Annals of Hematology & Oncology

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Austin Publishing Group

Case Report

Stage IV *ALK*-Positive Lung Adenocarcinoma: 7.5-Year Complete Remission with Crizotinib

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Received: April 03, 2021; **Accepted:** May 13, 2021; **Published:** May 20, 2021

Abstract

Multiple lines of Anaplastic Lymphoma Kinase (*ALK*) Tyrosine Kinase Inhibitors (TKIs) are recommended for the treatment of *ALK*-positive Non-Small Cell Lung Cancer (NSCLC). This article provides an unusual case report of a 33-year-old male patient with a 91-month Progression-Free Survival (PFS) on a first-generation TKI, crizotinib.

Keywords: Lung adenocarcinoma; Crizotinib; Long progression-free survival

Case Presentation

Lung cancer is the most common cause of cancer-related death worldwide. Approximately 85% of those cases are Non-Small-Cell Lung Cancer (NSCLC); Anaplastic Lymphoma Kinase (*ALK*) rearrangements occur in approximately 2-5% of those tumours [1]. Crizotinib was the first *ALK* inhibitor used clinically in patients with *ALK*-positive advanced NSCLC. It has demonstrated markedly improved outcomes compared to chemotherapy, including longer PFS, greater reduction in lung cancer symptoms and greater improvement in quality of life, both in the first-line and subsequent-line settings [2-4]. In Profile 1014[2], median Overall Survival (OS) with crizotinib in treatment-naïve patients was not reached after a 4-year follow-up, but median PFS was only 10.9 months.

Newer, more potent *ALK* inhibitors (alectinib, brigatinib, lorlatinib) with improved blood-brain barrier penetration have since been developed and are preferred over crizotinib in the first-line setting, with median PFS ranging from 24 to 35 months (not reached for lorlatinib after a median follow-up of 18.3 months) [5-7]. However, crizotinib is still used when next-generation *ALK* inhibitors are not available. Cases of *ALK*-rearranged lung cancer with over 5-year PFS with crizotinib as initial therapy are rarely described. Here, we present a case of 7.5-year PFS with first-line crizotinib in a young patient with metastatic lung adenocarcinoma.

In July 2010, a 33-year-old male presented with lower respiratory infection symptoms and hemoptysis. He had a light previous smoking history (less than 5 pack-year), no past medical or family history of lung disease or cancer, no toxic or asbestos exposure. Chest radiograph showed a Left Upper Lobe (LUL) infiltrate that failed to improve with antibiotics and corticosteroids. A chest Computed Tomography (CT) scan and a Positron Emission Tomography (PET) showed a 1.6cm hypermetabolic nodule in the LUL as well as a hilar metabolic lesion, without distant metastasis. Trans-thoracic biopsy showed a TTF-1 positive adenocarcinoma. Brain Magnetic Resonance Imaging (MRI) and pulmonary function tests were normal.

The patient was referred to thoracic surgery and underwent left pneumonectomy in September 2010. Final pathology showed two separate adenocarcinomas, measuring 3cm in the left hilum and 1.5cm in the LUL. Resection was incomplete with a positive venous margin (R1), and positive lymph nodes were found in stations 7, 10L and 12L. Final staging was pT4N2M0. No molecular analysis was performed at that time. The patient underwent post-operative radiotherapy and received four cycles of adjuvant cisplatin and navelbine, which were well tolerated. He was on surveillance with regular imaging in the following years.

In April 2013, the patient presented with paresthesia and partial seizures in the right arm. Brain MRI showed a 3.3cm single left parietal lesion with oedema (Figure 1). He was referred to neurosurgery in a tertiary care center and underwent surgical resection. Pathology revealed a metastasis of well differentiated adenocarcinoma of bronchopulmonary origin. Following brain surgery, the patient was

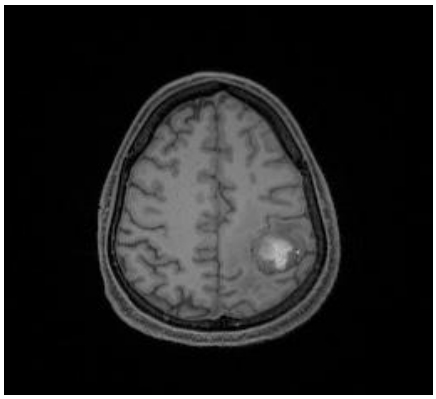

Figure 1: Brain magnetic resonance imaging showing the 3.3cm single left parietal lesion in April 2013.

Citation: Rouabhia D, Audet R, Desmeules P and Labbé C. Stage IV *ALK*-Positive Lung Adenocarcinoma: 7.5-Year Complete Remission with Crizotinib. Ann Hematol Oncol. 2021; 8(6): 1350.

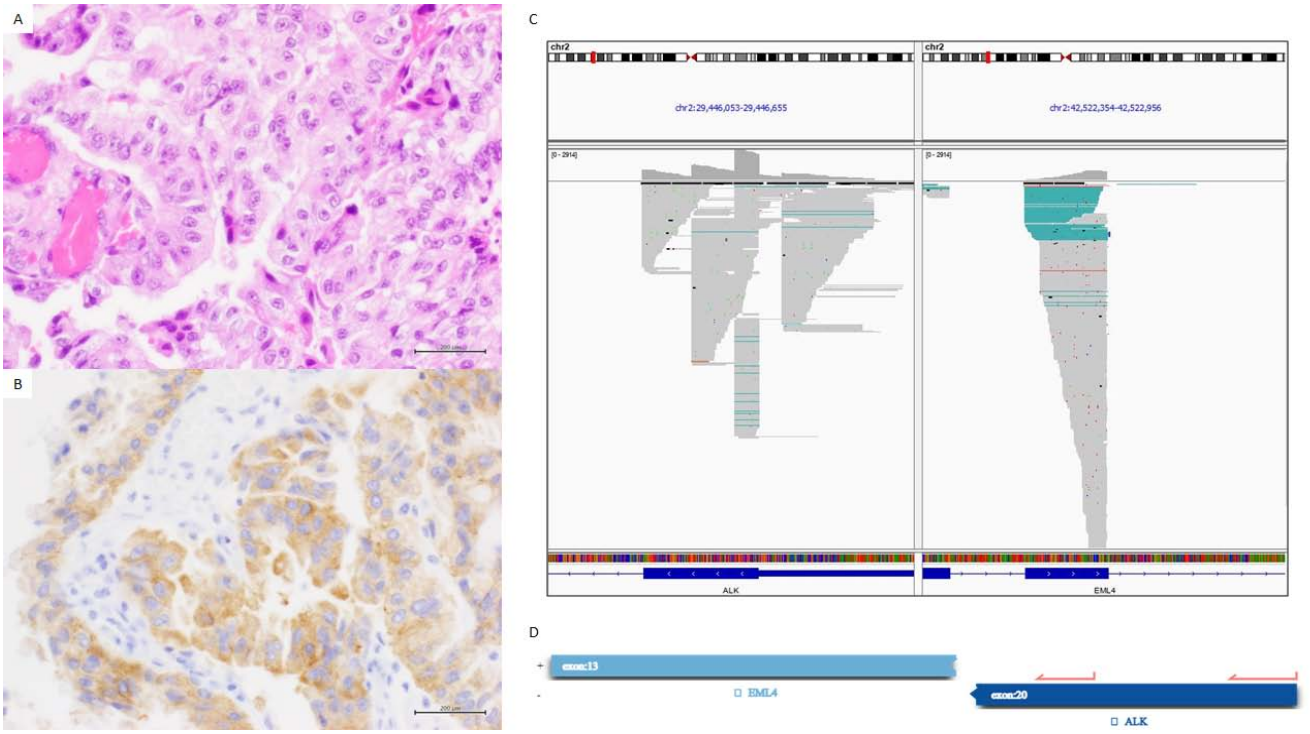

Figure 2: Morphology (Hematoxylin & Eosin stain (A); and *ALK* 5A4 immunohistochemistry (B) of the metastatic lung adenocarcinoma to brain from the left craniotomy. Representation of the *EML4-ALK* fusion with corresponding paired end reads mapping to *ALK* and *EML4* on chromosome 2 (Integrated Genome Viewer (C); and visualization of the fusion transcript obtained from the Archer Analysis Software showing exon 13 of *EML4* fused to exon 20 of *ALK* with 936 supporting reads and 92 start sites (Archer Fusion Plex Lung next-generation sequencing (D).

also treated with gamma knife radiosurgery on the surgical bed and on a 3mm right temporal lesion that didn't appear on the initial MRI. The contemporary PET scan unfortunately showed multiple (>5) osteoblastic bone metastases.

The surgical specimen was sent to a tertiary care center for molecular testing, and an *ALK* rearrangement was found (Figure 2). A follow up brain MRI also showed a new 3mm right frontal lesion. The patient was started on crizotinib in July 2013.

On crizotinib treatment, bone scans showed a progressive decrease in the known bone lesions and eventually complete response. Serial brain MRI and chest CT scans showed no evidence of recurrence. The only toxicities experienced by the patient were asymptomatic bradycardia and mild neutropenia. Treatment is still ongoing, as of February 2021. The patient remains very active, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, and has no history of rehospitalization.

Discussion

In this article, we shared our experience with crizotinib in a treatment-naïve patient with *ALK*-rearranged metastatic lung adenocarcinoma, who experienced a 91-month PFS, which is the longest reported to our knowledge in the current literature. There are a few case reports with exceptional PFS ranging from 60 to 76 months [8-10]. Our patient shows to this day a remarkable long-term evolution with a great quality of life.

The absence of risk factors usually seen at his age at the time of diagnosis is still a source of unanswered questions since neither clear toxic exposition nor hereditary factor was identified. Lung cancer in young patients appears to be a distinct disease, which often presents upfront as stage IV and with an increased frequency of gene alterations, emphasizing the importance of molecular testing [11]. In this case, as the patient was initially diagnosed and treated in a rural setting, collaboration with tertiary centers for molecular testing and neurosurgery were vital, to ensure fair and optimal care. Moreover, young age and long-term survival brings the question of appropriate intervals for imaging follow-up, with secondary cancer risks associated with radiation. The estimated absolute additional risk of second tumor induction in the literature can be as high as 10% [12,13].

As mentioned in the introduction, current evidence shows that new agents like alectinib, brigatinib and lorlatinib are preferred first-line options for *ALK*-positive NSCLC, with superior efficacity and lower toxicity compared to crizotinib [14]. However, in a patient who was first started on crizotinib, the recommendation is still for the therapy to be continued as long as there is a clinical benefit. There is evidence available from multiple retrospective studies and systematic reviews showing long term OS with a sequential approach using multiple *ALK* TKIs [15-19].

Emerging data suggest that the *ALK* fusion variant exhibit different biological properties that may affect clinical outcome [20-23]. Variant one (v1; exon 13 of *EML4* fused to exon 20 of *ALK* [E13;A20]), is the most common identified to date and was associated with longer responses to crizotinib as compared to other variants in one study [20]. In the present case, we retrospectively analyzed the

specimen from the brain surgery with anchored multiplex Polymerase Chain Reaction (PCR) next-generation sequencing (Archer Fusion Plex Lung) and identified the *EML4-ALK* variant 1 (Figure 2), which possibly contributes to the exceptional outcome observed with crizotinib.

Conclusion

We present the case of a 33-year-old patient with metastatic *ALK*-positive NSCLC treated with first-line crizotinib and showcasing the longest PFS in the literature to our knowledge. The patient remains in complete response, with a 91-month PFS; treatment is still ongoing and well tolerated. This case demonstrates that TKIs in patients with molecularly driven NSCLC can lead to exceptional results in terms of survival and quality of life.

Acknowledgments

We thank the patient for granting permission to present this case report.

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