CLINICAL VIGNETTE

CDK4/6 Inhibitor-Induced Pneumonitis: A Case Report and Review of the Literature

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Case Presentation

A 56-year old woman with metastatic breast cancer was hospitalized for acute hypoxemic respiratory failure. More than 20 years ago she was diagnosed left breast cancer treated with lumpectomy. One year prior to presentation she was diagnosed with ER/PR-positive and HER2-negative breast cancer metastatic to bone and lung. She initially sought alternative therapies but developed progressive bone and pleural metastases. Two months prior to presentation she accepted standard therapy and was started on abemaciclib, fulvestrant, and denosumab. She had a decline in tumor markers but developed dyspnea, weight loss, generalized weakness, and diarrhea. Staging PET CT showed a reduction in the size of the lung and bone metastases, with a new right lower lobe ground glass infiltrate.

She presented to the emergency department with hypoxemic and hypercapnic respiratory failure. CT chest showed worsening bilateral lower lobe airspace and ground glass infiltrates [Figure 1]. Laboratory data was notable for normal WBC, negative procalcitonin level, and elevated inflammatory markers (ESR 100 mm/hr and CRP 14.7 mg/dL). She was treated with empiric antibiotics for pneumonia but failed non-invasive ventilatory support and required endotracheal intubation. Bronchoscopy with bronchioloalveolar lavage was performed; cell count was 80% lymphocyte predominant and cultures were negative. She was empirically started on dexamethasone for pneumonitis and was subsequently extubated. She was discharged home on supplemental oxygen and steroids, abemaciclib was stopped.

Steroids were tapered off over 6 weeks and oxygenation normalized. She was monitored off cancer therapy until PET CT showed progression of disease four months later; this imaging also demonstrated resolution of the bibasilar airspace and ground glass opacities. She was treated with ribociclib for 3 months without respiratory side effects, but with mixed tumor response. She was subsequently switched to everolimus and exemestane, and is currently doing well with stable metastatic disease.

Discussion

Cyclin-dependent kinase 4/6 inhibitors are a novel cancer therapy targeting cell cycle transition and cell division. Cyclin dependent kinases 4 and 6 regulate cells' transition from G1 to S phase by inactivating the tumor suppressor retinoblastoma (Rb) protein. Estrogen receptor (ER)-positive tumors maintain functional Rb protein and are therefore potentially susceptible to CDK4/6 inhibition.[1] The orally available small molecule CDK4/6 inhibitors are palbociclib, ribociclib, and abemaciclib. The FDA granted palbociclib Breakthrough Therapy designation in 2013, then accelerated approval in 2015[2] after the PALOMA-1 trial demonstrated the combination of palbociclib plus letrozole significantly increased progression-free survival in ER-positive/HER2-negative metastatic breast cancer, as compared to letrozole alone.[3] Findings were confirmed with the phase 3 PALOMA-2 and PALOMA-3 trials.[4,5] Ribociclib was approved by the FDA in 2017 based on the MONALEESA-2 trial comparing ribociclib plus letrozole in metastatic ER-positive/HER2-negative metastatic breast cancer. Abemaciclib was approved by the FDA in 2017 after receiving breakthrough designation in 2015. Abemaciclib plus endocrine therapy led to improvement in progression free survival in metastatic ER-positive/HER2-negative breast cancer in the MONARCH 1 phase 2 trial,[6] followed by the large phase 3 trials, MONARCH 2 and MONARCH 3.[7,8]

Palbociclib, ribociclib, and abemaciclib are approved for the treatment of ER-positive metastatic breast cancer in combination with hormonal therapy. Common side effects include neutropenia (although rarely febrile neutropenia), leukopenia, infections, nausea, diarrhea, transaminase elevation, and fatigue. QTc prolongation from ribociclib and thromboembolic events from palbociclib are also described.[1]

CDK4/6 inhibitors were not initially linked with pulmonary toxicity, but isolated cases from the clinical trials plus emerging case reports in the post marketing arena have raised concern for a potential class effect.[9] There was no report of pneumonitis related to palbociclib in the PALOMA trials.[4] In the MONALEESA-2 trial of ribociclib two participants died of acute respiratory failure. In the second interim analysis of the MONALEESA-3 trial there were 6 cases [1.2%] of interstitial lung disease (1 case [0.2%] grade 3 or 4) in the ribociclib arm and 2 cases (none grade 3 or 4) in the placebo arm.[10] In the interim analysis of the MONARCH 3 trial of abemaciclib, one patient died of pneumonitis.[11]

A case of suspected acute respiratory failure associated with palbociclib was first reported in 2017 by Ahsan, et al. This patient expired after transitioning to palliative care.[12] Ofer, et al, subsequently described a case of diffuse parenchymal lung

injury (organizing diffuse alveolar damage on transbronchial biopsy) that developed 3 months after initiation of palbociclib, and resulted in death despite use of corticosteroids.[13] Jazieh et al, reported a case of palbociclib-related pneumonitis that developed a year after initiating therapy and responded to corticosteroids and discontinuation of palbociclib.[14]

Wider knowledge of the risk of pneumonitis related to abemaciclib occurred when in May 2019 the Japanese health ministry announced that 14 patients had pulmonary side effects and 3 patients died after treatment with abemaciclib, after 2000 patients had been treated with abemaciclib in Japan.[15] Eli Lilly, the manufacturer of abemaciclib, initially added a warning regarding the risk of interstitial lung disease only in their Japanese market, citing a general greater frequency of pneumonitis in the East Asian population.[16] However the FDA later announced on September 13, 2019, that there were reports of serious cases of pneumonitis and interstitial lung disease, including fatalities, in patients treated with palbociclib, ribociclib, and abemaciclib – in ongoing clinical trials and post marketing safety databases.[9]

We present a patient with metastatic ER-positive breast cancer on abemeciclib for 2 months who developed acute respiratory failure with bilateral pulmonary infiltrates. Although lung biopsy was not performed, infection was excluded with bronchoalveolar lavage, and the patient clinically improved after withholding abemaciclib and receiving corticosteroids, compatible with abemeciclib-induced pneumonitis. The mechanism of injury in CDK4/6-inhibitor induced pneumonitis is unknown, but may be related to the recruitment of inflammatory cells to the lung, as shown with palbociclib administration in a mouse model of bleomycin-induced pulmonary fibrosis.[17] Human lung biopsies where available have shown nonspecific diffuse alveolar damage, and our patient demonstrated a lymphocytic predominant inflammation on bronchoalveolar lavage. The exact incidence of pneumonitis related to CDK4/6 inhibitors is also not known, but may approximate 0.2% as seen in the larger clinical trials.[10] The timing of pneumonitis after initiation of therapy has been described from months to a year.[12-14] Whether the development of pneumonitis is associated with tumor response is an interesting and unanswered question. An individual's risk for pneumonitis may not cross to other drugs in the class. Our patient tolerated ribociclib after experiencing pneumonitis from abemaciclib, and the patient described by Jazieh et al, developed pneumonitis from abemaciclib after previously tolerating palbociclib.[14]

This case demonstrates the value of post-marketing surveillance for rare drug side effects that become apparent only with widespread use. Drug-induced pneumonitis should be considered when encountering patients on CDK4/6 inhibitors with acute respiratory failure and pulmonary infiltrates.

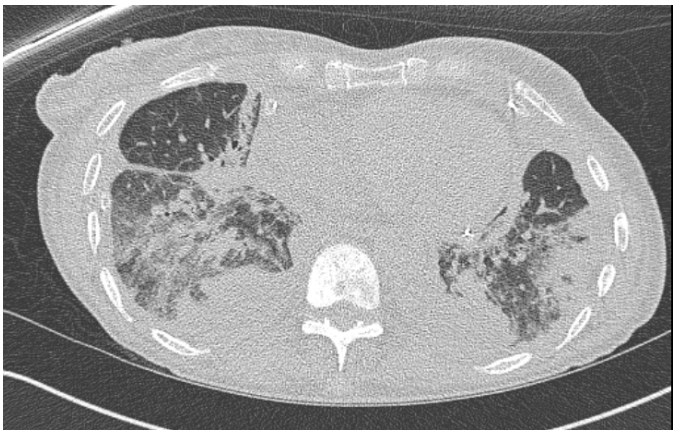

Figure 1.

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