Imaging after six months of treatment. CT scan showing complete remission and post-pleurodesis lesions

Figure 2. The integrative genomics viewer (IGV) image of EGFR nucleotide sequencing reads for the patient

Caucasic series [5, 6]. Even though the sensibility of exon 19 deletions to EGFR-TKIs has been established, data about differential sensitivity among several subtypes of ex 19 deletions are emerging.

As mentioned, Truini et al. explored *in vitro* TKI sensitivity of a lung adenocarcinoma cell line harboring specific L747-A750>P comparing it with lung cancer cell lines carrying canonical exon 19 deletions. The study demonstrated that L747-A750>P is associated with high sensitivity to low afatinib concentrations and reduced sensitivity to first- or third-generation EGFR-TKIs [2].

Di Federico et al. reported the case of a patient who received first-line afatinib for an "unclassified"

EGFR exon 19 deletion, that was *a posteriori* identified as L747-A750>P. The patient achieved a partial response and extended progression free survival of 48 months [5]. Similarly, Wei et al. reported the case of a patient with L747-A750>P mutant lung cancer resistant to first-line gefitinib [7].

Conclusions

To the best of our knowledge, this is the first case reporting afatinib as potential elective first-line therapy in the osimertinib era, given the specific detection of L747-A750>P *EGFR* mutation. The initial hesitation regarding the potential suboptimal tolerability of afatinib in an elderly patient (sustaining the dose of 30 mg daily) was averted, with no toxicity and complete response maintained after 18 months [8]. This case underlines the need to have the results of EGFR gene status with NGS test in order to know all different mutation types and how this can be decisive in the best choice of TKI, respect to the prevalent standard represented by osimertinib, according the FLAURA trial [9, 10].

Conflict of interest

None declared.

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