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Original Research Article

Pneumonitis, a common adverse event of cyclin-dependent kinase 4/6 inhibitors: a case report

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ABSTRACT

The cyclin-dependent kinase (CDK) 4/6 inhibitors are approved for women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer, these can develop common adverse events. We present the case of a woman diagnosed with metastatic hormone receptor-positive, HER2-negative breast cancer, who developed pneumonitis related to palbociclib. Pulmonary toxicity of CDK 4/6 inhibitors is not an uncommon adverse event that has been increasing in incidence.

Keywords: CDK 4/6 inhibitors, Breast cancer, Pulmonary toxicity, Common adverse event

INTRODUCTION

Cyclin-dependent kinase (CDK) 4/6 inhibitors in combination with endocrine therapy (ET) are considered the preferred first line of treatment for most patients with advanced hormone receptor-positive breast cancer.[1] The currently available inhibitors are: palbociclib, ribociclib and abemaciclib.[2]

CDK 4/6 regulate the transition from the G1 to S phase, their binding causes hyperphosphorylation of the retinoblastoma suppressor protein leading to the release and activation of the E2F1 transcription factor that activates critical genes for cell proliferation; CDK 4/6 inhibitors cause cell cycle arrest in estrogen receptor-positive breast cancer neoplastic cells; these receptors keep retinoblastoma protein functional, making cell more susceptible to CDK 4/6 inhibition and making these drugs a particularly useful treatment in this subtype of cancer.[3]

The toxicity profile of each of the CDK 4/6 inhibitors changes depending on the cyclin to which they have the highest affinity. For example, palbociclib and ribociclib have a higher affinity for CDK 4, a cyclin involved in a very important way in hematopoietic stem cell differentiation. It is therefore expected that most common toxicity of these 2 inhibitors is hematological toxicity. On other hand, abemaciclib has greater selectivity for CDK 6, producing greater GI toxicity such as diarrhea.[4]

Some rare adverse events, although reported in literature, are prolongation of the QT interval for ribociclib and increased transaminases for ribociclib and abemaciclib.[5-6]

Cases of pulmonary toxicity secondary to these cyclin inhibitors have been reported, and although these were not initially reported as common adverse effects in phase 3 studies, incidence related to this type of drug increasing.[7-13]

CASE REPORT

We present the case of a 69-year-old woman diagnosed with infiltrating ductal carcinoma of the right breast, luminal B, HER2 negative with clinical stage IV due to lung, liver, lymph node, bone, and soft tissue disease.

She was initially treated for a clinical stage IIB (T2 N1 M0) with sequential neoadjuvant chemotherapy without a complete pathological response after modified radical mastectomy and axillary dissection (ypT ypN1 M0). She received extended adjuvant endocrine therapy for 10 years. During surveillance, a new lesion in right chest wall was detected and distant lesions were reported in computerized tomography (CT). A biopsy of chest wall lesion revealed an infiltrating ductal carcinoma hormone-receptor positive, HER2 negative.

She received first line of treatment with exemestane until progression. She subsequently started the second line of treatment in April 2020 with palbociclib plus fulvestrant with standard doses for three cycles.

During her follow-up, the patient went to the emergency room for presenting cough with expectoration. On clinical examination she had an oxygen saturation by pulse oximetry of 89% on room air, for which reason extension studies were performed. Chest tomography showed findings compatible with pneumonitis. During the diagnostic approach, an infectious process was ruled out, with no bacterial or fungal isolations.

The patient received steroid treatment based on methylprednisolone at a dose of 1mg/kg for 3 days with clinical improvement and decrease in oxygen requirements, as well as radiological improvement. She was discharged with oral steroid treatment.

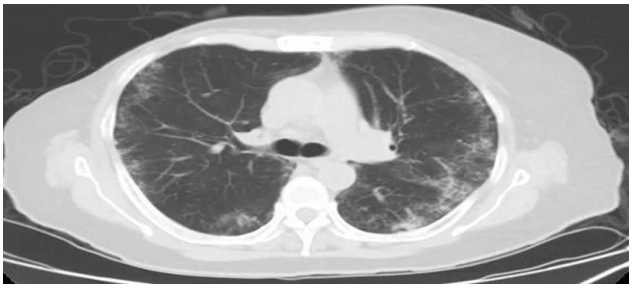

Figure 1: Chest CT: ground-glass opacities in the bilateral upper lobes (axial view).

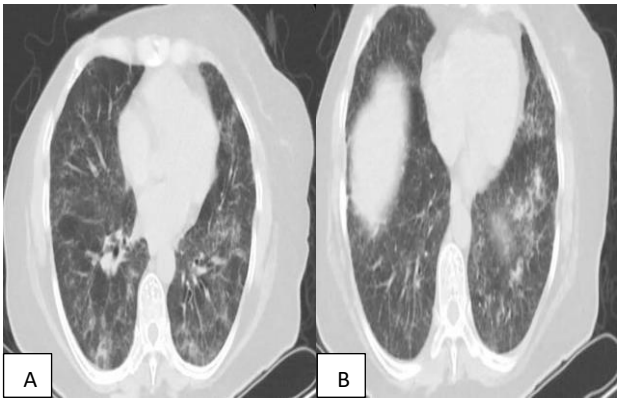

Figure 2 (A and B): Chest CT: ground-glass opacities in the bilateral lower lobes (axial view).

DISCUSSION

The exact mechanism by which these drugs induce lung inflammation is unknown. An experimental study in rodents showed that the use of these drugs increased the recruitment of inflammatory cells to the lung parenchyma (monocytes, neutrophils, T lymphocytes).[14]

Pulmonary toxicity secondary to drugs encompasses a wide variety of lung diseases, with different clinical phenotypes, different histopathological patterns, even with the same treatment. The term interstitial lung disease (ILD) refers to a heterogeneous pathology of difficult clinical diagnosis encompassing several entities: pneumonitis (autoimmune, eosinophilic and hypersensitivity pattern), pulmonary fibrosis, sarcoidosis, and pleural effusion. The incidence varies between 4.1 and 12.4 cases/million per year with drugs for rheumatological diseases, antibiotics, and antiarrhythmic drugs, such as amiodarone.[15]

Pulmonary toxicity with CDK 4/6 inhibitors does not necessarily occur immediately after starting treatment; there are case reports where it occurs even one year later.[11]

The best therapeutic approach includes stopping the drug, administering steroids and supportive care.[11] However, the response to these treatments is variable.[12]

Numerous cancer treatments have been associated with adverse pulmonary events, including gemtamycin, bleomycin and recently immunotherapy with anti-PD1/ PDL-1 agents, pembrolizumab and nivolumab.[12,15]

In 2019, the FDA issued an alert on the use of CDK 4/6 inhibitors and their association with serious pulmonary adverse effects.[16] Likewise, the Japanese Ministry of Health issued a warning due to four patients in Japan who developed pulmonary toxicity likely related to abemaciclib exposure, one of whom died.[17]

In the final report of MONARCH 3, 8 deaths secondary to adverse events due to abemaciclib are reported, of which 3 correspond to pulmonary infection, 2 to pulmonary embolism, 1 to cerebral ischemia, 1 to pneumonitis and 1 to respiratory failure, with no evidence of pulmonary adverse events.[18]

In phase III of the MONALEESA-3 study, 5 deaths secondary to adverse events due to ribociclib were reported, the causes were heart failure, pneumonia, pulmonary embolism, hemorrhagic shock, and ventricular arrhythmia. Likewise, the only pulmonary adverse event reported is cough.[19]

In the final PALOMA-3 report, no deaths or adverse pulmonary events were reported.[20]

In the article by Raschi et al the incidence of pneumonitis was compared with CDK 4/6 inhibitors and bleomycin. It was concluded that CKD 4/6 inhibitors should be included in the list of drugs that cause ILD.[15]

CONCLUSION

Due to the increased incidence of common adverse effects secondary to pulmonary toxicity and the findings presented, we emphasize the need for better pulmonary monitoring in patients who will receive this type of treatment and for greater caution when prescribing them in patients with a history of pulmonary disease, because exacerbations can be fatal.

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