Ribociclib-Induced Delayed Dermatological Reaction: Case Report of a Rare Adverse Effect and Review of Literature

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Abstract

Ribociclib is a selective cyclin-dependent kinase (CDK) 4/6 inhibitor approved in combination with endocrine-based therapy for the treatment of hormone receptor-positive (HR +)/human epidermal growth factor receptor 2-negative (HER2 −) advanced or metastatic breast cancer. It can significantly prolong the progression-free survival and improve the objective response rate compared with hormone therapy alone. However, the combined regimen results in a higher risk of adverse events, one of them being dermatological reactions. We present a case of late severe skin toxicity in a patient who had received ribociclib for 5 months. The toxicity led to severe pruritus and maculopapular and patchy rash on upper and lower extremities, which completely resolved 1 month after cessation of the drug. We conclude that ribociclib-induced skin toxicity is a noteworthy side effect that can lead to permanent cessation of this drug and is reversible. There are clinical decision dilemmas related to continuation, withholding, or switching CDK4/6 inhibitors, and benefits should be weighed against toxicities and costs.

Keywords

- metastatic breast cancer
- ribociclib
- skin toxicity
- CDK4/6 inhibitors

Introduction

Cyclin-dependent kinase (CDK) 4/6 inhibitors have demonstrated higher efficacy compared with hormone therapy alone in hormone receptor–positive metastatic breast cancer. These agents include palbociclib, ribociclib, and abemaciclib. Although these regimens are more efficacious and generally well tolerated,[1] they have a higher risk of side effects, to the extent of approximately two times that of hormonal therapy alone. However, these agents have an acceptable toxicity profile, which can be handled with symptomatic treatment or dose adjustment. CDK4/6 inhibitors combined with endocrine therapy result in higher rates of neutropenia, leukopenia, thrombocytopenia, anemia, fatigue, diarrhea, febrile neutropenia, nausea, and increased liver enzymes.[2] The severity of side effects with CDK4/6 inhibitors is, however, less as compared with chemotherapy. The toxicity spectrum of palbociclib and ribociclib is similar, neutropenia being the more frequent adverse event, while abemaciclib causes less neutropenia and more gastrointestinal symptoms (nausea, vomiting, and diarrhea), reduction in appetite, and fatigue.[3]

As shown in several different studies, oncologic patients are at a higher risk of developing severe cutaneous adverse reactions.[4–6] However, dermatological reactions to CDK4/6 inhibitors have rarely been reported, most often with ribociclib. Studies have shown that the commonest side effects are mild, with grade 3 rashes occurring in 0.9% of patients.[7] Early detection of skin lesions is crucial to permit the

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discontinuation of ribociclib given the predictable and unacceptable risk level.[8] Hence, skin toxicity raises an important concern as it affects quality of life and could lead to termination of a particular therapy.

We report a case of severe skin reaction that occurred 5 months after the initiation of ribociclib, mandating cessation of this drug for complete resolution.

Case Report

A 40-year-old premenopausal female patient presented to our institution in 2015 with locally advanced breast cancer with pathological evaluation suggestive of invasive ductal carcinoma, grade III, estrogen receptor positive (Allred score 8/8), progesterone receptor positive (Allred score 6/8), and HER2 negative. The patient underwent a right-modified radical mastectomy, following which she received four cycles of doxorubicin and cyclophosphamide followed by 12 weekly cycles of paclitaxel. Locoregional radiotherapy was concluded in June 2016 and the patient was started on tamoxifen thereafter. After a disease-free interval of 2 years and 9 months, the patient experienced disease relapse with multiple bone metastases. She received palliative radiotherapy to the right seventh rib (8 Gy/single fraction) in March 2019 and was started on letrozole daily and luteinizing hormone-releasing hormone (LHRH) agonist once every 3 months along with zoledronic acid once per month.

Following this treatment, the patient developed letrozole-induced tendon rupture, resulting in discontinuation of this drug. Thereafter, the patient was given fulvestrant injection 500 mg once every 4 weeks and zoledronic acid was continued. Clinical control was seen for ~18 months, following which the disease progressed. The patient was then started on CDK4/6 selective inhibitor ribociclib with exemestane and zoledronic acid. She was not receiving any other medication. She had completed five cycles of ribociclib when she started noticing skin changes on both upper and lower limbs. She developed an ashy, flat macular-papular rash that appeared on the upper and lower extremities together sparing areas like the face and trunk as shown in ►**Fig. 1**. It was associated with severe pruritis, but no other associated complaints like fever, pain, ulceration, or bleeding from the skin lesions. On physical examination, multiple, well-defined, erythematous, scaly plaques and patches were present symmetrically on the lateral aspect of both upper limbs. Diffuse scaling was seen on the extensor aspects of both lower limbs with surrounding skin showing diffuse hyperpigmentation and few excoriations.

On blood investigations, the patient had a low white blood cell count of 1.97×10^9/L and low absolute neutrophil count of 0.5×10^9/L. On the basis of clinicohematological picture of ribociclib-induced skin reaction and patient distress, administration of ribociclib was ceased. However, exemestane was continued. The sixth cycle was postponed and the patient was advised to take parenteral iron and vitamin B12 supplementation.

The patient was reviewed after 1 week for follow-up with complete blood count (CBC). On examination, the skin reactions had distinctly reduced on both upper and lower limbs as shown in ►**Fig. 2A**, **B** and there was an improvement in the blood counts, thus confirming the adverse reaction to be ribociclib induced. This led to a change in treatment to palbociclib instead of ribociclib along with exemestane and zoledronic acid. On follow-up after 1 month, skin reactions had resolved completely as shown in ►**Fig. 2C**, **D** and blood investigations were normal. Hence, the patient was continued on palbociclib-based treatment.

Discussion

We present here a case of severe skin toxicity secondary to the use of ribociclib, which started relatively late, in the fifth cycle of treatment, required discontinuation of this drug and reversed completely after stopping it without the need for any specific medication. The patient also had neutropenia at the time of skin toxicity, which also reversed. The patient did not develop any skin toxicity after changing the CDK4/6 inhibitor to palbociclib until the time of this report, by when she had completed three cycles of this treatment.

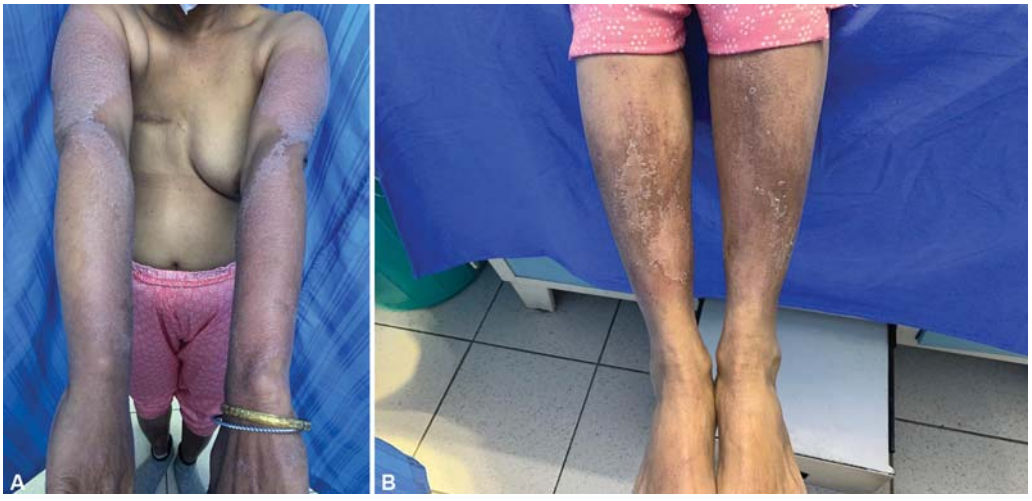

Fig. 1 Appearance of ashy, flat macular rash sparing areas like the face and trunk after the fifth cycle of ribociclib. **(A)** Upper extremities. **(B)** Lower extremities.

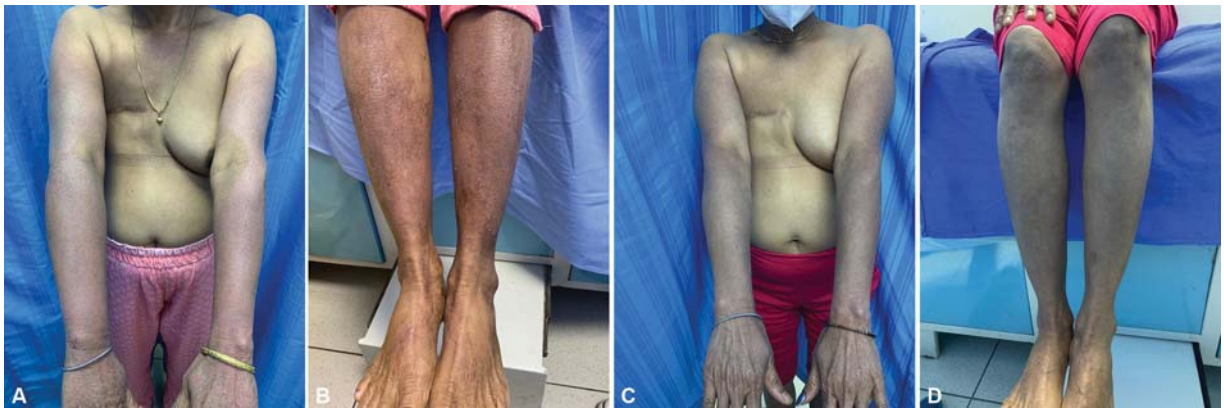

Fig. 2 Distinct reduction in skin toxicity after cessation of ribociclib. **(A)** Upper extremities after 1 week. **(B)** Lower extremities after 1 week. **(C)** Upper extremities after 1 month. **(D)** Lower extremities after 1 month.

Our report is noteworthy for several reasons. First, clinicians should be cognizant of the possibility of ribociclib-induced skin toxicity of a severity that may require its discontinuation. The most common dermatological toxicities associated with CDK4/6 inhibitors are mild alopecia, stomatitis, or skin rash.[9] In the PALOMA-2 trial, 17.8% patients developed rash of any grade with the addition of palbociclib to letrozole.[10] The most frequently reported cutaneous reaction has been alopecia, which is usually seen between 2 and 3 months after treatment initiation. Although it has been suggested that the incidence of alopecia may be higher with the use of palbociclib compared with other CDK4/6 inhibitors, other reports indicate that the incidence may be similar.[11]

Other common side effects are rash and pruritus, usually recorded in the first month of treatment. However, severe degrees of skin toxicity, including leukocytoclastic vasculitis, Steven–Johnson syndrome, and toxic epidermal necrolysis, have been reported rarely.[8,12,13] Bullous eruptions are one of the few skin toxicities that should require early discontinuation of therapy to prevent progression to severe and life-threatening toxicity.[14] In a recent review of CDK4/6 inhibitor–induced skin toxicities, 41 articles were included with a total of 13 reported dermatologic reactions including alopecia, bullous skin rash, Stevens–Johnson syndrome, toxic epidermal necrolysis, radiation recall and radiation dermatitis, Henoch–Schonlein purpura, cutaneous leukocytoclastic vasculitis, subacute and chronic cutaneous lupus erythematosus, histiocytoid, Sweet syndrome, vitiligo-like lesions, and erythema dyschromicum perstans.[15] Life-threatening clinical conditions of Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported to be associated with ribociclib[16,17] wherein complete necrosis of the epidermis, blistering, and subsequent skin detachment occur resulting in dehydration, electrolyte imbalance, and multiorgan failure. According to some preclinical data and few retrospective clinical studies, CDK4/6 inhibitors have a synergistic radiosensitizing effect, which can manifest as severe skin toxicity within the radiation field. There have been reports of radiation dermatitis in patients receiving palbociclib with radiotherapy and its reversal after discontinuation of palbociclib.[18] At present, data on safety of CDK4/6 inhibitors and radiotherapy are scarce. The phase II ASPIRE trial assesses the combination of radiotherapy with palbociclib and hormone therapy for bone metastases in breast cancer patients.[19]

Second, the skin toxicity in our patient was relatively late in onset, occurring in the fifth cycle of treatment. This suggests the need for regular scheduling of patient visits in patients on CDK4/6 inhibitors, once every 4 weeks, despite the lack of significant toxicity in the initial months of treatment. Third, others have reported the benefit of topical or systemic steroid use in managing severe skin toxicities,[20–22] but the toxicity resolved completely in our case with discontinuation of ribociclib. This suggests that the first intervention should be withdrawal of CDK4/6 inhibitor followed by careful monitoring of skin toxicity.

In summary, our case of severe ribociclib-induced skin toxicity illustrates an uncommon adverse effect of this drug and its natural history after withdrawal of this drug. Our patient developed severe maculopapular skin rash in the fifth cycle of ribociclib treatment, which resolved after its discontinuation. Prompt recognition and management of cutaneous adverse effects by oncologists and collaboration between them and dermatologists may limit negative impact on patients, including by reducing treatment interruptions.[23]

Declaration of Patient Consent

The patient has provided written informed consent for the publication of this case report including clinical pictures, without including any patient identification.

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None.

Conflict of Interest

None declared.

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