Ribociclib-Induced Pneumonitis: A Case Report

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Established Facts

- Cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors have proven efficacy against hormone receptor-positive, HER2-negative metastatic breast cancer.
- Ribociclib is known to cause adverse effects such as leukopenia, neutropenia, and QT interval prolongation requiring ECG monitoring.

Novel Insights

- CDK 4/6 inhibitors are newly approved medications and their toxicity is poorly understood.
- FDA issued a warning about possible drug-induced lung toxicity by CDK 4/6 inhibitor agents, including ribociclib.

Keywords

Ribociclib · Cyclin-dependent kinase 4/6 · Pneumonitis · Target therapy · Breast cancer

Abstract

Background: Cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors have been a significant breakthrough in the management of hormone receptor-positive, HER2-negative metastatic breast cancer based on the results of several large phase III randomized trials. The most common reported toxicity is myelosuppression due to disease such as leukopenia, neutropenia, and thrombocytopenia. Other toxicities associated with CDK 4/6 inhibitors include mucositis, fatigue, gastrointestinal side effects, hepatic toxicities, and QTc prolongation. Despite a good toxicity profile in pivotal studies, the

increased rates of use in clinical practice may show less prevalent but lethal toxicity such as lung injury. **Case Presentation:** Here, we describe a female patient with metastatic hormone receptor-positive/human epidermal growth factor 2-negative breast cancer who developed lung toxicity while on ribociclib. **Discussion:** Lung injury is a possible side effect of CDK 4/6 inhibitors and there is an increasing need to understand the management of this side effect.

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Introduction

Cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors have been proven to improve progression-free survival in women with advanced-stage hormone receptor (HR)-

Fig. 1. CT images showing subsegmental pulmonary embolism with bilateral ground-glass opacity.

positive, HER2-negative breast cancer, resulting in approvals of three different agents (palbociclib, ribociclib, abemaciclib) and, in combination with endocrine therapies, in both first-line and second-line indications [1–6]. Recently, these drugs have been shown in phase III trials to prolong overall survival (OS) in this population. The phase III MONALEESA-3 trial showed that the combination of ribociclib and fulvestrant led to an approximate 28% reduction in the risk of death compared with placebo and fulvestrant in postmenopausal patients with HR-positive, HER2-negative advanced breast cancer [7–9]. The median OS was not reached with ribociclib and was 40.0 months with placebo (hazard ratio, 0.724; 95% CI, 0.568–0.924; $p = 0.00455$). Similarly, the MONALEESA-7 trial looked at the addition of ribociclib to endocrine therapy in peri-/premenopausal women with advanced HR-positive, HER2-negative breast cancer. In updated findings, median OS was not reached for the patients on ribociclib versus 40.7 months for those on placebo (hazard ratio, 0.699; 95% CI, 0.501–0.976) [10, 11]. In the phase III MONARCH 2 trial, adding the CDK4/6 inhibitor abemaciclib to fulvestrant led to a median OS of 46.7 months

Fig. 2. Chest X-ray showing ground-glass opacity.

compared with 37.3 months for placebo/fulvestrant in patients with HR-positive, HER2-negative advanced breast cancer who progressed on prior endocrine therapy (hazard ratio, 0.757; 95% CI, 0.606–0.945; $p = 0.0137$) [12, 13].

Ribociclib is also in development for several indications in phase II trials such as liposarcoma, endometrial carcinoma, and high-grade neuroendocrine tumors [14].

Fig. 3. Dose-volume histogram for the initial tangential fields.

The most common adverse reactions were neutropenia, thrombocytopenia, mucositis, nausea, vomiting, fatigue, diarrhea, alopecia, constipation, headache, back pain, and QTc interval prolongation. The most common grade 3 or 4 adverse reactions (reported in >2%) were neutropenia, leukopenia, abnormal liver function tests, and vomiting. In the MONALEESA-2 trial, there were 2 deaths secondary to acute respiratory failure in patients receiving ribociclib plus letrozole [3].

Since the publication of the trial, there has been no case of ribociclib-induced pulmonary toxicity reported. There has been such evidence in the literature on the other CDK 4/6 inhibitors: palbociclib and abemaciclib. Three case reports on palbociclib-induced pneumonitis have been published, two of which improved after discontinuation of the drug, and one case report on abemaciclib-associated lung injury [15–17]. Recently, the Japanese ministry of health has released a warning as 4 patients developed pulmonary toxicity likely secondary to abemaciclib exposure, one of whom died [18].

In this article, we present a case of ribociclib-induced pneumonitis in a 46-year-old female with metastatic breast cancer.

Case Description

In January 2017, a 46-year-old premenopausal female presented to us with locally advanced breast cancer. The tumor biology revealed invasive ductal carcinoma grade 3: HR-positive, HER2-negative, and Ki67 of 30% (luminal B subtype). Neoadjuvant chemotherapy consisting of epirubicin in combination with cyclophosphamide (EC protocol) was initiated for two cycles with poor response, which was then switched to weekly paclitaxel for 12 weeks. Right modified radical mastectomy was performed in September 2017. Postoperatively, a residual of invasive ductal carcinoma of 6 cm in size and 3/18 lymph nodes positive were reported with extensive lymph-vascular invasion. The immuno-histochemical profiles were repeated and revealed the same the tumor biology with no evidence of receptor conversion. After the completion of adjuvant radiotherapy, adjuvant Zoladex (goserelin acetate) and tamoxifen were started in October

2017. Unfortunately, the patient presented with burning pain at the cervical and thoracic regions associated with numbness, tingling, and lower limb weakness bilaterally. In July 2019, MRI of the spine showed diffuse metastatic bony lesions with pathological fractures of T1 and T2 vertebral bodies abutting the spinal cord in keeping with cord compression. The spine surgery team was involved; however, the patient was deemed to be inoperable. Palliative radiotherapy to the spine was administered, with the initiation of Zoladex (3.6 mg s.c.), fulvestrant (500 mg i.m. on days 1 and 14, then every 28 days), and ribociclib (600 mg daily for 21 days and 1 week off). Four weeks later, the patient was admitted with grade 4 adverse reactions (mucositis, neutropenia, and thrombocytopenia). On admission, ribociclib was withheld until complete recovery of mucositis and hematopoietic lineages. However, there was no significant improvement in her neurological deficits, which required approximately 8 weeks. She was then resumed on the same regimen, with dose reduction of ribociclib to 200 mg daily. In addition, bone-targeted therapy was added. While planning discharge, the patient experienced acute chest pain and shortness of breath. The differential diagnosis at that time included pulmonary embolism, chest infection, cardiac toxicity, and pulmonary edema. Clinically, the patient was not overloaded, and chest examination was not indicative of pulmonary edema. Cardiac enzymes (including pro-brain natriuretic peptide and troponin), electrocardiogram, and echocardiogram were carried out, and all were unremarkable of cardiac cause. Clinical impression was in favor of pulmonary disease. A CT scan with contrast was performed showing subsegmental pulmonary embolism with bilateral ground-glass opacity more pronounced on the right side (Fig.1). The patient continued to be in respiratory distress and follow-up chest X-ray showed worsening of bilateral ground-glass opacity compared with previous films despite being started on heparin infusion (Fig. 2). With the involvement of the pulmonary team, bronchoscopy and bronchial alveolar lavage were performed. The fluid from the bronchoalveolar lavage was colorless, with RBC of 3 and WBC of 107 (45% neutrophils). It was negative for malignant cells, viral cytopathology, and special stains for hemosiderin-laden macrophages, fungi, and pneumocystis. Blood and sputum cultures remained sterile, and comprehensive infectious disease workup was negative. Polymerase chain reactions for atypical pneumonia and respiratory viruses were all negative as well. Radiation therapy planning was revisited with the radiation oncology team. Dose-volume histogram for the adjuvant tangential fields showed that lung V20 was 33% while opposing parallel fields for the upper dorsal spine did not affect lung volume,

Fig. 4. Parallel opposing fields for palliative irradiation of upper dorsal vertebrae.

which excluded the possibility of radiation-induced pneumonitis (Fig. 3, 4). Therefore, ribociclib was stopped along with starting methylprednisolone (1.5 mg/kg/day), with noticeable clinical improvement within 1 week. Six weeks later, the patient showed complete recovery clinically and radiologically. Therefore, the steroids were slowly tapered down. Ribociclib was permanently discontinued and the patient was discharged on Zoladex and exemestane and to continue the bone-targeted therapy.

Discussion

The FDA issued a warning on the entire class of the CDK 4/6 inhibitors used to treat advanced breast cancer due to the possibility of causing rare but severe inflammation of the lungs. Anti-cancer drugs have been associated with pulmonary toxicity, ranging from asymptomatic radiological changes to respiratory failure [19]. It is considered a common side effect, as it presents in 10–20% of the patients who have received any type of anti-cancer therapy [20]. There is far less data linking CDK 4/6 inhibitors to pulmonary toxicity. However, it is vital to appreciate the potentially fatal drug-associated lung injury that may be linked to them, as demonstrated in articles on pablociclib- and abemaciclib-induced lung injury. As of now, it has not been reported that ribociclib causes lung injury, but with the literature supporting that other CDK 4/6 inhibitors induced lung injury, ribociclib-induced pneumonitis in our patient is a possibility. Of note, our patient received radiotherapy to the same side as pneumonitis 1 year prior to the onset. Although it is deemed less likely to be the cause as mentioned in the case description, radiotherapy remains a well-known risk for lung toxicity [21]. As concluded in a case series by Jazieh et al. [17], CDK 4/6 inhibitors are highly likely to be the causative agent of pulmonary toxicity in sev-

eral patients who have received the therapy. Due to the novelty and rarity of these medications, their side effects are still poorly understood. However, as with the treatment of drug-induced pneumonitis, the common recommendation is discontinuation of the causative agent and to initiate steroids [19]. It is important for clinicians to remember that fatal interstitial pneumonitis may happen in patients who are treated with ribociclib, as early diagnosis may be vital.

Statement of Ethics

The patient's written consent was obtained for the writing and publication of her case, including the publication of images.

Disclosure Statement

Dr. Taher Al-Tweigeri has received speaking honoraria from Roche, Novartis, and Lilly. He also received travel support from Roche and Novartis, and has served on advisory committees for Roche, Lilly, and Novartis. Other authors declare no potential conflicts of interest.

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Author Contributions

Concept: Ghada Algwaiz and Ahmed Ali Badran. Manuscript writing and final approval: Ghada Algwaiz, Ahmed Ali Badran, Mahmoud A. Elshenawy, and Taher AL-Tweigeri.

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