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Open Access Journal of Cancer & Oncology

A Case Report of a Breast Cancer Patient Developing Pneumonitis as a Result of Abemaciclib Therapy

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Case Report
Volume 8 Issue 2
Received Date: September 09, 2024
Published Date: October 21, 2024
DOI: 10.23880/oajco-16000198

Abstract

Introduction: Breast cancer is the most common cancer affecting women in the United States, and the prognosis is good, with a 5-year survival rate of 91.2%. Advancements in treatment options using molecular profiling have allowed therapies to be more personalized and have improved patient outcomes. Of the many specific therapy agents, cyclin-dependent kinase (CDK) 4/6 inhibitors, such as abemaciclib, are commonly used.

Case: We present a case of a 74-year-old female with a history of HR+ breast cancer who has been on abemaciclib for over two and a half years and developed pneumonitis.

Discussion: Pneumonitis, as a direct result of abemaciclib or other CDK 4/6 inhibitors, is a rare side effect with an unknown mechanism of action. The Federal Drug Administration (FDA) has warned about the potential for this severe and potentially fatal inflammation of the lungs when using these agents. No studies have investigated additional risk factors in developing this side effect. However, reviewing other case reports supports that patients typically develop this side effect within the first three years of treatment initiation. The mechanism of manifesting this side effect has not been explored. However, it has been proposed that it is related to over activation of the immune system. Treatment includes clinical observation for asymptomatic and glucocorticoids for symptomatic patients.

Conclusion: This case highlights the complexities of breast cancer therapies and the rare side effects of pneumonitis with CDK 4/6 inhibition from drugs like abemaciclib. More research should be conducted to better understand and prevent the manifestation of this potentially fatal side effect.

Keywords: Checkpoint Inhibitor; Pneumonitis; HER+ Breast Cancer; Immunotherapy

Abbreviations

CDK: Cyclin-Dependent Kinase; FDA: Federal Drug Administration; ER: Estrogen Receptor; PR: Progesterone Receptor; HER: Human Epidermal Growth Factor; HR: Hormone Receptor.

Introduction

Breast cancer is the most common cancer affecting women in the United States, accounting for 15.5% of all new cancer cases in the United States. It is estimated that there are over 300,000 new cases per year.

Around 13% of women will be diagnosed with breast cancer at some point during their lifetime. Breast cancer typically presents in the sixth and seventh decade of life, with the median age at diagnosis being 63 years old. The prognosis of breast cancer is good, with a 5-year survival rate of 91.2% [1]. In developed countries with established breast cancer screenings, most patients are diagnosed based on abnormal mammograms. The typical mammogram findings of breast cancer are the presence of soft tissue mass or density with a suspicious appearance of microcalcifications [2]. There are various pathologies involved in different breast cancers, and once a cancer is diagnosed, hormone receptor status is determined to help guide therapeutic approaches. Particularly of interest is the testing of Estrogen Receptor (ER), Progesterone receptor (PR) expression, and Human Epidermal growth factor 2 (HER2) expression. Breast cancer treatment is a multidisciplinary approach consisting of a combination of surgical oncology, medical oncology, and radiation oncology. This multidisciplinary treatment, along with the introduction of new therapies and earlier detection methods, has been associated with improved survival and patient outcomes over the last several decades [3].

Hormone receptor-positive (HR+) breast cancer is when there is both estrogen and progesterone receptor expression. This is the most common subtype of breast cancer, representing around 80% of all breast cancers [4]. Until recently, the mainstay treatment for HR+ breast cancer consisted of estrogen blockade, such as aromatase inhibitors such as exemestane, anastrozole, and letrozole. However, treatment with this alone has not provided optimal outcomes. Recent advancements in checkpoint inhibitor therapy targeting cyclin-dependent kinase 4 and 6 (CDK4/6) have been utilized in HR+ treatments. Three approved CDK4/6 medications are palbociclib, ribociclib, and abemaciclib. The molecular pathway includes the production of CDK4/6 from estrogen stimulation, which then phosphorylates retinoblastoma (Rb) tumor suppressor protein, ultimately allowing cell cycle progression and cellular proliferation [5-7]. Research has shown that CDK4/6 is overexpressed in HR+ breast cancer and leads to uncontrolled cellular proliferation [8,9].

Abemaciclib is approved for HR+ breast cancer, both with the use of anti-estrogen therapy or as a monotherapy. Compared to palbociclib and ribociclib, it has a higher specificity for CDK4 and greater potency. The commonly reported toxicities are diarrhea, nausea, and fatigue, with more severe complications including neutropenia, leukopenia, infections, and anemia [10].

Here we present a case of a 74-year-old female who developed pneumonitis while being treated for HR+ and HER2- breast cancer with abemaciclib for two years.

Case Description

The patient is a 74-year-old female with a past medical history significant for HR+ stage IIA (T3N1, M0) breast cancer diagnosed in 2022 currently on abemaciclib and exemestane, hypertension, hyperlipidemia, type 2 diabetes, and chronic kidney disease who presented to the emergency department in February 2024 for stroke-like symptoms, including altered mental status. The stroke workup was negative, but her lab results showed an elevated lactic acid at 3.6. The source of the sepsis was unknown; however, the workup was not completed as the patient left against medical advice. Twelve days later, she returned to the emergency department after her lactic acid was noted to be 6.0 during a chemotherapy infusion session.

The patient's cancer history of left-sided stage III breast cancer was initially diagnosed in 2022 when a clinically palpable breast mass was associated with skin thickening and was evaluated via ultrasound and mammogram. Upon mammogram evaluation, an increased density was observed throughout the left breast.

Additionally, a mass with associated calcifications grouped indistinct calcifications was present, measuring 19 mm x 25 mm x 21 mm in the low axilla. US demonstrates three abnormal axillary lymph nodes, the largest measuring 20 x 29 x 18 mm high with cortical thickening/effacement. Biopsy of the left masses followed along with axillary lymph node biopsy noted invasive carcinoma of no special type (ductal), grade 2 (of 3) ER pos 100%, PR pos 100%, Her 2 1+ to 2+, FISH neg, MIB 10%, Stage IIA (cT3, cN1, cM0). PET scan 10/3/2022 noted mild to hypermetabolic 3.1 cm x 3.3 cm soft tissue mass in the upper outer quadrant of the left breast consistent with known primary breast

Cancer, with multiple foci of mild hypermetabolic metastatic left axillary lymphadenopathy. There was no metabolic evidence of metastatic disease within the neck, lungs, mediastinum, abdomen, pelvis, and osseous structures. The patient declined any surgical intervention and was then started on Abemaciclib on 11/1/2022 with delay due to a change in renal function, followed up by starting Arimidex therapy on 8/23/2023. The patient initially saw progress in her treatment with serial mammograms, noting decreasing size, and she tolerated treatment well through 14 cycles of Abemaciclib and Arimidex. Until a mammogram and ultrasound in January of 2024 noted progression of the lesion and an increase in size. Prompting a scheduled change of Arimidex to Aromasin while opting to continue Abemaciclib.

During this emergency department visit, the patient's lactic acid was found to be elevated at 6.6, with labs also

noting worsening kidney function. A review of the systems was negative. However, her vitals showed tachycardia and tachypnea. Urinalysis showed positive leukocyte esterase and nitrite, > 182 WBC, and many bacteria, leading her to be admitted to the intensive care unit to be treated for Sepsis. The patient was started on vancomycin and cefepime. Upon her admission, her treatment continued with only exemestane 25mg due to the unavailability of abemaciclib inpatient. Further testing revealed decreasing renal functioning with a GFR of 46 mL/min/1.73 m2 and a creatinine of 1.23. Upon further workup of the elevated lactic acid, suspicion was raised for type B lactic acidosis, which was attributed to an interaction between abemaciclib and metformin.

Chest X-ray showed cardiomegaly and strand lower lung opacities present bilaterally with atelectasis. Upon further work with chest CT, bi-apical pulmonary nodules were noted, measuring up to 3-4 mm, and diagnosed as progressing pneumonitis. Following this extensive workup, it was determined that the underlying cause of the pneumonitis was her use of abemaciclib, which she had been taking since November 2022. Corticosteroids were suggested as treatment, but she was already on a course from her outpatient provider.

Discussion

CDK 4/6 inhibitor therapy has shown significant clinical effects in cancer patients and has been particularly helpful in the treatment of hormone receptor-positive breast cancers. This includes drugs such as abemaciclib, which has been approved by the FDA for treatment in patients with HR+ breast cancer [10].

However, like all drugs and therapies on the market, there are adverse effects, and the FDA has put out a warning that CDK 4/6 inhibitors palbociclib, ribociclib, and abemaciclib may cause rare but severe inflammation of the lungs (pneumonitis) [11]. Clinical practices recognize that the overall benefit of these drugs outweighs the risks as this side effect is rare. Checkpoint inhibitors have been shown to have an incidence rate of pneumonitis at 3-5% overall [12]. However, a more specific meta-analysis of 12 randomized control trials in patients using CDK4/6 inhibitors showed that the rate of interstitial lung disease and pneumonitis patients was 1.6% (131/8407) compared to 0.7% (50/7349) in the control group [13]. The risk factors for developing pneumonitis with CDK 4/6 inhibitors are currently unknown. Suspected factors include sex, age, smoking history, baseline lung disease, and pulmonary radiotherapy, among others [14]. However, further studies must be conducted to determine the risk factors for CDK4/6 inhibitor-precipitated pneumonitis.

While other cases of pneumonitis in patients using CDK 4/6 inhibitors have been reported, we report a patient who developed pneumonitis after two years of treatment, far longer than any other reported in the literature. Mathew N, et al. Al reports a 67-year-old post-menopausal lady who was diagnosed with metastatic HR+ HER2- breast cancer started on palbociclib. Four months into treatment, she developed a dry, nonproductive cough and worsening breathlessness on exertion, with workup attributing pneumonitis to the use of palbociclib [14]. Ashraf A, et al. describe a case of a 65-year-old female with a history of HR+ metastatic breast cancer who was diagnosed with pneumonitis one month after initiating abemaciclib. At the time of diagnosis, the patient reported that she had recently discontinued her abemaciclib due to ongoing worsening respiratory failure requiring supplemental oxygen via nasal cannula [15]. Al Ghabban A, et al. report a patient developing pneumonitis after treatment with abemaciclib for one year [16]. Jazieh KA, et al. when a 74-year- old female with a history of HR+ breast cancer developed pneumonitis while on palbociclib after three months of treatment [17]. While the literature has not described a median onset of pneumonitis in patients after initiating CDK4/6 inhibitors, these case reports show most patients presenting within one year. However, we report on a patient who had been using these medications for over two and a half years.

Additionally, the mechanism of pneumonitis development in patients taking CDK 4/6 inhibitors, such as abemaciclib, is unknown. One hypothesis is that checkpoint inhibitors activate the immune system, leading to activated T-cells that attack normal tissues in the lungs, causing pneumonitis [14]. Further studies should be conducted to determine the specific mechanism of CDK4/6 precipitated pneumonitis.

The treatment of patients with CDK4/6 precipitated pneumonitis has not been described as any different from that of other patient populations. The mainstay of treatment is glucocorticoids, with studies showing that 70%-80% of checkpoint inhibitor pneumonitis is controlled by this therapy. More specifically, grade 1 (asymptomatic) pneumonitis in these patients should be clinically observed for progression of pneumonitis, and upon reaching grade 2 (symptomatic) and 3 (severe symptoms) pneumonitis, treatment with glucocorticoids should be initiated. Treatment duration is correlated to clinical symptom remission. An overall course of steroids is approximately 6-8 weeks but no more than 12 weeks [18]. After complete regression, the decision to continue CDK4/6 inhibitors must be made.

Conclusion

Overall, this case highlights the complexities of breast cancer therapies and the rare side effects of pneumonitis of CDK 4/6 inhibitor therapy. While the FDA has warned about this potential side effect, they still endorse that the overall benefit of CDK 4/6 inhibitors outweighs the risks when used as prescribed. More research should be conducted into how additional risk factors, such as the duration of therapy, are related to the incidence of developing this side effect. Additionally, as no known mechanism has been described, more research should be conducted on this topic. When the development of pneumonitis is caught in these cases, progression should be monitored. Intervention should be initiated when clinical symptoms and imaging show progression, with treatment lasting until clinical symptoms remission.

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