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Hand–Foot Skin Reaction Associated With Palbociclib

Victoria Lee PhD,[a] Angad A. Chadha MD[b]
[a]Pritzker School of Medicine, University of Chicago, Chicago, IL
[b]Section of Dermatology, Department of Medicine, University of Chicago, Chicago, IL

INTRODUCTION

Palbociclib is one of three new small-molecule inhibitors of cyclin-dependent kinase 4 and 6 (CDK4/6) approved for use in the treatment of hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (Her2-) advanced or metastatic breast cancer. CDK4/6 inhibitors have a good overall safety profile but reported side effects include cytopenias, diarrhea, QTc prolongation, and hepatobiliary toxicity.[1] While skin rash has been reported in patients treated with palbociclib, to date the cutaneous adverse events of CDK4/6 inhibitors have remained poorly characterized.[2,3] We report a case of hand–foot skin reaction (HFSR) in a patient treated with palbociclib for advanced breast cancer.

CASE

A 57-year-old African American woman presented with a 2-week history of painful blisters progressing to hyperkeratotic plaques on her palms and soles 6 weeks after initiation of palbociclib 125mg once a day for stage IIIA HR+Her2- breast cancer. Her other medications included fulvestrant. Previous therapies had included mastectomy and lymph node excision followed by chemotherapy (paclitaxel, doxorubicin, and cyclophosphamide), radiation, and anastrozole. She had no personal history of cutaneous disorders. Physical examination revealed multifocal hyperkeratotic plaques on the palms and soles with severe associated tenderness (Figure 1). The clinical characteristics of this patient's presentation were consistent with HFSR due to targeted chemotherapy, which typically presents with hyperkeratotic papules or plaques on the hands and feet, dry and/or cracked skin, callous-like dry blisters, dysesthesia, and paresthesia.[4] Given her severe skin changes and extreme pain limiting activities of daily living, she was diagnosed with grade 3 HFSR using the Common Terminology Criteria for Adverse Events (CTCAE) scoring system, version 5.0.[5] Hand-foot syndrome appeared unlikely due to the lack of erythema or desquamation.

Due to the severity of her HFSR, palbociclib was discontinued and the patient was treated with urea 40% cream BID, clobetasol 0.05% ointment BID, and oral prednisone 60mg daily for 1 week. Two weeks after discontinuation of palbociclib, her rash had improved to CTCAE grade 1 with no new lesions, interval improvement in previous tenderness and hyperkeratosis, and associated desquamation (Figure 2). The patient subsequently developed cutaneous metastastic lesions from her breast cancer 1 month after discontinuing palbociclib and was started on alpelisib.

FIGURE 1. CTCAE grade 3 hand–foot skin reaction (HFSR) after initiating palbociclib therapy. Left hand, right foot.

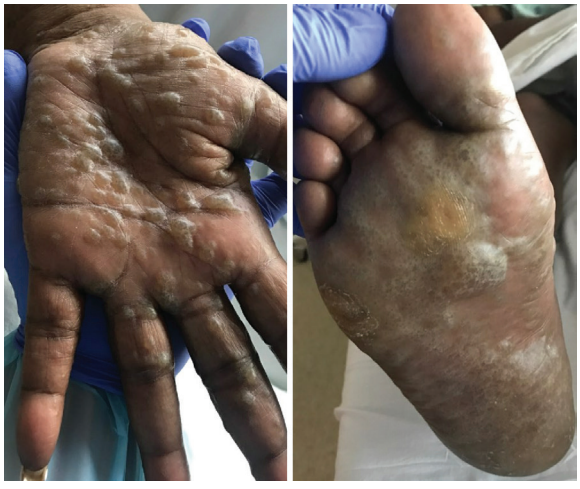
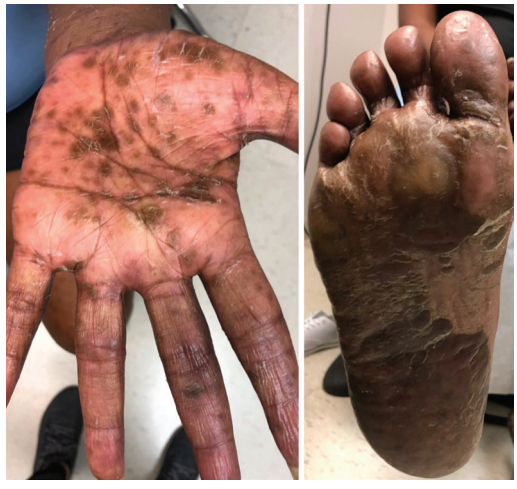


FIGURE 2. HFSR resolution to CTCAE grade 1 after discontinuation of palbociclib. Left hand, right foot.



DISCUSSION

The temporal course of the HFSR suggests a palbociclib-induced etiology. The skin changes appeared a few weeks after initiating palbociclib and resolved rapidly after discontinuation, which is consistent with other reports of drug-induced HFSR. For example, in the setting of tyrosine kinase inhibitor (TKI) induced HFSR, the skin changes typically appear during the first month of treatment and remit within weeks of discontinuing therapy.[4,6] The patient was not on other medications that could have caused the HFSR.

Drug induced HFSR is a well described side effect of selective Raf inhibitors as well as multikinase inhibitors that target Raf. Interestingly, Raf inhibition has been shown to upregulate expression of endogenous CDK inhibitors (p16, p27, p57).[7] Thus, there may be a mechanistic link between Raf-inhibition-induced and CDK4/6-inhibitor-induced HFSR, though this relationship remains undefined and warrants further study. The currently accepted theory for the pathogenesis of HFSR is that of dermal capillary micro-trauma leading to drug extravasation, tissue damage, and inhibition of vascular repair at sites prone to mechanical and frictional stress.[8]

Physicians should be aware of this potential side effect of palbociclib as early consultation with dermatology and early intervention may avoid the need for dose interruption of life-sustaining oncologic therapy.[9] Treatment centers around symptomatic therapy with urea-containing keratolytic emollients followed by high-potency topical steroids or oral corticosteroids in severe cases.[4,6,8] Patients should also avoid tight-fitting shoes, use shock absorbers, and keep skin well moisturized.[4,6,8] For cases requiring dose interruption or discontinuation, whether palbociclib can be reinitiated without recurrence of HFSR remains to be determined.

DISCLOSURES

The authors have no conflicts to disclose.

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AUTHOR CORRESPONDENCE

Angad A. Chadha MD

E-mail:..... chadha@medicine.bsd.uchicago.edu