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Pharmacotherapy Applied to ALK-Positive Lung Cancer Patient

Gabriele Bee[1], Jane Mary Lafayette Neves Gelinski[2*], Marcus Eduardo Muller[3]

[1]*Pharmaceutical Bachelor, University of West of Santa Catarina, Departmentof Pharmacy, 198 Paese, street – Videira, State of Santa Catarina, Brazil*

[2]*PhD in Bromatology by University of São Paulo-USP, Professor at University of West of Santa Catarina, Department of Pharmacy, SC, Brazil.*

[3]*Oncologist Physician, Federal University of Santa Catarina, CRM 6723 SC, 261 Eleonora Satler Pradi, street – Jaraguá do Sul, State of Santa Catarina, Brazil*

Corresponding Author:** ***Jane Mary Lafayette Neves Gelinski, *Professor at University of West of Santa Catarina, Department of Pharmacy, 198 Paese, street – Videira, State of Santa Catarina, Brazil.*

Abstract

Lung cancer is among the diseases that most affect the world population. In addition to genetic susceptibility, the development of the disease is also associated with smoking, besides factors such as use of marijuana, hookah and exposure to radon, asbestos, diesel exhaust and ionizing radiation. Lung cancer is classified as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). However, ALK positive lung cancer is not associated with smoking. In this study, pharmacotherapy applied to a patient with ALK positive lung cancer was evaluated as a clinical case study of cancer treatment. The patient´s medical documents were organized and observed in chronological order of the events, emphasizing the main points of all the treatment performed. All patient records were analyzed, as well as positron emission tomography-computed tomography (PET-CT) and clinical reports. Radiotherapy and pharmacotherapy sections with Crizotinib, at the first moment and afterwards, Alectinib promoveda good progression of treatment; i.e., in according to positive indicators, such as decreased volume, size and metabolic activity of the tumor. Although there is a low life expectancy of ALK positive patients, the treatment indicated to the patient reported here was decisive for a significant expectation and quality of survival.

Abbreviations: *ALK = anaplastic lymphoma kinase, EGFR= growth factor receptor, NSCLC= non-small cell lung cancer, PET-CT = positron emission tomography – computed tomography, RMI = resonance magnetic image, SCLC= small cell lung cancer, T= Tomography, TKI= tyrosine kinase inhibitor*

Keywords: *Lymphoma, Mutation and Cancer, Carcinoma, Anaplasia, Adenocarcinoma, ALK gene, PET-CT.*

1. INTRODUCTION

Lung cancer is the most common malignant disease worldwide, and in relation to new cases of cancer, 13% are lung cancer [1]. According to Siegel et al. [2], the projection for 2019 was 1,762,450 new cancer cases and 606,880 cancer deaths in the United States. In India, data pointed to a forecast of around 1,200,000 cases for 2020 [3].

In Brazil, according to the National Cancer Institute[4], an estimated 18,740 cases of lung cancer among men and 12,530 in women for each year of the 2018-2019 biennium. These values correspond to an estimated risk of 18.16 new cases per 100 thousand men, as the second most frequent tumor; and with an estimated risk of 11.81 for every 100 thousand women, occupying the fourth position. Lung cancer in men is the second most frequent in the South (36.27 / 100 thousand) and Midwest (16.98 / 100 thousand) regions, not considering non-melanoma skin tumors [5]. The cancer incidence rate (2006–2015) was stable in women and decreased by approximately 2% per year in men, while the cancer mortality rate (2007–2016) decreased by 1.4% and 1.8% annually, respectively [4]. The overall cancer mortality rate dropped continuously from 1991 to 2016 by a total of 27%, resulting in approximately 2,629,200 cancer deaths less than would be expected if mortality rates had remained at their peak [4].

According to Reck and Rabe [6], the correlation between smoking and mortality from lung cancer was confirmed, whose decrease in mortality was verified with the cessation of

tobacco use, as observed for the United States from the beginning of the 1990s for the men and since the 2000s for women. Additional risk factors include exposures to radon, asbestos, diesel exhaust and ionizing radiation [6]. Increasing evidence suggests a correlation between lung cancer and chronic obstructive pulmonary disease that is independent of tobacco use and is probably mediated by genetic susceptibility [6, 7].

Rosas et al. [7] cite from other studies that cancer is caused, in almost all cases, by mutations of genes that control cell growth and division. These mutant genes are called oncogenes, and in general, two or more oncogenes must be present in a cell before it can become cancerous.

Great advances in understanding the pathogenesis and management of lung cancer have been made by changing the way cancers are diagnosed and treated [8]. Specifically, the discovery of the biological and therapeutic importance of the genetic changes acquired in two genes that encode pharmacologically targeting tyrosine kinases and that are involved in signaling the growth factor receptor, the epidermal growth factor receptor and anaplastic lymphoma kinase (ALK) [8].

According to Shaw et al. [9] ALK is a validated tyrosine kinase target in several types of cancer, including non-small cell lung cancer, large cell anaplastic lymphoma and pediatric neuroblastoma. ALK gene rearrangements are found in approximately 5% of non-small cell lung cancer cases and define a distinct molecular sub type of lung cancer. With an estimated 1.3 million new cases of NSCLC per year worldwide, this is true of over 60,000 patients with ALK-positive NSCLC annually [10,11,12].

This research addresses a clinical case study of a patient with a rare case of lung cancer. The pharmacological treatment is reported, without surgical intervention, and the evolution of the case. Therefore, the overall objective of the study was to monitor pharmacotherapy applied to a patient with ALK positive lung cancer. We also sought to understand the reasons for choosing pharmacotherapy by investigating the initial and final clinical condition (2017 to 2018). It was expected that the patient with ALK positive lung cancer would have a significant improvement of the disease with the applied pharmacotherapy.

2. Material and Methods

This study is based on fundamental concepts about ALK positive lung cancer. The study was divided into two parts: Part 1: Literature review research on the main aspects of Lung Cancer (ALK), having as key descriptors in health, the following terms: a) Lung Neoplasms: imaging diagnosis, effect of drugs, pharmacological treatment, radiotherapy; b) Case Reports: Clinical History of the Patient; Medical records. Publications that did not directly address lung cancer were excluded. Literature consultation was free and without restriction of the analyzed period. Part 2: Clinical case of a patient diagnosed with positive ALK lung cancer, following the treatment of the patient by a specialized medical team in Santa Catarina, southern Brazil, for a period of six months.

2.1. Ethical Aspects

All data were obtained with the approval of the national ethics committee to carry out research with human beings, in the category of access to clinical data and medical records and medical records, that is, without direct intervention with the patient or with his treatment. All those involved signed an informed consent form. Thus, it was conducted in accordance with the Declaration of Helsinki.

The contact with the patient was made through visits to his home or through internet communication tools (Skype and other), to offer assistance, or to seek support, information and update his clinical condition. The data were made available by the patient through documents and these were organized and observed in chronological order of events. Emphasis was placed on the main and crucial points of the patient's treatment. We have gained access to specific and technical information; study of documents and performed examinations, in addition to access to drugs used during treatment. In addition, we also had the personal report, medical analysis and conversations to help there adding and explanation of the tests performed, thus avoiding an erroneous interpretation of the results.

3. Results

3.1. Lung Cancer

Lung cancer is classified as small cell lung cancer (SCLC) and the heterogeneous group of non-small cell lung cancer (NSCLC) [10, 11]. The term NSCLC is used for any lung epithelial

tumor that does not have a small cell component, which is represented for about 80% of the cases of lung tumors and encompasses several subtypes, among them, adenocarcinoma, squamous cell carcinoma (squamous cells) and large cell carcinoma are the most common [9,10,11].

Reck and Rabe [5] exposed from review, that samples of lung cancer tissue (obtained through bronchoscopy or surgical biopsy) or cytological samples (effusion, aspirates or brushing) show clear morphological characteristics of adenocarcinoma or carcinoma of squamous cells. Thus, the diagnosis can be firmly established and, in these cases, immunocyto chemical or immunocyto chemical analyzes are not routinely necessary. Although cytotoxic chemotherapy remains the basis of treatment for most patients with advanced non-small cell lung cancer (NSCLC), tyrosine kinase-based the rapies have taken on an increasingly important role, particularly in sub groups of genetically defined patients [8].

Cooper et al. [12] report that lung cancers develop through a multi-stage process, involving the development of multiple genetic and epigenetic changes, particularly the activation of growth-promoting path ways and the inhibition of tumor suppress or pathways. A greater understanding of the multiple biochemical pathways involved in the molecular pathogenesis of lung cancer is crucial for the development of treatment strategies that can target molecular aberrations and their activated pathways [12].

The anaplastic lymphoma kinase gene (ALK) plays an important physiological role in brain development and can be oncogenically altered in several malignant neoplasms, including non-small cell lung cancer and large cell anaplastic lymphomas [13]. According to Inamura et al. [14] the ALK gene can be activated in an aberrant way by mutation, gene amplification or chromosomal rearrangement, leading to the expression of a potent oncogenic conductor and in non-small cell lung cancer (NSCLC); this ALK rearrangement occurs in approximately 5% of cases.

3.1.1. Diagnostic and Cancer Treatment

As reviewed by Liang and Wakelee [15], although surgery is considered the main treatment modality for non-small cell lung cancer (NSCLC), only 20-25% of tumors are suitable for potentially curative resection and even after resection, a substantial percentage of these patients have recurrences or metastases [15]. Consequently, 5-year survival rates after surgery are disappointingly low, ranging from 58% to 73% in stage I, 36% to 46% in stage II and only 19% to 24% in patients with tumors in stage IIIA [15]. Therefore, more effective treatment strategies are needed to reduce lung cancer mortality and there currence rate.

Systemic therapy, including platinum-based chemotherapy and targeted therapy, should be provided to patients with stage IV non-small cell lung cancer (NSCLC) [16].Targeted therapy applications, such as an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) and ALK, in patients with NSCLC and an EGFR mutation or ALK gene rearrangement allowed for dramatic improvements in efficacy and tolerability [16].

According to Wei et al. [17], the benefit of chemotherapy is quite limited and almost all advanced cases of NSCLC have a poor prognosis, with an average survival of less than one year. Previous studies comparing chemotherapy with the best supported care showed a median survival between 8 and 4 months, respectively.

3.1.2. Pharmacotherapy:Crizotinib

Crizotinib (PF-2341066; XALKori, Pfizer, New York, USA) is a small orally bio available molecule that has inhibitory properties for the tyrosine kinase receptor (RTKs) of c-MET (hepatocyte growth factor receptor) and ALK [19, 20]. Therefore, the inclusion of ALK screening in the molecular diagnosis of lung cancer is mandatory, considering that the frequency of changes in ALK was reported in 2% to 25% of patients with lung cancer between different series [14, 18].

Crizotinib has marked anti tumor activity in patients with positive NSCLC for ALK rearrangement, all treated patients end up developing resistance to this drug [20]. The estimated 6-month probability of progression-free survival (PFS) was 72% with the use of crizotinib, considered a safe drug [16].

3.1.3. Pharmacotherapy: Alectinib hydrochloride

Alectinib hydrochloride (CH-5424802, Alecensa®, Roche, Chugai Pharmaceuticals) is a potent and selective ALK inhibitor, with little or no inhibitory activity for other protein kinases. [21].

In Brazil, according to the National Health Surveillance Agency [22], Alecensa® is indicated for the first line treatment of patients with NSCLC for locally advanced or metastatic ALK positive. It is also indicated for those cases that have progressed during the use of crizotinib, or who are intolerant to it [22].

3.1.4. Clinical Approach to the Patient

The most frequently used procedures for diagnosing lung carcinoma are Chest x-ray, CT or combined PET–CT, Cytopathology examination of pleural fluid or sputum, usually bronchoscopy-guided biopsy and core biopsy and in some cases, open lung biopsy [22]. An individualized approach to the treatment of patients with NSCLC begins with an accurate pathological diagnosis and staging [5] and with the comprehensive use of appropriate imaging methods, as well as endoscopic techniques for tissue sampling. In addition to an accurate description of histological characteristics, the rational use of immune histochemical markers is recommended [5].

3.2. Clinical Case Study

The Box 1 shows the summary of the clinical case of patient with positive ALK lung cancer.

Clinical Case:
A 36-year-old white male, resident in the stateof Santa Catarina, Brazil Santa Catarina, non-smoker, sought medical help with evidence of flu. Due to the symptoms, he was medicated for H1N1 influenza, withTamiflu® (Oseltamivir) for seven days. After undergoing treatment, here turned to the doctor with the same complaints, being medicated again with antibiotics for another ten days of treatment. After this, there was no change in his clinical condition, Thus, a tomography of the chest, neck and abdomen was indicated for the patient. This occurred in May 2017 and there was an increase in the lower right cervical lymph node (level IV, V and VI), an increase in coalescent and supraclavicular mediastinal lymph node and subpleural nodular opacity. Biopsy examination revealed malignant tumor. The material was sent to a reference laboratory in order to define the origin of the cancer. Result: pulmonary origin.

3.2.1. Patient Treatment

The timeline with chronological data and treatment of patient performed before and during the production of this case report are shown in Tables 1 and 2. Next, Figures 1A, B present, respectively, the first PET-CT image examination of the patient's entire body. And the second PET-CT image exam showing the reduction in the dimensions, number and glycotyl metabolism of the patient's cervical, mediastinal and pulmonary hilar lymph nodes.

Table1. *Timeline according to the chronology of diagnosis and treatment of clinical case study: positive ALK lung cancer patient - Year2017*

Year: 2017	Diagnostic and Treatment
17 May	First tomography of the chest (T), neck and abdomen.
22 May	Result First T neck indicating the presence of low-right cervical lymph node enlargement (level IV, V and VI), coalescent mediastinal and supraclavicular lymph node enlargement on the right, and subpleural nodular opacity.
29 May	Neck biopsy
30 May	Result of biopsy indicating malignant tumor. The first result indicated cells with pulmonary origin.
5 June	First positron emission tomography – computed tomography- PET-CT image examination of thew holebody. The patient´s oncologist (Phisician) defined: six (6) chemotherapy sections spaced 21 days apart, using taxol and carboplatin, drugs considered as first-line treatment for lung cancer (according to internation alrecommendations) [23]. (Figure 1A)
21 June	First Chemotherapy;

12 July	Second Chemotherapy; Result of the immunohistochemical examination:a positive ALK gene mutation.
1 August	Second T, neck and abdomen that indicated cervical lymph node enlargement with homogeneous attenuations, with an increase in the dimensions of the lymphomegalies; small nodular lesion in theleft adrenal that may correspond to metastatic focus and multiple lymph omega lies extending through the pre-vascular, upper and lower paratracheal chains, aortopulmonary window, pulmonary and subcarinalhiluses.
7 August	Beginning of radiotherapy on the neck, performed on the right side of the neck. Total often (10) sections of radiotherapy [23]. With applications from Monday to Friday, ending on18 August 2017. Chemotherapy was suspended.
19 August	Treatment started with Xalkori™ 250mg (Crizotinib): two tablets daily (morning and night): first-line medication for the treatment of NSCLC – ALK positive [23].
10 Octuber	T: monitoring;
1 December	T: presented an important volumetric reduction of meadistinal lymph node enlargement.

Table2. *Timeline according to the chronology of diagnosis and treatment of a clinical case study: positive ALK lung cancer patient - Year 2018*

2018	**Diagnostic and Treatment**
12 January	Second PET-CT image exam that reported a reduction in the dimensions, number and glycotyl metabolism of cervical, mediastinal and pulmonary hilar lymph nodes, with a persistent discrete glycotyl metabolism of viable neoplastic tissue; reduction in dimensions, number and metabolic activity in pulmonary nodules, with no significant metabolic activity being evidenced. (Figure 1B).
14 May	First Magnetic Resonance Imaging of the skull that revealed multiple intraparenchymal lesions suggestive of secondary neoplastic involvement. The examination was done because the patient had reported the appearance of photopsies in the corner of his eyes. Figure 2A.
15 May	Patient follow-up
30 May	Detectionof cerebral metastasis. The patient started radio therapy treatment on the head: 10 sections of radio therapy with applications from Monday to Friday, ending on12 June 2018. During radiotherapy treatment Xalkori™ (Crizotinib)was suspended.
12 June	Start of treatment with the drug Alecensa™ 150 mg (Alectinib), with 8 tablets daily: four (4) in the morning and four (4) at night. A first-line medicine in cases of brain metastasis [23]*.
12 June	Magnetic resonance imaging of the skull with nodular lesions (yet).
13 June	Tomography of the chest, performed for oncological monitoring, showed the disappearance of enlarged lymph nodes in the cervical region.
10 August	Tomography of the chest and neck: follow-up;
11 August	Magnetic resonance imaging of the skull showing an important reduction in the size of multiple nodular brain lesions, including the dissipation of some of these lesions. Figure 2A.
24 October	Tomography of the chest and neck: follow-up;
25 October	Magnetic Resonance Imaging of the skull, counting nodular lesions without significant change in size and dimension, and without tumor metabolic activity.Figure 2B.

* Since the end of 2018, Alectinib has started to be used as a first-line treatment for cases of ALK cancer, since it provides the decrease in the incidence of metastases in the central nervous system [22, 24].

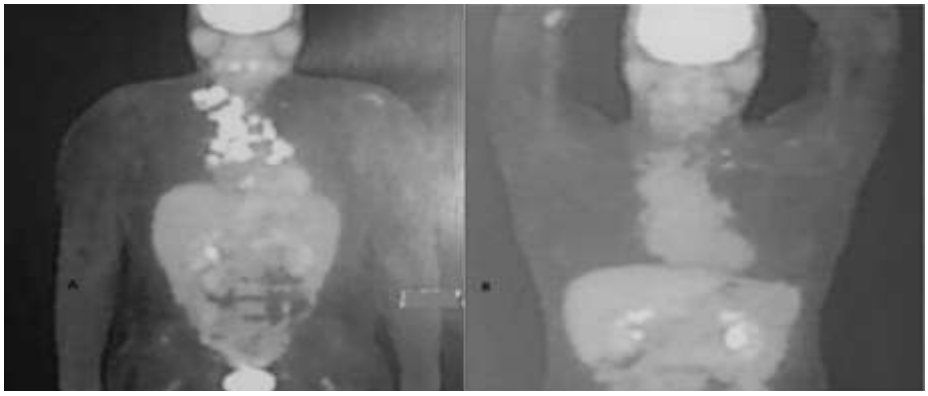

Figure1. *A – First Positron Emission Tomography-Computed Tomography-PET-CT of patient after 20 days of diagnostic of ALK positive lung cancer; B – Second PET-CT after 8 months of radio therapy and/or pharmacotherapy throughout treatment*

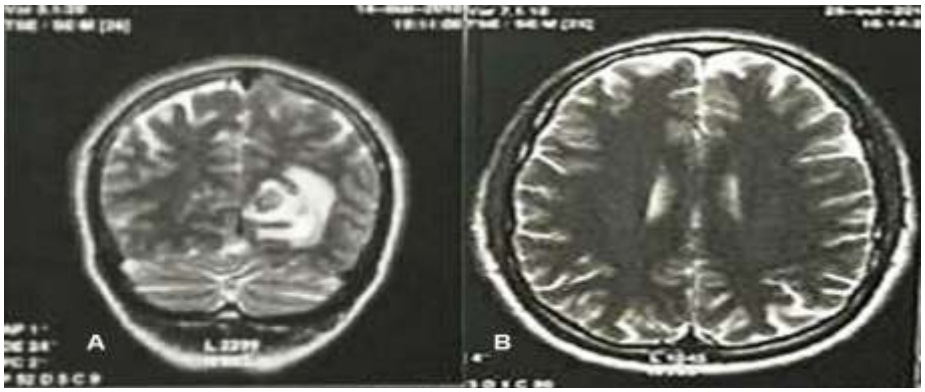

Figure2. *A-Magnetic Resonance Imaging of the skull showing multiple intra parenchymal lesions suggestive of secondary neoplastic involvement of ALK positive lung cancer patient; B- Magnetic Resonance Imaging of the skull counting nodular lesions without significant change in size and dimension, and without tumor metabolic activity*

As reported by the patient, by the end of 2018, he was using the medicine Alecensa® (Alectinib) orally. He was still performing routine imaging exams to monitor his health with specialized medical monitoring for his case. To the patient was also instructed to consult an nutrologist to guide him to adapt his diet and life style. Currently, according to the patient, he maintains a strict diet to stay healthy in order to have a positive influence on his treatment.

4. DISCUSSION

In cases of NSCLC, ALK rearrangements are found in an approximate number in 5% of cases [9] so they have a low life expectancy.

For Liu et al. [24] and Awad and Shaw [26], the use of chemotherapy associated with an oral ALK rearrangement inhibitor drug is considered a first-line treatment for patients with positive ALK NSCLC. However, the patient in this study underwent, at the first moment, only chemotherapy (carboplatin + paclitaxel), as he still did not know about the complete diagnosis that he would report to be a positive ALK cancer.

After having had two sections of chemotherapy, the rapid progression of the disease came along with the laboratory result, and the treatment was modified. Then, the patient underwent 10 radiotherapy sections on the right side of the neck, where his tumors were more concentrated; the precise location was in the supraclavicular region in the internal jugular chain and the right posterior cervical chair (level IV, VE VI), the largest being 1.2 cm in its smallest diameter; in addition to mediastinal coalescent lymph node enlargement, predominating in the para tracheal chain on the right and subcarinal, with the largest measuring 4.7 x 3.0 cm. Radiotherapy for NSCLC is generally used when the tumor (s) are inoperable due to their size and / or location.

Crizotinib was the oral medication chosen to be the patient's pharmacotherapy after radiotherapy. It was an oral drug considered to be of first line for treatment in cases of advanced NSCLC for rearrangements of ALK, MET and ROS-1 kinase [9].

Studies carried out by Choi et al. [27] and Holla et al. [13] on Crizotinib reveal that during treatment, resistance mechanisms lead to disease progression. Although the mechanism of resistance is not yet fully understood, it is known that they may be due to secondary mutations acquired in the ALK kinase domain or amplification of the ALK gene. The mutation may also come from the activation of ALK-independent survival path ways that lead to the in effectiveness of Crizotinib [13, 27].

At the present clinical case, the daily use of the drug was maintained for an average of 11 months, then the exams indicated a brain metastasis. As reviewed by Ceresoli et al. [26] he central nerve system (CNS) is a frequent site for this progression, and lung cancer is the main source of brain metastases and NSCLC patients develop CNS metastases in about 20-40% of cases. Lagerwaard et al. [29] comment that brain metastases are generally associated with poor results, and treatment is palliative in most cases. Standard treatment options include symptomatic corticosteroid therapy and total brain radiation (WBRT), which lead to a median survival of 3-6 months [29, 31].

In the present study, the patient had his oral medication changed to Alectinib after have under gone ten (10) sections of radiotherapy in the skull region. After radiotherapy sections an MRI was requested to evaluate the situation of the intraparenchymal lesions. The result of the MRI revealed that the lesions did not progress. The Alectinib was the drug of choice to continue treatment until then because it is considered the most specific for cases where there is progression to the CNS [22, 24, 30]. It proved to be effective in the treatment, because until that moment the patient had a stable condition. Thus, as previously exposed, currently Alectinib has started to be used as a first-line treatment for cases of ALK cancer, since it provides the decrease in the incidence of metastases in the central nervous system (22, 24].

In a study by Lin [30], Alectinib demonstrated a potent activity in the CNS, both in situations of resistance or not to crizotinib, having a penetration through the blood-brain barrier [29, 30] was significantly higher than Crizotinib. Looking for a stability for the tumor, the ideal in this case would b that the patient understudy, had used a more specific pharmacotherapy for cerebral ALK positive metastasis, that is, a drug that would cross the blood-brain barrier with more expressiveness would be necessary.

As we have seen, it is important to note that, in general, studies have shown the use of oral drugs for ALK inhibitors associated with another therapy, mainly chemotherapy, where it presents more expressive results (even with resistance). However in the case of the studied patient, the first medication to inhibit ALK was only inserted after completion of cervical radiotherapy, that is, there was no association of drugs, and even then it was sufficient and effective until metastasis (cerebral) occurred. The second pharmacotherapy was also not associated, and maintained the patient's clinical condition in a stable, controlled and effective way, since the last exams were favorable to the treatment and with positive perspectives.

5. CONCLUSIONS

Recognizing these verity that positive ALK lung cancer expresses in a patient, we sought to understand how pharmacotherapy, without surgical interventions, contributed to the evolution of a patient's clinical condition, considering that lung cancer is one of the most aggressive and that has a low expectation of survival.

Although the patient did not use combinations of simultaneous pharmacotherapy for NSCLC ALK positive, the applied therapy resulted in positive indicators, that is, reduction in volume, size and tumor metabolic activity.

Crizotinib and Alectinib were extremely important for the positive advancement of the patient's clinical condition. Even though the patient developed resistance to crizotinib and, consequently, a brain metastasis, an already predicted event of the drug's action. Anyway, this medication has been canceled for use by the patient, since Alectinib is the most indicated today for its most favorable results for the treatment of cancer.

Alectinib maintained the patient's stable health, at least until the follow-up performed here, that is, the cancer did not evolve. Thus, the positive clinical evolution observed here, gave indicators of a better quality of patient survival.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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