LONG-TERM RESPONSE TO CRIZOTINIB IN A 17-YEAR-OLD BOY WITH NAÏVE ALK-POSITIVE NON-SMALL-CELL LUNG CANCER

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ABSTRACT

Lung cancer is the leading cause of cancer-related death. NSCLC accounts for 80-90% of cases. In younger patients, adenocarcinoma is the most frequent histotype and 3-7% expresses the rearrangement of ALK oncogene, sensitive to TKIs. Crizotinib is the first ALK inhibitor approved by FDA. We present the case of a 17-year-old male with metastatic naïve ALK-positive adenocarcinoma, treated with crizotinib. He received crizotinib and obtained a prolonged response with PFS of 33 months. Crizotinib can be extremely effective in adolescent with naïve ALK-positive NSCLC but it hardly penetrates blood-brain barrier. Resistance mechanisms will be investigated for a better management.

Keywords: lung, adenocarcinoma, ALK, adolescence, crizotinib

BACKGROUND

Lung cancer is the leading cause of cancer-related death. [1] The incidence peak is found above 70 years. In Italy, lung cancer is the first cause of death from cancer in males and the third cause in women, [2] and tobacco smoke is the main risk factor (85% of cases). [3]

The incidence of primary lung cancer in children is rare, representing 0,2% of all childhood malignancies. [4]

In adulthood, over 95% of lung cancers are attributable to small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). [5,6] Among NSCLC histotypes, adenocarcinoma is the most represented in younger patients [7-9] Clinical presentation is the same as in adults (cough, chest pain) but not smoking-related. The rarity of this condition in younger people usually causes a delay in diagnosis. Indeed, stage IV disease is present in up to half of the cases at diagnosis. [10,11]

In the last 15 years, molecular studies have highlighted a specific role of some genes, called "Oncodrivers" involved in tumor genesis, particularly Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK), which have become the target of specific and selective drugs. [12]

In the Caucasian population, 10-15% expresses activating mutations of EGFR and 3-7% expresses rearrangement of the ALK oncogene. These are predictive for response to TKIs.

Crizotinib, one of the first ALK inhibitor approved by Food and Drug Administration (FDA), allowed the development of ALK target therapy [13]. After this drug, next-generation ALK inhibitors such as alectinib and ceritinib were approved for the treatment of ALK-positive NSCLC patients [14-19]

ALK mutations are reported in a higher proportion of younger patients about 11% of adenocarcinoma compared to 2-7% of adenocarcinoma in adults. [20-22]

There are no data specific to pediatric population affected by oncogene-addicted lung cancer and there is no evidence of optimal management in this population; the treatment is modulated according to adult protocols.

We present the case of a seventeen-year-old male with naïve ALK-positive NSCLC treated with Crizotinib. To our knowledge, this is the fifth report of a pediatric case treated with ALK-inhibitors, the first experiencing a prolonged response and progression-free survival (PFS).

We thoroughly reviewed the current literature about ALK positive NSCLC in childhood and the tailored management in pediatric age.

CASE REPORT

A diabetic, never-smoker, 17-year-old boy was referred for cough and increasing dyspnea. A chest x-ray showed bilateral pulmonary nodules. A chest and abdomen Computed Tomography (CT)-scan confirmed multiple bilateral pulmonary nodules and showed thoracic lymphadenopathies (Fig.1A), hepatic and numerous vertebral bone metastases confirmed by bone scintigraphy and spine Magnetic Resonance Imaging (MRI). No secondary brain lesions were observed at MRI.

A supraclavicular node biopsy was performed with the diagnosis of metastases from pulmonary adenocarcinoma, Cytokeratine 7+ (CK 7+), Transcriptional Thyroid Factor 1+ (TTF1+), p63+, ALK-rearranged. EGFR and c-Ros Oncogene 1 (ROS1) wild type."
The patient started therapy with Crizotinib 500 mg/day.
The first chest and abdomen CT-scan evaluation, performed after two months of treatment, showed partial response to treatment on lung (Fig.1B), nodes, liver and bone lesions (confirmed by a spine MRI). The CT-scan and MRI re-evaluations after 6 and 10 months of therapy showed a further reduction in pulmonary, hepatic and vertebral lesions. At 30 months of therapy, the patient maintained lung and hepatic disease stability with further response on vertebral lesions.
No grade 3 or 4 toxicity according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 was recorded during treatment.
After 33 months from crizotinib, the patient underwent brain CT scan due to headache and loss of consciousness, showing a voluminous roundish lesion, in the right fronto-parietal site, of approximately 35 x 31 x 30 mm, characterized by inhomogeneous density with a central hypodense portion. Marked perilesional edema and 8 mm shifting of midline structures were also evident. A smaller lesion was detectable on the right lateral ventricle (about 10 mm). Cerebellar tonsils were at the limit of foramen magno. Thus, a craniotomic excision of the fronto-parietal lesion was urgently performed. Histology confirmed a metastasis from ALK-rearranged pulmonary adenocarcinoma. Post-surgical brain MRI showed residual tumor in the surgical bed and the persistence of the centimetric rounded area of altered signal located in the posterior parietal front over right ventricle. Radiotherapy was then performed; 3000 cGy were administered on residual tumour and 850 cGy on right paraventricular posterior lesionConcomitantly, the patient started a second line therapy with alectinib.
After 2 months of treatment, a chest and abdomen CT-scan showed pulmonary stability and partial response of the hepatic lesions. Liver metastases rapidly progressed after 7 months of alectinib and the patient died of liver failure.

DISCUSSION AND CONCLUSIONS

According to our knowledge, this is the fifth case reported of adolescent with diagnosis of pulmonary ALK-translocated adenocarcinoma [23-26], and the third treated with crizotinib as first-line treatment. [23,24] (Table 1). Our report is the first of a prolonged response and PFS (33 months) with crizotinib.
At the time of our diagnosis, crizotinib represented the first-line treatment available for our patient.

At onset he received crizotinib. After 3 months he obtained a response to all lesions, demonstrating high sensitivity to tyrosine kinase inhibition and confirming that best response to crizotinib is achieved by 12 weeks as in adult ALK-positive NSCLC. [27]

During treatment with crizotinib, our patient achieved a PFS of 33 months, making it peculiar in regards to the other cases described and the results of PROFILE1014 trial [28]. In this trial, crizotinib showed a median PFS of 10,9 months. Moreover, the patient tolerated the treatment well, experiencing only grade 1 neutropenia and grade 1/ 2 hypertransaminasemia.

In our case, crizotinib demonstrated good control of extra-Central Nervous System (CNS) disease but limited control on brain progression, probably due to its poor ability to cross the blood-brain barrier (BBB). [29-31]

After CNS dissemination, our patient performed surgery, radiotherapy and a second-line therapy with alectinib. As demonstrated by the ALEX trial [32], alectinib was significantly superior to crizotinib in controlling brain progression.

The permeability of the BBB from alectinib and the results obtained on the control of brain metastases [32] limited the role of radiotherapy and surgery in this setting, particularly in naive patients.

In our case, we choose to surgically treat the symptomatic frontal brain lesion. We also decided to use radiotherapy, considering the post- surgical residual tumor and the paraventricular lesion. Then, we started alectinib as second-line TKI.

Our report suggests that crizotinib, as first-line therapy, can be extremely effective in ALK-positive lung adenocarcinoma without CNS involvement, and raises the need for new TKI sequence studies to optimize the management of ALK-translocated lung cancer.

The optimal sequence of TKI in ALK-positive lung cancer and the role of surgery and radiotherapy on CNS dissemination remain critical. Resistance mechanisms to TKIs will be investigated for a better management of these cases in childhood and adolescence.

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Declarations:

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- All authors give contribution to the elaboration of this case report.
- All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
- All authors report no conflicts of interest.