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Case Report Open Access

Patient with Primary T790M Mutation in Lung Adenocarcinoma Treated with Gefitinib as a First-Line and Osimertinib as a Second-Line Therapy: A Case Report

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Abstract

The identification of Epidermal Growth Factor Receptor (EGFR) mutations represents a major milestone in the treatment of advanced non-small-cell lung cancer. The activating mutations of EGFR occur in 10%-15% NSCLC Caucasian and 30%-40% East Asian patients, approximately. The EGFR T790M mutation is present in approximately 50%-60% of resistant cases as a secondary mutation, but as a primary less than 1%. Treatment with thyrosine kinase inhibitors (TKIs) is more efficient with fewer side effects compared with classic treatment modalities. We reported a rare case lung adenocarcinoma patient with primary T790M mutation treated with gefitinib as a fist line and osimertinib as a second line therapy.

Keywords: NSCLC; EGFR; Primary T790 mutation; Gefitinib; Osimertinib

Introduction

The treatment of advanced Non-Small Cell Lung Cancer (NSCLC) has progressed seriously in the last fifteen years [1]. The identification of Epidermal Growth Factor Receptor (EGFR) mutations has caused the development of targeted therapies for NSCLC. The activating mutations of EGFR occur in 10-15% NSCLC Caucasian and 30%-40% East Asian patients, approximately [2,3]. Exon 19 deletions and point mutations in L858R are the most common somatic activating mutations in the Epidermal Growth Factor Receptor gene [4]. Despite the initial good response to thyrosine kinase inhibitors (TKIs), all patients will develop resistance. One of the most frequent mechanisms of resistance is acquisition of a second mutation at exon 20 which causes a T790M substitution [5]. The EGFR T790M mutation is present in approximately 50-60% of resistant cases as a secondary mutation, but as a primary less than 1% [6].

Case Report

In September 2015, 75-year-old female, never-smoker, presented to our institution with persistent cough. The clinical examination revealed that she was in good overall condition. Her Eastern Cooperative Oncology Group (ECOG) performance status was 1. She also suffered from arterial hypertension and rheumatoid arthritis.

In the blood laboratory analyzes the finding was within the limits of normal values. Arterial blood gas values were without a pathological finding. Chest x-ray showed rihgt upper lobar infiltration. Computed tomography (CT) of the chest revealed a primary mass lesion in the right upper lobe, 65 mm in diameter with multiple bilateral pulmonary nodules, without lymph nodes enlargement (Figure 1), which were confirmed by positron emission tomography-CT (PET-CT). CT scan of the abdomen was without a pathological finding.

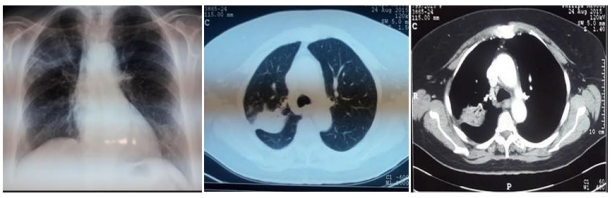

Figure 1: Chest x-ray and CT at the time of diagnosis.

Bronchoscopy was done, without a pathological endoscopic finding. A pathohistological examination of transbronchial biopsy from the right upper lobe confirmed adenocarcinoma of the lung. Definitive tumor stage was cT4N0M1a, according to the 7th AJCC/UICC tumor staging system [7]. EGFR testing confirmed the existence of the L858R mutation in Exon 21 and the T790M mutation in Exon 20. Following confirmation of EGFR mutation status the patient received first-line treatment with gefitinib (Iressa TM, AstraZeneca) the moment approved in Serbia for this indication. Total treatment with gefitinib was carried out for a period of 16 months and during this time a stable radiological response (SD) was achieved according to RECIST v.1.1 criteria-*Response Evaluation Criteria* In Solid Tumors *v 1.1* [8]. The patient was good general condition with no significant side effects. In April 2017, the patient suffered chest pain with shortness of breath. CT scan showed progression because of right pleural effusion, which is confirmed by the cytological examination (Figure 2).

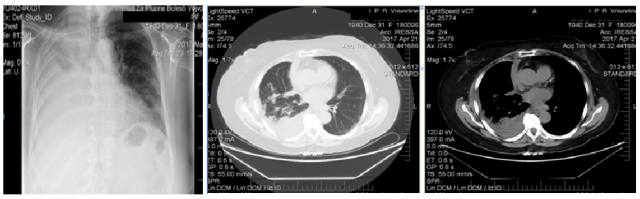

Figure 2: Chest x-ray and CT in the time of progression to ge itinib.

After radiological progression we performed liquid biopsy and ctDNA analysis showed unchanged mutation status; the L858R mutation in Exon 21 and the T790M mutation in Exon 20.

The patient was administered second-line therapy with osimertinib (Targisso TM, AstraZeneca) as a part of Early Access Program, at a dose of 80 mg/day. During the treatment, the patient showed no major adverse events and ECOG performance status was 1. CT scan after 4 months of therapy revealed primary tumor in the right upper lobe, 47 mm in diameter with multiple bilateral pulmonary nodules, right pleural effusion without lymph nodes enlargement (Figure 3). According to RECIST v.1.1 criteria this was a partial radiological response (PR).

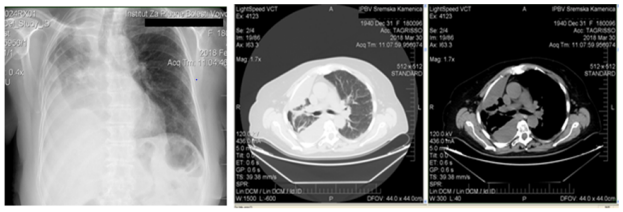

Figure 3: Chest x-ray and CT after 4 months of treatment with osimertinib.

Unfortunately, the patient experienced severe shortness of breath with a performance status of 3 after 7 months. The time to progression or death from the initial administration of osimertinib for the patient was 11 months. Overall survival was 32 months.

Discussion

We reported a rare case lung adenocarcinoma patient with primary T790M mutation treated with gefitinib as a fist line and osimertinib as a second line therapy. Our patient reported a very good quality of life while being treated with EGFR-TKIs in first and second-line therapy and her symptoms were under control for more than 30 months.

Although T790M mutations have developed as second mutations after TKIs treatment, rare cases of de novo, primary mutations have been reported in the literature [8-10]. Lou et al. reported that primary or *de novo EGFR* T790M mutations are found at a higher frequency in patients who carry dual or multiple EGFR mutations. In this study, 55 out of 427 (13%) patients with lung adenocarcinoma were found to have *EGFR* mutations; twelve of which were identified to have either dual or multiple *EGFR* mutations. Five of these 12 patients (42%) had primary T790M mutation [11].

Our patient was a non-smoker, and the metastases were present in the form of bilateral nodules in the lung parenchyma. Little is known about clinical characteristics patients with primary EGFR T790M mutation. Lee et al. described clinical features of 124 patients with EGFR positive mutations. There were no differences in age, sex, histology, or initial stage between T790M (24 pts) and non/low T790M (100 pts) groups. There were significantly more never-smokers in the T790M group (P=0.017). The proportion of patients with more than 2 metastatic site was greater in the patients with T790M mutation (P=0.066) and brain metastasis was also more common in the T790M group (P=0.036) [12].

In our case report EGFR testing confirmed the existence of the L858R mutation in Exon 21 and the T790M mutation in Exon 20 and this is consistent with clinical presentation from the literature. In the analysis 15 observational studies Chen et al. found that pretreatment T790M was more frequent in L858R than in Exon 19 mutated patients [13]. Clinically, these findings imply that routine testing of T790M in untreated especially L858R positive patients, may have influence in treatment decision-making, such as use 3rd generation TKIs.

Primary T790M can be considered as a bad prognostic sign. In our case report, the overall survival of the patients was 32 months, which is consistent with the literature data. Li et al. retrospectively analyzed primary and acquired T790M mutation in a total of 8866 Chinese patients with NSCLC. Primary T790M was identified in 0.5% of TKI-naive patients, whereas acquired T790M was detected in 49.7% of TKI-relapsed patients. In this study sixteen acquired T790M-mutant patients received osimertinib and median progression-free survival (PFS) was 8.1 months. Four primary T790M-mutant patients were treated with osimertinib and the median PFS was 8.0 months. This study confirms that primary and acquired T790M-mutant patients show different clinical and molecular characteristics, but may both respond to osimertinib [14]. Same studies confirmed that the presence of the primary EGFR T790M mutation may reduce the efficacy of first generation TKIs in EGFR mutant lung cancer patients [15,16]. Li et al., performed the analysis resected tumors from 1903 NSCLC patients, and they were found primary EGFR T790M mutation in 16 patients (2, 04%). Overall survival (OS) was significantly shorter for patients harboring *EGFR* T790M mutation than it was in patients with Exon 19 deletions (P=0.008) and L858R point mutation (P=0.09). These results suggest that primary *EGFR* T790M mutation might be a predictor for poor prognosis [17].

Conclusion

Primary *EGFR* T790M presents a rare molecular change EFGR mutant NSCLC, but the therapeutic options for these patients should be carefully considered. Our patient reported a very good quality of life while being treated with EGFR-TKI in first and second-line therapy and her symptoms were under control for more than 30 months. Presence of the primary EGFR T790M mutation may reduce the efficacy of first generation TKIs in positive patients. It has important detect latent mutation before treatment decisions with the aim of improving personalized therapy.

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