

Late-onset Ribociclib related Severe Dermatological side effects: Erythema Multiforme/ Steven Johnson's Syndrome (SJS) like reaction

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Abstract

CDK inhibitors have demonstrated a higher efficacy compared to hormone therapy alone for advanced Hormone receptor-positive (HR+)/HER2 negative breast cancer and also have a manageable toxicity profile. Specific severe dermatological reaction to CDK inhibitors has been rarely reported. We are reporting a case of severe skin reaction more than six months after the initiation of Ribociclib requiring treatment cessation of Ribociclib.

We are reporting a case of a 46-year-old lady diagnosed with locally advanced hormone receptor-positive HER2 negative inflammatory breast cancer in November 2016 associated with pleural based masses and prominent retroperitoneal lymph nodes. She was commenced on Tamoxifen but developed a solitary brain lesion in cerebellum. She underwent stereotactic radiotherapy and was commenced on Ribociclib and Anastrozole. On the second week of the 8th cycle of Ribociclib, she developed a rash on her breasts and forearms. The rash spread to her forehead, face, arms, chest, back and lower limbs. There was no definite mucosal involvement and had mild crusting on her lips but no ulceration. She was also systemically well and did not have any active mucosal lesions at the time of review. This was thought to be consistent with erythema multiforme/SJS like reaction as per dermatology review. It was determined to be related to Ribociclib due to the temporal association. She had resolving skin changes with residual hyperpigmentation after eight weeks of cessation of Ribociclib without systemic steroid therapy.

This case emphasizes the need for ongoing vigilance even beyond first 6 months of commencing Ribociclib. It also highlights that some of the patients with severe skin reactions can be managed with only topical steroid treatment.

Keywords: CDK inhibitors • Ribociclib • Metastatic breast cancer • Erythema multiforme • Steven Johnson's Syndrome • Severe dermatological side effect • Rash

Introduction

CDK inhibitors are one of the new targeted therapies that have been approved by the FDA in the treatment of advanced Hormone positive HER2 negative metastatic breast cancer. Second-generation agents are now available and have demonstrated a higher efficacy compared to hormone therapy alone for advanced Hormone receptor-positive (HR+)/HER2 negative breast cancer and also have a manageable toxicity profile. These agents include Palbociclib, Ribociclib, and Abemaciclib [1].

Multiple phase 3 clinical trials [1-6] has consistently demonstrated improved progression-free survival with the use of CDK inhibitors alone or in combination with aromatase inhibitors or fulvestrant. Cyclin-dependent kinase 4/6 inhibitors are generally well tolerated [2].

Other trials are also currently investigating the use of CDK inhibitors in HR-positive and HER2 positive breast cancer (ClinicalTrials.gov identifier: NCT03304080; PATINA trial, ClinicalTrials.gov identifier: NCT02947685) including in neoadjuvant setting (NA-PHER2, ClinicalTrials.gov identifier: NCT02907918).

Ribociclib (LEE011) is an orally bioavailable, selective inhibitor of CDK4/6. It blocks the phosphorylation of retinoblastoma protein, thereby preventing cell-cycle progression and inducing G1 phase arrest [3]. Most of the significant adverse effects reported in clinical trials with CDK4/6 inhibitors include neutropenia, fatigue and diarrhoea. Dermatological side effects are relatively common, but the majority are mild. Specific severe dermatological reaction to CDK inhibitors have been rarely reported except for a case report on SJS like reaction with Palbociclib [4].

We are reporting a case of severe skin reaction more than six months after the initiation of Ribociclib requiring treatment cessation of Ribociclib.

Case Report

A 46-year-old lady who was initially diagnosed with locally advanced hormone receptor-positive HER2 negative inflammatory breast cancer in November 2016. She had left axillary lymph node involvement with pleural based masses and prominent retroperitoneal lymph nodes. Nodal and breast biopsies confirmed Oestrogen and Progesterone receptor-positive breast carcinoma. She received chemotherapy followed by radiotherapy to the breast and nodal region.

In regards to her medical background, besides obesity, DVT, and hypothyroidism, there was no other significant medical history. She had history of allergy to penicillin that was associated with periorbital oedema and oral ulcers. She also had history of developing mild rashes after use of aspirin, ibuprofen and cephalexin along with localised reaction to adhesive tapes. Other regular medications included iron supplements, multivitamin, apixaban, levothyroxine, and esomeprazole.

She had a good response to first line chemotherapy, and was commenced on Tamoxifen but developed a solitary brain lesion in cerebellum in November 2017. The solitary brain lesion was treated with Stereotactic radiotherapy in December 2017 and then on May 2018 for another isolated new intracranial lesion.

She was then commenced on Ribociclib and anastrozole in June 2018. She developed a macular rash on her abdomen after two weeks of starting Ribociclib which resolved spontaneously. In November 2018, she developed intermittent episodes of palpitations related to supraventricular tachycardia. These episodes resolved spontaneously within three weeks of onset. There were no other abnormalities, including normal QTc interval and was continued on the same treatment. In early January 2019, she developed a chest infection which was treated with a course of doxycycline without any initial allergic reactions.

However, on second week of the 8th cycle of Ribociclib, she developed a rash on her breasts and forearms. The rash spread to her forehead, face, arms, chest, back and lower limbs progressing within a week. There was no definite mucosal involvement, although she reported a self-limiting oral ulcer that had resolved prior to our review. She had mild crusting on her lips but no ulceration. Initially, she used betamethasone cream to peripheries and cortisone cream to her face without any response. Oral loratadine was also introduced without much effect. She had stopped Ribociclib almost a week before being reviewed in the clinic. Hence, the pictures taken on the day of presentation in clinic is a few days after cessation of Ribociclib (Figure 1 to 4). As she reported the rashes to be improving after cessation of Ribociclib, decision was made to hold off on initiating systemic steroid therapy. She was also systemically well and did not have any active mucosal lesions at the time of review.



Figure 1. Rashes on upper back.



Figure 2. Rashes on upper chest.



Figure 3. Rashes on right arm.



Figure 4. Rashes on face.

The papular rashes were confluent and associated with target lesions and desquamation in some areas. After formal dermatology opinion, this was thought to be consistent with erythema multiforme/SJS like reaction. It was determined to be related to Ribociclib due to the temporal association. The onset of rashes was more than four weeks after the completion of treatment with doxycycline and started to resolve after discontinuation of Ribociclib.

On further follow-up, pictures 5 and 6 show resolving skin changes with residual hyperpigmentation after eight weeks of cessation

of Ribociclib (Figure 5). Other differentials that were considered included viral infections like herpes and Epstein Barr virus (EBV) infection. But there were no clinical features suggestive of herpes simplex or EBV infection. She also didn't have any other new medication. Hence, these were considered unlikely.



Figure 5. Resolving rashes with residual hyperpigmentation.

We did not find any significant interactions between her regular medications that could have explained this. Most of the interactions were related to either decreased absorption or altered serum levels. These interactions were noted between doxycycline, esomeprazole, iron tablets, apixaban and levothyroxine.

She was commenced on Abemaciclib once the rashes resolved which she continues to tolerate. She had an episode of Clostridium difficile colitis during which it was withheld. Her most recent CT restaging scan from March 2020 and MRI brain from April 2020 shows ongoing response including stable intracranial findings.

Discussion

Dermatological side effects of CDK4/6 inhibitors

Erythema Multiforme (EM) or Erythema polymorphe is a hypersensitivity reaction more commonly observed in younger population. It can be in response to medications, infections or illness. Common drugs include anticonvulsants, sulfonamides, non-steroidal anti-inflammatory medications and antibiotics [5,6]. Tetracyclines are considered to be moderately associated with it but most cases present within a few days of exposure [7].

Erythema Multiforme (EM) can have a wide spectrum of severity from mild forms to erythema Multiforme majus, which is a severe form of EM characterized by mucosal involvement along with systemic symptoms like fever.

Cyclin-dependent kinases 4 and 6 (CDK4/6) in conjunction with their protein regulator, cyclin D1 (encoded by CCND1), a direct transcriptional target of oestrogen-receptor signaling, regulate cell-cycle progression [8]. CDK4/6 over expression and CCND1 amplification are frequently encountered in HR-positive breast cancers and are critical mediators of endocrine resistance [9,10]. The Cancer Genome Atlas found that Hormone receptor-positive, HER2 negative breast tumors have a cyclin D1 amplification in 29-58% of the cases and a Cyclin-Dependent Kinase (CDK) 4 amplification in 14-25% of cases [11-14].

The MONALEESA-2 study enrolled 668 treatment-naïve postmenopausal women with HR-positive, HER2-negative advanced breast cancer. The patients who were receiving first-line treatment with Ribociclib plus letrozole had a significantly longer duration of progression-free survival than did those receiving placebo plus letrozole (median PFS of 25.3 months versus 16.0 months; HR 0.56, 95% CI 0.43-0.72) [15,16]. After 18 months, the progression-free survival rate was 63.0% (95% CI, 54.6 to 70.3) and 42.2% (95% CI, 34.8 to 49.5) respectively with a 44% lower relative risk of progression in Ribociclib arm [14].

Out of 334 patients in Ribociclib arm, 57 (17.1%) were reported to have a rash of any grade, and only two patients had grade 3 rash without any grade 4 cases. 14% of patients had grade 1 or 2 pruritus with one patient reported to have grade 3 pruritus.

In case of other CDK4/6 inhibitors like Palbociclib in PALOMA3 trial, Grade 3 rash (severe reaction, requiring hospitalisation and causing limitation of activities) occurred in 1% of the participants receiving Palbociclib plus fulvestrant, but grade 1 to 2 rash occurred in 14% of participants. No grade 4 or higher rashes (life-threatening reaction requiring urgent intervention) were reported [16].

Steven Johnson Syndrome like reaction has been reported with Palbociclib [4]. However, other than this case, Ribociclib has not been reported to be associated with Erythema multiforme, SJS/TEN like reactions. With Palbociclib 17 to 18% skin rash was reported compared to 17 to 23% with Ribociclib. Abemaciclib has only been so far reported to cause alopecia [17-20]. Other common Ribociclib related adverse events includes transaminitis and QTc prolongation. Abemaciclib is associated with more fatigue and gastrointestinal-related toxicity compared with Palbociclib [14,19].

Of note, there have been reports of increased dermatological toxicity with concurrent radiation therapy. In one case report, the reported patient with metastatic breast cancer received radiation treatment to a metastatic supraclavicular lymph node to planned 60 Gy in 30 fractions while on Palbociclib. The patient developed early radiation toxicities, including esophagitis and dermatitis that progressed to severe skin breakdown in the radiation field, resulting in the need for hospitalisation [20].

There has been no head to head comparison between different CDK4/6 inhibitors, but overall efficacy has been considered to be comparable. Hence, side effect profile of each CDK4/6 inhibitor will be an important factor to be considered to select a specific CDK4/6 inhibitor in addition to the pharmaceutical accessibility in postmenopausal women with metastatic HR-positive and Her2 Negative breast cancer.

It is also important to consider drug interactions as it could alter pharmacological safety profile and efficacy. The interaction of note in this case was between Ribociclib and apixaban. Ribociclib is a moderate CYP3A4 inhibitor which can potentially increase the serum levels of apixaban. Although this didn't have any relevant clinical implication in this case, it should be considered by all clinicians while making any alterations in drug regimen. The other potential explanation for the delayed hypersensitivity would include immunomodulatory effect of tetracyclines although previous animal models have indicated inhibitory effect on the cell mediated immunity [11,12]. Hence, we need more understanding and evidence about drug interactions with novel cancer treatments.

Conclusion

This case emphasises the need for ongoing vigilance even beyond first 6 months of commencing Ribociclib. It also highlights that some of the patients with severe skin reactions can be managed with only topical treatment which can reduce the risk of systemic steroid exposure in this population who are already at high risk of osteoporosis and other steroid related side effects.

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