USE OF OSIMERTINIB 160mg FOR TREATMENT OF NSCLC: CASE REPORT

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ABSTRACT

Introduction: Lung cancer is the most prevalent cancer in the world, and it is also the cancer with the highest mortality. Non-small cell lung cancer (NSCLC) accounts for 85% of cases, and is related to bone metastases in the central nervous system (CNS), and liver. It is known that a large part of the mutations involved in the development of NSCLC is the mutation in the epidermal growth factor receptor (EGFR) gene, leading to the production of EGFR with permanent activation, and thus, generating a lack of control over cell growth pathways. Thus, drugs capable of blocking the mutated EGFR receptor and reversing the constitutive activation of the receptor have been developed. Currently, the drugs available with this capacity are tyrosine kinase inhibitors (TKIs), including osimertinib (third-generation TKI), which has the ability to act on EGFR T790M mutations, and penetrate the blood-brain barrier, allowing the treatment of leptomeningeal and brain metastases. Currently, osimertinib is used in doses of 80 mg for the treatment of NSCLC with CNS metastasis resistant to first- and second-generation TKIs, and there are few studies on therapeutic and side effects at higher doses. Thus, the present case report seeks to elucidate the effects caused by osimertinib 160mg on NSCLC associated with meningeal metastasis and to understand the side effects observed with the increase in the dose of the drug. Case report: A 53-year-old female patient diagnosed in 2018 with NSCLC with EGFR mutation and meningeal metastasis. She used osimertinib 80 mg, with tumor growth in the lung and meninges. In 2020, the dose was increased to 160 mg after developing meningeal syndrome and observing the presence of tumor cells in cerebrospinal fluid. The patient developed adverse reactions to the medication and dose increases. She presented clinical worsening at the end of 2021, evolving to death in 2022. Conclusion: Osimertinib 160mg has high efficacy for the control of neoplasms and metastases with EGFR mutations, and more intense side effects than the usual dose, and further studies are needed to understand the efficacy of the drug in meningeal metastases in the long term.

Keywords: Antineoplastic drugs. Non-small cell lung carcinoma. Meningeal neoplasms.

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INTRODUCTION

Lung cancer is the most prevalent malignant disease in the world, accounting for 13% of cancer diagnoses. In Brazil, it is the second most common type of cancer in men, and the fourth in women. Lung cancer is also the leading cause of mortality among types of cancer, responsible for 1.8 million deaths per year worldwide. In Brazil, the 5-year survival rate is 18%, close to global averages (10% to 20%) (ARAUJO *et al*., 2018). Non-small cell lung cancer (NSCLC) accounts for 80-85% of lung cancer cases, 30% to 40% of people with NSCLC develop bone metastasis over the course of the disease (RAJAPPA; KRISHNA; NARAYANAN, 2019) and, 20% to 40% develop metastasis in the central nervous system (CNS) (LEE *et al*., 2019).

Epidermal growth factor receptor (EGFR) mutation is present in 11% to 43% of NSCLC cases (OH *et al*., 2019), in bone metastases (HIGUCHI *et al*., 2020), and in leptomeningeal and brain metastases (RAJAPPA; KRISHNA; NARAYANAN, 2019). EGFR is a tyrosine kinase receptor of the ErbB family that is activated by epithelial growth factors (EGF) and induces cell division. Mutations in EGFR genes lead to constitutive activation of the receptor and uncontrolled activation of cell division pathways, which can lead to cancer development and progression (RAJAPPA; KRISHNA; NARAYANAN, 2019). Deletion mutations in exon 19 and point mutations in exon 21 are the most common mutations in the EGFR gene. In these cases, treatment with first- and second-generation EGFR-tyrosine kinase inhibitors show satisfactory responses (OH *et al*., 2019). In some cases, resistance mechanisms are acquired, reducing the action of first and second generation EGFR-tyrosine kinase inhibitors. The EGFR Thr790Met mutation (T790M) is the most common mechanism of resistance, present in 48 to 62% of cases (PROVENCIO *et al*., 2021). Other mechanisms such as amplification of the proto-oncogene MET, human epidermal growth factor 2 (HER2), and hepatocyte growth factor (HGF) are present in 20 to 30% of mutations. With the development of mutations and the failure of the therapeutic regimen of first- and second-generation drugs, third-generation EGFR-tyrosine kinase inhibitors selective for mutations in T790M have been developed, with osimertinib being the only drug currently approved by the Food and Drug Administration (FDA) (OH *et al*., 2019). Osimertinib is an irreversible EGFR-tyrosine kinase inhibitor selective for EGFR and T790M (PROVENCIO *et al*., 2021), being able to penetrate the blood-brain barrier (BBB) (SAKURAI; TUCHIDA; NISHIDA, 2021). The passage of the drug through the BBB demonstrated activity on leptomeningeal and brain metastases with mutations in EGFR T790M. The AURA 3 study demonstrated that the objective response rate for brain metastases is 70% with osimertinib,

versus 31% with the dual regimen of platinum-based chemotherapy (RAJAPPA; KRISHNA; NARAYANAN, 2019).

The AURA 3 study demonstrated a significant increase in progression-free survival in patients using osimertinib (10.1 months) when compared to using platinum-based chemotherapy (4.4 months), and increased progression-free survival in patients with central nervous system metastases. AURA 3 revealed that the time for the onset of the main symptoms of deterioration was longer in patients who used osimertinib, increasing the quality of life and overall quality of the individual (RAJAPPA; KRISHNA; NARAYANAN, 2019). OH *et al*., 2019 observed that the mean progression-free survival time in patients who used osimertinib 80 mg/day orally was 7.4 months, and after 12 months, 24.1% of the patients remained without disease progression. After disease progression, it was observed that the T790M mutation became undetectable in 70% of patients (OH *et al*., 2019).

NSCLC metastases often involve mutations in EGFR genes. Vascular endothelial growth factor (VEGF) is overexpressed in NSCLC tumors, and contributes to tumor growth. VEGF inhibition is an attempt to reduce tumor growth and decrease tissue action. The study by HIGUCHI *et al*., 2020 compared the treatment efficiency of osimertinib in contrast to bevacizumab, an anti-VEGF monoclonal antibody, in rodents with bone metastases by NSCLC. The study observed that there is a significant difference in tumor evolution between treatments, with a reduction in the presence of tumor cells in rodents treated with osimertinib, and an increase in survival time compared to those treated with bevacizumab (HIGUCHI *et al*., 2020).

In patients with leptomeningeal metastasis, osimertinib is administered at a dose of 160 mg in an attempt to increase the concentration of the drug in the cerebrospinal fluid. The study by PARK *et al*. (2020), demonstrated that 75% of patients who developed leptomeningeal metastasis during treatment with osimertinib 80 mg had the disease controlled with the use of 160 mg of the drug. During treatment, it was observed that patients have greater progression of extracranial lesions than intracranial lesions, but there are disagreements between the site with the best response (PARK *et al*., 2020).

The most common adverse effects reported by the use of 80 mg osimertinib include diarrhea, pruritus, paresthesia, erythematous plaques, rashes, stomatitis, and nausea (FANG *et al*., 2019), effects such as skin rash, loss of appetite, thrombocytopenia, and leukopenia may also be observed during treatment (WANG; CANG; LIU, 2016).

Based on the studies presented, this study proposes the comparison of efficacy, side effects and modifications of the organism with the use of 160 mg of the drug osimertinib, since the use of 160 mg of osimertinib for the treatment of NSCLC with metastasis in the

leptomeninges is still little reported in recent studies, with a lack of information on the efficacy of the treatment. side effects and effects not yet well clarified with the use of the dose. A better understanding of the body's response to NSCLC treatment with osimertinib 160 mg will allow the evaluation of effectiveness, anticipation of probable side effects, and the best therapeutic choice for the patient. The information obtained from the proposed work will allow the comparison of the use of 80 mg, usually described in studies, with the use of 160 mg of osimertinib, in order to understand the differences in therapeutic effect and side effects related to the different doses.

METHODOLOGY

A description of the history of the patient diagnosed with NSCLC was performed, with metastasis in the leptomeninges and submission to treatment with osimertinib 160 mg per day. Clinical data were collected from the patient's follow-up records, laboratory and radiological tests performed during the period, upon acceptance of the informed consent form by the patient, and with authorization from the place where the data were collected. As there are few conclusive studies on the efficacy of Osimertinib 160mg for the treatment of EGFR-mutated NSCLC (del19), and side effects of the drug, the evolution of the disease, efficacy of the treatment and side effects reported by the patient have been described in detail. The case report project was approved by the CEP. CAAE: 59936022.6.0000.5539. Opinion number: 5.529.386.

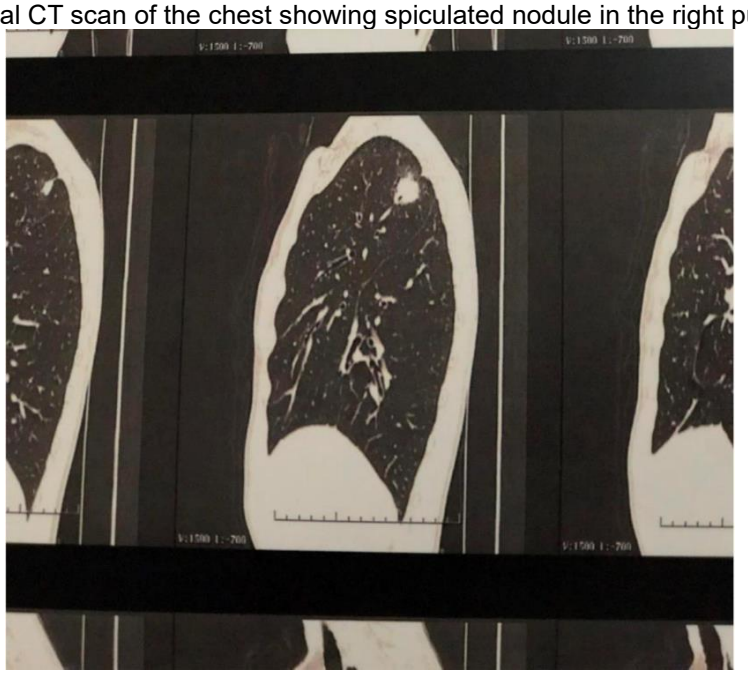
DEVELOPMENT

A 53-year-old female patient was diagnosed with non-small cell lung cancer, mutated EGFR adenocarcinoma (exon 19 deletion) associated with meningeal metastasis. The patient sought medical care on 07/18/2018, in which she reported diffuse low back pain, vertigo and unilateral hypoacusis. Previously performed NB (degenerative discopathy), and bone scintigraphy was requested. Computed tomography previously performed showed findings of pulmonary masses and CNS involvement.

On 07/24/2018, a chest CT scan was performed, showing a nodular lesion in the right lung apex, in a posterior situation, there is a nodular, spiculated and imprecise lesion, measuring approximately 24.3 x 22.1 x 21.2 mm (Figure 1). A lesion with a similar appearance is found in the anterior segment of the upper lobe of the left lung, measuring 11 x 10 x 9 mm (Figure 2). Other portions of the lung parenchyma showed normal attenuation, with no evidence of consolidative lesions, nodules, or interstitiopathies. Leading to the diagnostic impression of spiculated and imprecise nodules located in the upper lobes of

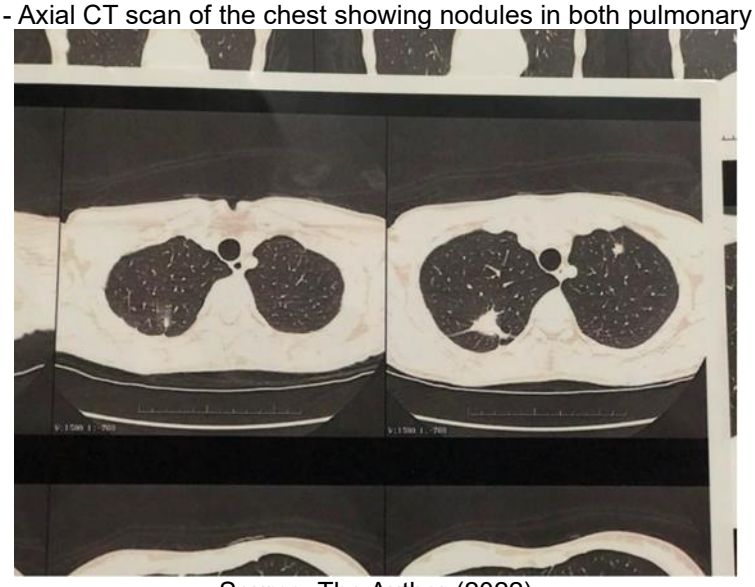
both lungs, and with the other characteristics described above. A better diagnostic investigation is indicated.

Figure 1 - Sagittal CT scan of the chest showing spiculated nodule in the right pulmonary apex.



Source: The Author (2022)

Figure 2 - Axial CT scan of the chest showing nodules in both pulmonary apexes.

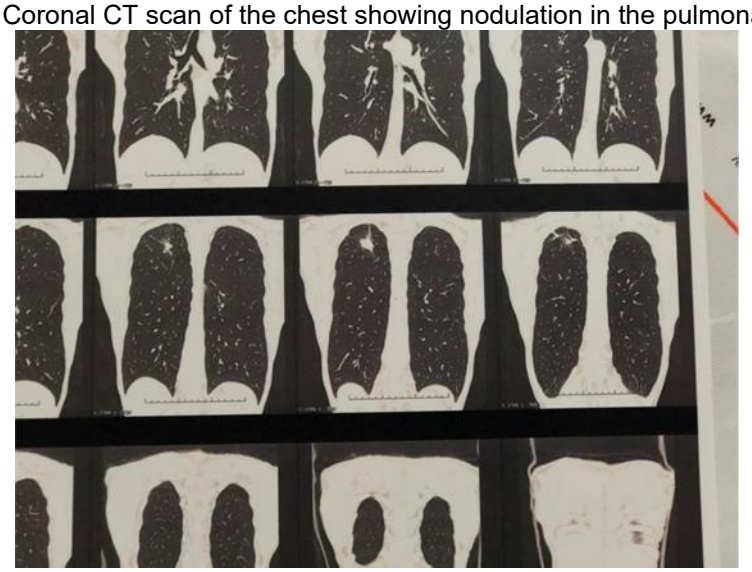


Source: The Author (2022)

On 07/27/2018, a positron emission tomography/computed tomography (PET/CT) scan, and a percutaneous computed tomography-guided biopsy/drainage were performed, due to a history of pulmonary nodule evaluation. Report, two solid pulmonary nodules with spiculated contours located at the right apex measuring 2.8 x 2.4 cm and at the left apex (Figure 3) measuring 1.2 x 0.9 cm, with increased metabolism (maximum SUV 6.8 and 2.1 cm, respectively). Additional TC findings without metabolic alterations: Smooth thickening of

the interlobular septa at the apices. Calcified pulmonary granuloma in LSE (sequelae). Some rare sparse, punctiform, non-calcified solid pulmonary nodules measuring less than 4 mm. Diagnostic impression: 1. two pulmonary nodules, with increased metabolism, suspicious for neoplasia. The one on the right was biopsied on the day.

Figure 3 - Coronal CT scan of the chest showing nodulation in the pulmonary apices



Source: The Author (2022)

Osimertinib was started on 08/04/2018 with a conventional dose of 80mg/day, after confirmation of metastasis in the central nervous system (CNS) - meningeal carcinomatosis - through oncotic cerebrospinal fluid cytology, in which the presence of EGFR mutation with exon 19 deletion in metastatic cells in the meninges was found. With the initiation of the medication, the clinical picture and the evolution of the disease were stabilized, with no other symptoms associated with NSCLC or metastasis in the meninges.

26 months after the start of treatment with Osimertinib 80mg/day, the patient underwent a new oncotic cytopathology of the cerebrospinal fluid in September 2020, after developing symptoms of meningeal syndrome, characterizing disease progression. The examination identified isolated cells, with the presence of atypia and cells in cell division, which is a positive characteristic for malignancy. On the date of collection, the patient had a stage of pulmonary adenocarcinoma (CAC) IV. Due to the condition developed by the patient, and the clinical evolution of disease progression, treatment with an increase in the dose of Osimertinib to 160mg/day was instituted on 10/03/2020, associated with the use of corticosteroids.

After 9 months of using Osimertinib 160mg, the patient reported paresthesia on the face, with predominance on the right side, visual acuity in the right eye, and pressure in the head region. In addition, a skin rash was observed in the dorsal region of the forearm and

bilateral periorbital edema. With the increase in the dose from 80mg to 160mg, it was possible to observe the same side effects as the initial dose, but more exacerbated. On physical examination, the patient had GTR and LOT, bilateral periorbital edema was observed, weight 43 kg, BMI 16.6 kg/m². EC IV (T2N0M1).

After 10 months of using the drug, the patient reported worsening of paresthesia in the face, and the appearance of paresthesia in the feet and hands. He reported worsening of visual acuity and worsening of hearing in the left ear. Improvement of the skin rash was observed. Serum samples were collected to evaluate the carcinoembryonic antigen (CEA), obtaining a result: < 1.73 ng/ml. Chest CT scan showed stable disease compared with previous CT, and abdominal CT showed no commemorative signs.

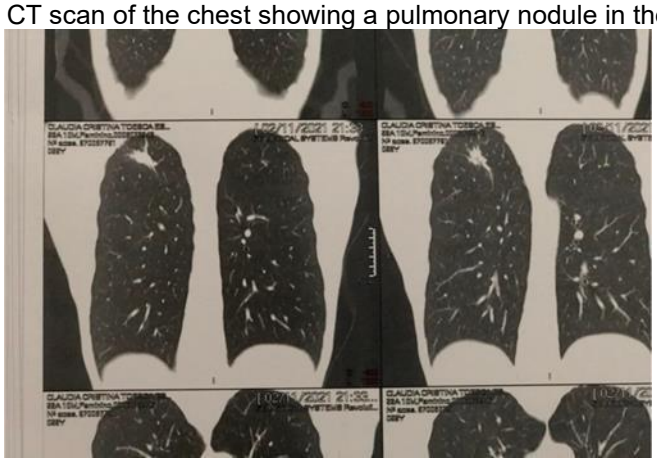
The patient was evolving well with the treatment, and the tumor had been encapsulated and had no significant changes in size. In 2021, the patient's condition was destabilized, it was thought to be related to side effects of the 3rd dose of the COVID-19 vaccine, being a condition of intense headaches, dizziness, vision alteration and partial hearing loss. Corticosteroids were then prescribed for symptomatic control. After a few months without improvement of the condition, a worsening of the meningeal metastasis was found after investigation: the patient returned to the doctor on 10/07/2021, reported having received the 3rd dose of the vaccine for COVID-19. In addition, she reported worsening of diplopia and balance, and increased syncope, in addition to severe headache. Due to the proximity of the vaccine, it was understood that the worsening of the condition would be related to this, but due to the lack of improvement and evolution, it was confirmed that these effects were due to an exacerbation of the meningeal metastasis. Recommended start of dexamethasone 4mg per day (09/22/2021). Laboratory tests showed pancytopenia and CEA < 1.73 ng/ml.

On 10/21/2021, the patient was consulted again, and improvement in the headache reported by the patient was observed, and the sensation of pressure in the head and paresthesia in the face persisted, in addition to diplopia and decreased visual acuity in the right eye. The laboratory test for CEA collection showed 2.58 ng/ml, indicating an increase in CEA compared to the previous consultation. On this occasion, he was instructed to wean off dexamethasone and perform tests to control the disease.

On 11/02/2021, a chest CT scan was performed, and the presence of non-calcified pulmonary nodules with irregular morphology associated with linear opacities in the posterior segment of the right upper lobe, measuring 23 x 20 mm in the axial plane, and in the anterior segment of the left upper lobe, measuring 8 mm in mean diameter (Figure 4). Millimetric calcified granuloma in the upper lobe of the left lung (Figure 5). Therefore, it was

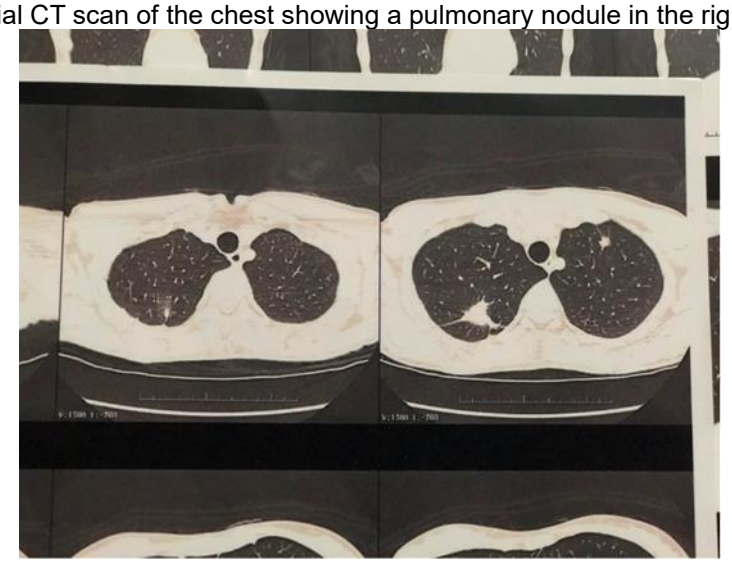
characterized that the examination does not present significant changes from other imaging studies performed previously, taking into account the findings described.

Figure 4 - Coronal CT scan of the chest showing a pulmonary nodule in the right upper lobe.



Source: The Author (2022)

Figure 5 - Axial CT scan of the chest showing a pulmonary nodule in the right upper lobe.



Source: The Author (2022)

The drug was not as effective in these final stages of treatment, the patient evolved with blindness, almost complete hearing loss, osteopenia, and an increase in pain intensity. A patient in November 2021 had to be bedridden, combining physiotherapy service and intravenous medications to control symptoms (corticosteroids and morphine), and it was no longer possible to use osimertinib due to the patient's impossibility of swallowing. In March, the patient began to have respiratory distress crises and reached a cachectic condition, requiring parenteral feeding when possible and oxygen therapy.

On 05/31/2022, the patient died due to complications from metastatic NSCLC to the meninges.

DISCUSSION

New scientific research on malignant neoplasms and the search for more modern treatments make it possible to increase overall survival and better prognosis of patients with this pathology. Cancer is responsible for the second leading cause of death in the world, with an annual incidence of 625 thousand new cases in Brazil (SOBRAL *et al*., 2022). Studies have shown an increase in the prevalence of neoplasms in the population, according to the increase in cardiovascular disease prevention policies. From this perspective, it is important that new antineoplastic drugs be developed and studied, supporting the clinical use in patients for the treatment of the disease. (BRAZIL, 2019).

Osimertinib, an oral drug, a third-generation EGFR tyrosine kinase inhibitor, was developed to combat neoplastic cells that have epidermal growth factor receptor (EGFR) mutation. The inhibitory action on EGFR tyrosine kinase prevents cell growth by suppressing the mutated protein, and thus inhibits the progression of the neoplasm. (ZHAO; CHEN, 2022). The relationship between non-small cell lung cancer (NSCLC) and EGFR receptor mutation is well-defined (OH *et al*., 2019), being present in 43% of lung adenocarcinomas and in meningeal metastases originating from NSCLC (RAJAPPA; KRISHNA; NARAYANAN, 2019). In the reported clinical history, the patient was diagnosed with adenocarcinoma NSCLC with EGFR mutation (del19) evaluated by immunohistochemical examination.

NSCLC is well described in association with the presence of brain metastases, meningeal (RAJAPPA; KRISHNA; NARAYANAN, 2019) and bone (HIGUICHI *et al*., 2020).

The metastases found usually have mutations in EGFR genes, and EGFR-tyrosine kinase inhibitors are used for the treatment and control of the disease. In cases of metastases in the meninges or brain, osimertinib is the drug of choice, as it is a third-generation EGFR-tyrosine kinase inhibitor, with a greater capacity to penetrate the blood-brain barrier and with better efficacy in treatment (SAKURAI; TUCHIDA; NISHIDA, 2021). Due to the presence of metastasis of NSCLC in the meninges, evidenced in an oncotic cytology examination of the cerebrospinal fluid, the medical team started treatment with Osimertinib 80mg, to stabilize the disease. In the following months, imaging tests revealed control of lung tumor size, with a mass of 24x22x21mm reported at the apex of the right lung lobe, on CT scans performed ten days before starting treatment (07/24/2018) with Osimertinib 80mg, in contrast to scans performed on 11/02/2021, using Osimertinib 160 mg, in which stabilization of the mass size (23x20mm) in the right lung lobe was observed.

In studies conducted using Osimertinib 80 mg, side effects experienced by patients included disseminated pruritus, stomatitis (FANG *et al*., 2019), inappetence, and skin rash

(PARK *et al*., 2020). In the case report described, after starting the use of Osimertinib 80mg, the patient reported xerostomia, paresthesia, and skin rash associated with the appearance of hyperemic plaques in the face, trunks, upper and lower limbs. Subsequently, with the need to increase the dose of osimertinib to 160 mg daily, the patient reported the maintenance of the side effects of the drug, highlighting the increase in the intensity of the sensation of paresthesia with progression to the hands and feet.

Carcinoembryonic antigen (CEA) is a glycoprotein that has a high serum concentration in the occurrence of production by the growing tumor. High CEA levels are related to tumor progression and a poorer prognosis. As a result, serum antigen evaluation aims to monitor tumor progression and the effectiveness of ongoing treatment (LAPORTE, 2019). Studies have shown that serum CEA levels > 10 ng/ml are related to poor prognosis, and a greater relationship with metastases (NUMATA *et al*., 2020). The patient had undetectable CEA levels (< 1.73 ng/ml) during the use of osimertinib 160 mg during treatment. A slight increase in CEA concentration was observed compared to the previous values (2.58 ng/ml) at the end of treatment with osimertinib 160mg, along with worsening of the symptoms of diplopia and headache reported by osimertinib 160mg.

CONCLUSION

The use of osimertinib at a dose of 160mg is not yet used widely and therefore there is still no satisfactory research material for direct conclusions, but visualizing the case presented, the drug has high efficacy for tumor control, avoiding evolutions, increasing the survival of patients who only have NSCLC, but in patients who progress to metastasis, more studies are needed to determine how effective the drug would be for control of other tumors, seeking to correlate their mutations and etiologies in order to cover the use of osimertinib for other similar types of cancer. It is likely that the continuous use of this medication can lead to an alteration in the tumor, making it resistant, due to the selectivity that tumor clones can develop. More studies are still needed for this confirmation, so it is only a hypothesis. Thus, we conclude that the 80mg dose of osimertinib was effective in controlling NSCLC. Increasing the dose to 160 mg was necessary after the progression of metastasis in the meninges. The patient responded well to treatment with 160mg in the first months, however, with possible clonal selectivity and reduced efficacy of the drug even at a higher dose after a certain period. With the increase in dose to 160mg, it was possible to notice a relative increase in the intensity of side effects, without the appearance of new adverse signs and symptoms compared to the 80mg/day dose of Osimertinib.

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