Alectinib rescue therapy in advanced ALK rearranged lung adenocarcinoma: a case report

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Abstract

Alectinib is a highly selective tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK) that is approved as first-line treatment in adult patients with ALK-positive non-small cell lung cancer (NSCLC) and as second-line in patients previously treated with crizotinib, and has been shown in the literature to significantly prolong progression-free survival compared to chemotherapy in patients with advanced non-small cell lung cancer. The authors describe a clinical case of a 24-year-old woman with malignant massive pleural effusion caused by ALK rearranged pulmonary adenocarcinoma with pleural and pericardial metastasis, in which, despite a dramatic clinical debut, the correct and timely management of the diagnostic and therapeutic path allowed for extraordinary therapeutic success.

Introduction

Lung cancer is the leading cause of cancer deaths worldwide. NSCLC represents approximately 85% of lung cancer and adenocarcinoma is the most common histological subtype. Malignant pleural effusion represents a prognostic negative survival factor conferring stage IV disease and is frequently associated with severe clinical conditions [1]. Chemotherapy alone or in combination with radiotherapy has been considered the standard of care for patients with advanced NSCLC [2]. Recent advances in depicting the role of immune checkpoints and the development of strategies for fine-tuning the network between cancer cells and tumor microenvironment have led to remarkable advancements in this field [3-5]. Thus, the identification of genetic driver alterations, gene mutation, rearrangement or amplification, has developed novel potential targets for targeted therapy, and many other targets will be available in the future [6]. The Anaplastic Lymphoma Kinase (ALK) transmembrane receptor belonging to the insulin receptor superfamily may be expressed in cyto-histological biopsy specimens from 5-6% of NSCLC patients. Patients expressing this mutation benefit from alectinib, which is as an elective inhibitor of anaplastic lymphoma kinase and represents the second-generation of ALK inhibitors that have been

developed to overcome crizotinib resistance showing remarkable results as a first-line therapy for advanced ALK-positive lung cancer and as second-line in patients previously treated with crizotinib **[7].**

Case Report

In February 2019, a 24-year-old non-smoking female was admitted to the emergency room complaining of sudden appearance of respiratory failure, cyanosis, incoercible cough and severe dyspnea at rest with auxiliary respiratory muscles recruitment. After a general clinical evaluation, the patient underwent a transthoracic chest ultrasound that revealed a massive right pleural effusion. A contrasted chest CT scan was therefore performed confirming the right massive pleural effusion with right upper lobe thickening and right lung subtotal atelectasis associated with multiple mediastinal lymph nodes involvement. Widespread thickening of the right costal, diaphragmatic and paramediastinal pleura was also observed **(**Figure 1 A,B). An ultrasound-guided thoracentesis was performed by draining about 1300cc of citrine-yellow exudative pleural fluid resulting in an immediate improvement of respiratory conditions. The patient was therefore transferred to the Pulmonology Unit and subjected to a total body positron emission (PET) with 18FDG (Figure 1C), which showed intense metabolic activity on the diffuse pleural thickenings (SUV 15.30); on the ventral segment of the right upper lobe (SUV 21,27); on mediastinal lymphadenopathy (SUV 23,32) confirming a clinical stage IVA (cT3N2M1a – TNM 8.0). A bronchoscopy was performed highlighting in the right upper lobe a smooth and capsulated neoformation stenosing the ventral segmental and determining reduction in caliber of the apical and dorsal segmental branches (Figure 1D). Multiple lesion biopsies and EBUS-TBNA of lymphnode stations 4R and 7 were performed. A pleuroscopy was also subsequently performed, aimed at obtaining biopsies of the pleural thickenings (Figure 1E) placing contextually a drainage tube. Histologic examination of mediastinal, pleural and bronchial biopsies (Figure 1 F,G) revealed lung adenocarcinoma with positive immune histochemical determination for translocation of the *ALK* gene. The patient was immediately prescribed alectinib, 600 mg twice a day, which within a few days resulted in an immediate resolution of the respiratory symptoms, the disappearance of pleural effusion, without any side effects. In 3 months, a chest CT scan showed the total disappearance of the primary tumor and follow-up CT scans after 3 years of therapy shows total disease disappearance (Figure 1H-I-J)

Discussion

Molecular genotyping is now currently used to guide clinical care of patients with lung adenocarcinoma, due to clinical trials that demonstrated superior efficacy of targeted kinase inhibitors compared to standard chemotherapy with marked improvement in survival. Therefore, accurate tissue handling and processing are essential to identify the response biomarkers and to define the optimal therapy for patients [8-10]. ALK rearrangements are observed in 2–7% of non-smoking young patients with a solid-pattern dominant adenocarcinoma histology [7]. ALK inhibitors have revolutionized the management of ALK-positive malignancies. Alectinib, a second-generation ALK inhibitor, is administered in oral monotherapy, 600 mg twice daily, and is approved as first-line treatment in adult patients with ALK-positive NSCLC and as second-line in patients previously treated with crizotinib [11]. The reported clinical case highlights the extraordinary objective response coupled with the absence of side effects in a young patient with ALK rearranged lung adenocarcinoma, corroborating previous literature results. Currently, three different RCTs comparing alectinib with crizotinib in patients with ALK rearranged lung adenocarcinoma have documented superiority in terms of improved progression-free survival (PFS) and better safety profile. Thus, based on the availability of agents (*e.g.*, lorlatinib, brigatinib) able to overcome ALK-resistance mechanisms, the pharmacological landscape for NSCLC harboring ALK rearrangement needs to be adequately considered in clinical practice [12]. Finally, in the author's opinion, this clinical case demonstrates that an advanced disease at the time of diagnosis with acute respiratory symptoms, the presence of pleural effusion, lung thickening or atelectasis, and pleural and pericardial metastases should not be considered contraindications to alectinib therapy.

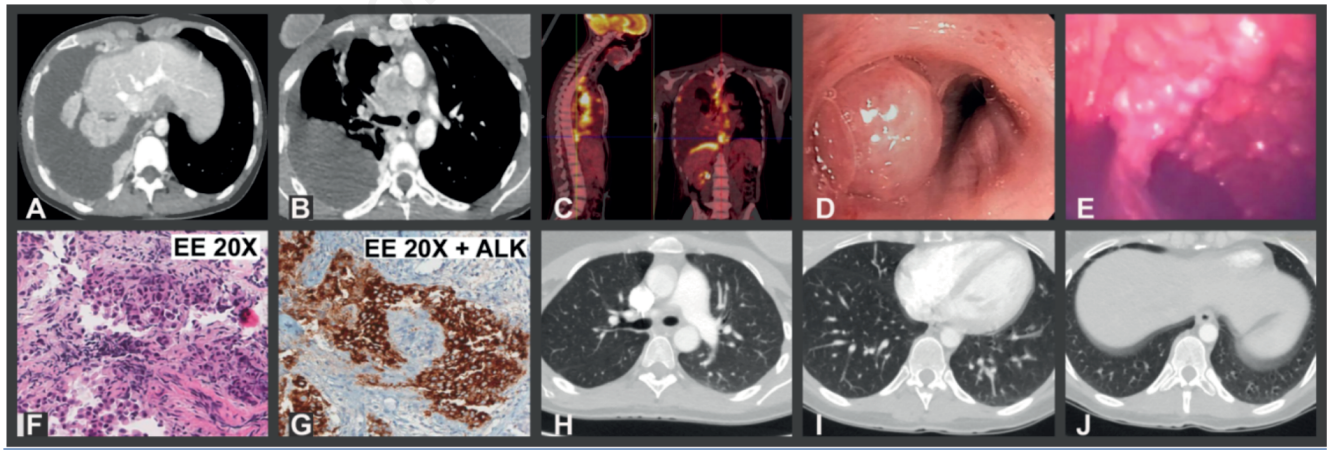

Figure 1. A,B) Chest CT images at the time of diagnosis. C) Positron emission total body computed tomography shows parietal and diaphragmatic pleural thickening, right hilar lesion and mediastinal lymphadenopathies to be intensely FDG avid. D) Endoscopic image of smooth and capsulated neoformation in the right upper lobe stenosing the ventral segmental. E) Metastatic nodules on the parietal pleura during pleuroscopy. F,G) Histological images of adenocarcinoma with acinar pattern showing eccentric nuclei and open chromatin (Hematoxylin & Eosin 20x; panel G: ALK+ 20×). H,I,J) Chest CT scan after 36 months showing disappearance of pleural and pulmonary lesions and a complete response to alectinib therapy.

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