Advanced, Non-Small Cell Lung Cancer with Anaplastic Lymphoma Kinase Rearrangement: Case Report And Literature Review

Manuel Segura-González1, Graciela Cruz2 and Oscar Arrieta-Rodríguez1,2*

1Thoracic Oncology Unit, Instituto Nacional de Cancerología, México, D.F.; 2Experimental Oncology Laboratory, Instituto Nacional de Cancerología, México, D.F.

Correspondence to:
*Oscar Arrieta
Jefe de la Unidad de Oncología Torácica y Laboratorio de Oncología Experimental
Instituto Nacional de Cancerología (INCan)
San Fernando #22, Col. Sección XVI, Tlalpan
14080 México, D.F., México
E-mail: ogar@unam.mx

ABSTRACT

Non-small cell lung cancer comprises different types of molecular subsets: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and non-otherwise specified. The most common mutation occurs in the epidermal growth factor receptor, particularly in exon 21 and exon 19 deletions. These mutations confer constitutive activation of the epidermal growth factor receptor tyrosine kinase domain. The frequency of epidermal growth factor receptor mutations varies among different ethnic groups. The anaplastic lymphoma kinase gene gained strong clinical interest when it was found to be translocated in anaplastic large cell lymphoma, and subsequently in diffuse large B-cell lymphoma, inflammatory myofibroblastic tumors, and non-small cell lung cancer. Activating anaplastic lymphoma kinase translocations dictate favorable and often dramatic responses to anaplastic lymphoma kinase tyrosine kinase inhibitors like crizotinib. Thus, the recognition of this molecular alteration is quite important in clinical practice. Therefore, the main objective of this manuscript is to confirm the relevance of the anaplastic lymphoma kinase tyrosine kinase inhibitors to treat non-small cell lung cancer. Hence, we report a case of advanced non-small cell lung cancer harboring anaplastic lymphoma kinase translocation treated at the Instituto Nacional de Cancerología in Mexico. We conclude that many questions remain unanswered: whether to use first- or second-generation anaplastic lymphoma kinase inhibitors, treatment time, sequencing, order, and the selection of an anaplastic lymphoma kinase inhibitor in clinically specific situations like brain metastasis. We need further investigations to address these problems. (J CANCEROL. 2015;2:34-8)

Corresponding author: Oscar Arrieta, ogar@unam.mx

Key words: Advanced non-small cell lung cancer. Epidermal growth factor. Mutations. ALK-tyrosine kinase inhibitor.

Received for publication: 03-03-2015
Accepted for publication: 11-03-2015
INTRODUCTION

Lung cancer is the first cause of cancer-related death worldwide. Annually, 85% of these lung cancer cases are diagnosed as non-small cell lung cancer (NSCLC). Despite efforts and progress in the diagnosis and treatment of this disease, overall survival at five years is only 5%1.

Adenocarcinoma represents 40.1% of all NSCLC cases, followed by squamous cell carcinoma 21.4%, large cell carcinoma 2.6%, and non otherwise specified 20.2%2. Different types of molecular subsets exist in adenocarcinoma, where nearly 50% of patients with this histology have a driver mutation3.

Epidermal growth factor receptor (EGFR) mutations occur more frequently in adenocarcinoma, non-smoker/light-smoker patients, female gender, and Asian ethnicity. Almost 90% of EGFR mutations comprise punctual mutation in exon 21 (L858R) and exon 19 deletions. These mutations confer constitutive activation of the EGFR tyrosine kinase domain4,5. The frequency of EGFR mutations varies among different ethnic groups: Caucasian, Asian, and African American populations harbor 15, 40, and 2-14% of mutations, respectively6-9. Latin American countries report an intermediate frequency between Asian and Caucasian patients of 33.2%. The Mexican population has a 31.2% EGFR mutation prevalence10.

The anaplastic lymphoma kinase (ALK) gene gained strong clinical interest when it was found to be translocated in anaplastic large cell lymphoma, and subsequently in diffuse large B-cell lymphoma, inflammatory myofibroblastic tumors, and NSCLC11,12. To date, ALK overall incidence seems similar in NSCLC unselected series conducted in Asian (4.2%) and Western (3.4%) populations13. Activating ALK translocations dictates favorable and often dramatic responses to ALK tyrosine kinase inhibitors like crizotinib, as demonstrated by phase I, II, and III clinical trials14-17. Thus, the recognition of this molecular alteration is quite important in clinical practice. To confirm it, we report a case of advanced NSCLC harboring ALK translocation treated at the Instituto Nacional de Cancerología in Mexico; likewise, a literature review was carried out to support it.

CASE PRESENTATION

A 53 year-old male patient, native and resident of Mexico City. He had a history of being a light smoker, with a tobacco index of three packs/year. The habit was suspended six months before diagnosis. Also he denies asbestos or wood smoke exposure. In the clinical history, he reported that in December 2012 he noticed a lump at the iliac crest, which turned out to be a 5 cm and story consistency tumor with a rapidly progressive growth up to 15 cm. Also, the patient experienced a more than 10% weight loss and cough with hemoptysis in the previous three months. At the physical examination, a large tumor of 15 × 20 cm was observed at the right hip, and spinal cord compression syndrome was diagnosed.

The patient was hospitalized and underwent extensive staging with computerized tomography (CT) scan, brain and neuro-axis magnetic resonance imaging (MRI), and full blood chemistry with carcinoembryonic antigen. A transthoracic-guided biopsy was performed.

The initial CT scan reported an 88.8 mm right lung lesion, an upper 37 mm paratracheal tumor, an aortopulmonary window nodal conglomerate (24.15 mm), a liver lesion on segment 3 of 34 mm, and an expansive 103 mm lytic lesion to the right iliac bone (Fig. 1 and 2). On brain and neuraxis MRI, tumor infiltration was observed in cervical, thoracic, and lumbosacral regions. Tumoral activity in the left parietal central nervous system and left thalamus was also detected (Fig. 3 and 4). Biopsy results report a moderately differentiated adenocarcinoma with predominantly solid pattern. Immunohistochemistry was positive to TTF1, and CK 7.
sequencing was negative to EGFR; however, ALK translocation was positive with FISH break-part dual color test (Fig. 5).

The patient was initially treated with external thoracolumbar spine radiation and holo-cranial radiotherapy, receiving 30 Gy in 10 fractions. In May 2013, crizotinib was given at standard doses. At the first three-month tumor assessment evaluation, a partial response of 41.2% was documented. After a 14-month follow-up, an 80% partial response was achieved (Fig. 6). At his last visit (18-month follow-up), the patient maintains partial response (74%) and remains progression-free, without dose reductions of crizotinib.
DISCUSSION

The discovery of ALK rearrangements in NSCLC took place in 2007 by two independent groups of researchers. In one of these studies, Soda, et al. found that an echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) fusion is a driver mutation in NSCLC, independent of EGFR and KRAS. The incidence rates of this molecular abnormality were shown to be 3.8% on average, with a wide range of 0.4-13.4%. Nowadays, we know there are approximately 21 EML4-ALK fusion variants, and EML4 is not the only fusion partner; ALK fusions with TGF, KIF5B, KCL1, and PTPN3 have also been described. Out of the 21 EML4-ALK fusion variants, the most common are: variant 1 (49.6%), 3a/b (25.6%), and variant 2 (10%)\. The NSCLC ALK-rearranged patients are generally associated with never smoking (< 100 cigarettes in a lifetime) or light smoking history (< 15 pack/years), younger age, and male gender. EML4-ALK is found almost exclusively in adenocarcinomas; no cases have been identified in pure squamous cell carcinoma, solid, micropapillary-predominant histologic patterns, and tumor cells with a signet ring or hepatoid cytomorphology were found to be related with ALK.

Patients with ALK-positive tumors detected by FISH have a favorable clinical response to the ALK inhibitor crizotinib, which has proven to be superior to standard chemotherapy in first- or second-line treatment. Nevertheless, progression presented usually after 7.0-10.9 months of treatment.

Acquired resistance in 30% of cases occurred due to a gatekeeper mutation on the tyrosine kinase ALK domain (L1196M). The other 70% of cases are the result of a copy number gain of ALK, expression of a second oncogene, and activation of alternative signaling pathways such as EGFR (9%), KRAS (36%) or KIT. Fortunately, second-generation ALK inhibitors, such as ceritinib or alec tinib, are active in crizotinib-naive or crizotinib-treated patients, with a seven-month progression-free survival (very similar to crizotinib); they also have a better blood-brain barrier penetration, with an outstanding 50-52% central nervous system response rate.

Many questions remain unanswered: whether to use first- or second-generation ALK inhibitors, treatment time, sequencing, order, and the selection of an ALK inhibitor in clinically specific situations like brain metastasis. We need further investigations to address these problems.
Our patients remain progression free and at time of progression will be sequenced with a second-generation ALK inhibitor.

REFERENCES