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Interstitial Lung Disease in Abemaciclib-treated Patients during SARS-CoV-2 Pandemic: A Case Series

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Abstract

Abemaciclib is a cyclin-dependent 4/6 inhibitor approved by FDA in 2017 and by EMA in 2018 for treatment of hormone receptors positive, HER2 negative metastatic breast cancer in association with endocrine therapy. In 2019 FDA warned for a rare but severe lung inflammation possibly related to CDK 4/6 inhibitors. At the end of 2019 the world comes to know to a new corona virus causing potential fatal lung injury. Here we report three different cases of interstitial lung disease in patients treated with Abemaciclib during SARS-CoV-2 pandemic at Modena Cancer Center.

Keywords: COVID-19; Metastatic breast cancer; Abemaciclib; Interstitial lung disease

Introduction

The Cyclin-Dependent Kinase 4/6 (CDK 4/6) inhibition is the new standard of care in patients with Hormone Receptors positive (HR+), HER2 negative (HER2-) Metastatic Breast Cancer (MBC) [1-6]. In September 2019, FDA warned for a rare but severe lung inflammation that could be related to CDK 4/6 inhibitors (palbociclib, ribociclib and abemaciclib) in patients with MBC. However unspecific, suspicious symptoms can include cough, dyspnea at rest or for low-grade activity, hypoxia and interstitial infiltrates in radiologic exams.

From December 2019 a new coronavirus causing potential fatal lung injury was isolated and named SARS-CoV-2. The outbreak was identified in Wuhan, China, and since the beginning of 2020 the novel virus spread to the whole world as a pandemic disease. Common symptoms of Coronavirus Disease-19 (COVID-19) are fever, dry-cough, fatigue, dyspnea and it can lead to Acute Distress Respiratory Syndrome (ARDS) and Interstitial Pneumonitis (ILD) [7-9].

The clinical manifestations as well as case fatality rates have been higher in the elderly, those with comorbidities such as cardio-pulmonary disease or cancer. In a Chinese case series of 138 in-patients, median age was 56 years old, 46.4% of them had preexisting medical conditions such as hypertension (31.2%), diabetes (10.1%) or malignancy (7.2%) [10]. Similar data were found in a greater Italian study by Grasselli et al., that described 1591 patients admitted to Intensive Care Unit (ICU), with at least one comorbidity in 68% of the cases, and in 8% of them it was cancer [11].

Since people with chronic diseases are prone to severe SARS-CoV-2 infection, from the outbreak in Italy at the end of February, the primary concern at the Modena Cancer Center was to protect patients on active oncological treatment. With control measures adopted at our institution (i.e. term scanner at the entrance, face masks for patients and professionals, hand sanitizer), in addition to lockdown arranged by Italian Government, only 9 patients (0.71%), on active anticancer treatment, were diagnosed with SARS-CoV-2 related disease [12].

Interstitial lung disease (ILD) during Abemaciclib treatment

The gold standard for SARS-CoV-2 etiological diagnosis is RT-PCR on respiratory tract specimens. People with suspected SARS-CoV-2 infection undergo nasopharyngeal swabs, which is the first test introduced in clinical practice for diagnosis, but it has potential pre-analytical and analytical vulnerabilities (i.e. inadequate collection, handling, storage, contamination, interfering substances). Recently serological assays have become available, but the time needed to develop immune response from infection may represent a limit of these tests [13,14]. Besides SARS-CoV-2 and idiopathic pneumonitis, other potential causes of ILD in MBC patients to keep in mind are: Viral

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infections, pneumocystosis, radiation-induced pulmonarytoxicity, lymphangitic carcinomatosis, cardiogenic pulmonary edema, lung involvement of rheumatological diseases and drug-induced pneumonitis (i.e. amiodarone, chemotherapies, immunotherapies and targeted therapies) [15-17]. An accurate diagnosis is crucial for the right management of MBC people with ILD unrelated to SARS-CoV-2, especially when on Abemaciclib or other CDK4/6 inhibitors.

Here, we discuss three suspected cases of ILD diagnosed in patients in treatment with Abemaciclib for MBC during COVID-19 pandemic.

Case Series

Case 1

AV is a 75 years old female diagnosed with lung relapse from hormonal receptor positive - HER2 negative BC, while on adjuvant letrozole. First-line endocrine treatment with Abemaciclib 300 mg daily plus Fulvestrant 500 mg monthly was started in October 2019. No relevant adverse events were recorded. On March 9th, 2020 routine restaging CT scan showed bilateral infiltrates of the lung (Figure 1); mild dry cough was the only associated symptom. SARS-CoV-2 swab along with standard bacterial/viral DNA analysis from gargle specimen were performed. The patient was quarantined until RT-PCR negative result. No pathogens in respiratory specimens or relevant blood alterations were identified. Abemaciclib was suspended with resolution of the respiratory symptoms in few weeks without new episodes at the date of the last follow up (July 8th, 2020).

Case 2

QM is a Chinese 59 years old patient with bone metastases from luminal A-like BC. She was on Abemaciclib 300 mg daily plus Fulvestrant 500 mg monthly since August 9th, 2019. Due to anamnestic adult onset still's disease, she is on continuative corticosteroids. On February 21st, 2020, a restaging CT scan described interstitial infiltrates in the pulmonary lower left lobe (Figure 2). SARS-CoV-2 swab was negative and no pathogens in respiratory specimens, or relevant blood alterations were identified. Due to the absence of symptoms and the monolateral infiltrates, Abemaciclib was not suspended. No worsening of the radiologic findings nor appearance of clinical symptoms are so far referred.

Case 3

MCP was a 62 years old women with bone, liver and lung metastases from Luminal B-like BC. Abemaciclib 300 mg daily plus Fulvestrant 500 mg monthly was started on February 14th, 2020. On March 27th she was admitted to emergency room due to cough, dyspnea and fever and was hospitalized as high suspicion of COVID-19. Urgent chest-X-ray showed bilateral interstitial infiltrates. Broad spectrum antibiotics coverage was started. SARS-CoV-2 swabs were performed every two days and resulted negative. Likewise, serology for bacterial, viral and fungal pathogens and repeated blood cultures resulted negative. RT-PCR for bacteria and viruses (SARS-CoV-2 included) on respiratory specimens did not detect any specific pathogen. Clinical conditions progressively worsened and urgent chest CT scan was performed, depicting diffuse bilateral pulmonary infiltrates (Figure 3). PCR remained stable (15 mg/dl) during hospitalization, PCT was repeatedly negative; LDH always remained above upper normal limit. Due to worsening of respiratory parameters despite high flow oxygen therapy and high dose corticosteroids, patient was finally transferred to Intensive Care Unit, but she passed away at the beginning of April.

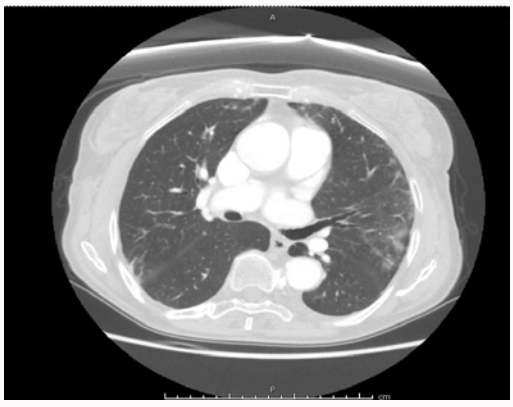

Figure 1: Case 1: Bilateral lung infiltrates found on restaging CT scan in patient with mild symptoms.

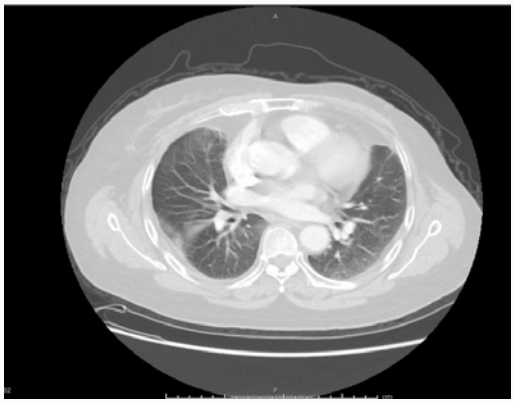

Figure 2: Case 2: Interstitial infiltrates in the pulmonary lower left lobe found on routine CT scan in asymptomatic patient.

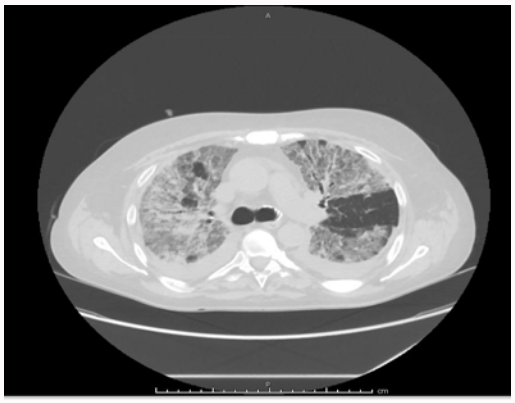

Figure 3: Case 3: Diffuse bilateral pulmonary infiltrates found on urgent chest CT scan in patients with severe respiratory symptoms.

Discussion

In the novel setting of COVID-19 pandemic, differential diagnosis in patients with respiratory symptoms undergoing oncological treatment, is crucial but challenging. ILD is described as a potential adverse event for many oncological drugs, for example immune-checkpoint inhibitors, antibody drugs conjugated, mTor inhibitors and others [18-20]. CDK 4/6 inhibitors are among them. Unlike other oncological drugs, the underlying mechanism of CDK 4/6 related pulmonary toxicity is still unclear, but probably multi factorial.

Abemaciclib is a CDK 4/6 inhibitor approved by FDA in 2017 and by EMA in 2018 in association with hormonal therapy for the treatment of HR+/HER2- MBC. In phase III trials the most common adverse events with all CDK 4/6 inhibitors available for clinical practice were diarrhea, nausea, neutropenia, thrombocytopenia and fatigue [3,4]. Recently, FDA warned for a rare but severe lung inflammation that could be related to CDK 4/6 inhibitors.

Here we have reported three cases differently managed at the Modena Cancer Center in the past two months.

Despite potential false negative results at the COVID-19 test on respiratory tract specimens as above discussed, our patients were likely affected by Abemaciclib-induced pneumonitis. In this experience, suspected Abemaciclib-related interstitial pneumonia can manifest with different degrees of gravity, starting from accidental radiological finding to fatal forms of ARDS, independently from the length of therapy. None of the patients was smoker or ex-smoker.

Conclusion

CDK 4/6 inhibitors have been shown to improve progression free survival in MBC patients compared to endocrine therapy alone. The overall benefit of these drugs remains greater than the risks, but development of respiratory symptoms and/or radiological findings compatible with diffuse interstitial infiltrates must be considered with caution, since the potential infection with SARS-CoV-2 should be excluded.

A limitation of our case series is that it refers to only three patients in a short period of time; prospective evaluation of specific risk factors for lung inflammation should be pursued, in a wide range of patients, to identify patients who are more likely to develop this potentially lethal adverse event.

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