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Case Report
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Dual TKI Therapy in Acquired ALK Gene Fusion as Mechanism of Resistance to Osimertinib in EGFR-Mutant Advanced NSCLC

Portugal GM[1]*, Sousa AC[2] and Alves P[1]

[1]Hospital Pulido Valente, Centro Hospitalar Universitário Lisboa Norte (CHULN), Portugal

[2]GenoMed—Diagnosticos De Medicina Molecular, S.A., Avenida Professor Egas Moniz, Portugal

Abstract

Epidermal Growth Factor Receptor (*EGFR*) gene somatic activating mutations account for approximately 20% of lung adenocarcinomas. Tyrosine Kinase Inhibitors (TKIs) are the standard therapy of advanced Non-Small Lung Cancer (NSCLC) harboring *EGFR* gene mutations. Response to TKI is inevitably followed by acquired resistance and disease progression. The mechanisms of resistance to EGFR-TKIs are remarkably heterogeneous. In recent years, the mutual exclusive possibility of EGFR mutations and ALK rearrangements has been questioned. In fact, several reports show a prevalence of 1.6% of these concomitant mutations in advanced NSCLC with only 0.13% of EGFR-mutated NSCLC developing TKI resistance by acquired ALK translocation. Inhere, a case of an acquired ALK rearrangement following the development of resistance to Osimertinib treatment is reported as well as the efficacy and safety of dual TKI therapy.

Introduction

Epidermal Growth Factor Receptor (*EGFR*) gene somatic activating mutations account for approximately 20% of lung adenocarcinomas [1]. Tyrosine Kinase Inhibitors (TKIs) are the standard therapy of advanced Non-Small Lung Cancer (NSCLC) harboring *EGFR* gene mutations with superior objective response rate, progression-free survival and overall survival [2]. Response to TKI is inevitably followed by acquired resistance and disease progression. The main mechanism of resistance to early-generation EGFR-TKIs consists of T790M mutation in EGFR exon 20 [3]. Other mechanisms of resistance are remarkably heterogeneous and are divided into EGFR-dependent and EGFR-independent (including histologic and phenotypic transformation) [2]. Inhere, a case of an acquired ALK rearrangement following the development of resistance to Osimertinib treatment is reported, as well as the efficacy and safety of dual TKI therapy.

Case Presentation

A 42-year-old female with a past smoking history (20 pack-years) and an unremarkable past medical history, was admitted to the emergency room in October 2020 after the onset of a generalized tonic-clonic seizure. A cranial Computed Tomography (CT) scan showed two space-occupying lesions – left temporal (16 mm) and pituitary stalk (7 mm). The patient underwent brain surgery for the temporal lesion removal and the pathology analysis revealed a moderate to poorly differentiated lung adenocarcinoma. Tumor Next-Generation Sequencing (NGS) detected *EGFR* exon 21 L858R and *HER2* exon 8 S310F mutations and a high Programmed Death Ligand 1 (PD-L1) expression (80% measured by Immunohistochemistry (IHC) using the PD-L1 IHC 22C3 antibody concentrate).

The initial staging included a chest and abdominal CT scan which identified a primary spiculated lung mass on the left superior lobe (35 mm × 35 mm × 44 mm) and a millimetric nodule on the right adrenal gland. A lung adenocarcinoma pT2bN0M1c – stage IVB was diagnosed. Patient decided to continue care in another center, where, in November 2020, Osimertinib 80 mg daily was started as first-line therapy. Best response achieved, as evaluated by FDG-PET, was a partial response.

Tenth-month after treatment initiation, re-evaluation by FDG-PET scan showed Progressive Disease (PD) on the lung mass and right adrenal gland (where an additional lesion was identified). Brain MRI revealed Stable Disease (SD) on the pituitary lesion. The patient underwent a biopsy of the lung mass with bronchoscopy, which showed the persistence of previously documented

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Correspondence:
Portugal GM, Hospital Pulido Valente, Centro Hospitalar Universitário Lisboa Norte (CHULN), Alameda das Linhas de Torres, 117 1769-001 Lisboa, Portugal

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mutations and the appearance of an ALK rearrangement (EML4-ALK). At this time, the patient came to our center for treatment and follow-up. After the Multidisciplinary Team Meeting (MDTM), the case was considered as oligometastatic disease progression. As such, surgery on lung mass and Radiotherapy (RT) on the adrenal gland was proposed and the Osimertinib treatment was maintained.

A left superior lung lobectomy and segment 6 resection with mediastinal lymph node dissection was performed in January 2022. EML4-ALK rearrangement was confirmed by pathology and NGS, with no neoplastic cells found in lymph nodes.

Three weeks after surgery, the patient presented a *de novo* 1 cm, hard, well-defined, subcutaneous nodule, adherent to deeper planes, on the right side of the neck. An ultrasound with biopsy confirmed metastasis of lung adenocarcinoma and, consequently, PD. MDTM decided to suspend Osimertinib treatment and, in February 2022, Alectinib 600 mg twice daily was initiated as monotherapy for the newly diagnosed ALK rearrangement. The patient ended up not undergoing RT on the adrenal gland.

After 3-month, CT scan showed a paradoxical response with progression on adrenal gland, complete response in cervical adenomegaly and no recurrence at thoracic level. The brain MRI demonstrated disease progression with the appearance of two bilateral frontal lobe lesions, for the both of which brain stereotactic radiosurgery was performed.

The team hypothesized the possibility of having different clones of the original adenocarcinoma, some having EML4-ALK as a mechanism of resistance to Osimertinib. Thus, dual therapy with Osimertinib and Alectinib was started in June 2022. At 3-month follow-up, imaging evaluation showed SD at both adrenal gland and brain. The patient, currently, maintains therapy with Osimertinib and Alectinib, with no adverse effects reported.

Discussion

The historic notion of EGFR mutations and ALK rearrangements being mutually exclusive has been brought to question [4]. Rare EML4-ALK translocation emerging as mechanism of resistance in EGFR-mutated lung adenocarcinomas is described in several case reports [5]. The prevalence of these concomitant mutations in NSCLC is reported to reach 1.6% [4]. However, only 0.13% of EGFR-mutated NSCLC develop TKI resistance by acquiring an ALK translocation [6]. In this setting, dual TKI therapy might have a role in controlling previously PD [1,3,5]. The true extent of its efficacy is under assessment in the phase II clinical trial ORCHARD (NCT03944772).

Our case contributes to the literature with a rare case of an acquired EML4-ALK translocation as mechanism of resistance to Osimertinib and highlights the importance of serial molecular testing whenever progressive disease is documented in order to detect emerging mutations and guide the choice of specific targeted therapies. Our patient received dual TKI therapy (Osimertinib and Alectinib) without experiencing adverse effects. Stable disease has been the best response to treatment during the follow-up period.

In conclusion, ALK rearrangement can emerge as a rare acquired mechanism of resistance to Osimertinib. Despite the role of dual TKI therapy is still uncertain, various case reports, including this one, suggest it might be safe and effective in delaying disease progression.

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