DOI: https://doi.org/10.2298/SARH240925092B
UDC: 615.277.3.065

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Ribociclib-induced phototoxicity – the era of new drugs and new toxicities

Simonida Bobić[1], Bojana Poparić-Banđur[1], Milana Matović[1], Lidija Pavlović[1], Marijana Milović-Kovačević[1,2]

[1]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction Ribociclib belongs to the family of cyclin-dependent kinases 4/6 inhibitors and it has been approved in 2017 for the treatment of patients with hormone receptor-positive (ER^+) and human epidermal growth factor receptor 2-negative ($HER2^-$) advanced breast cancer. As a drug that has been used for treatment of breast cancer for only few years its rare side effects are described through different case reports. Skin photosensitivity represents a range of dermatological conditions that are caused or exacerbated by sunlight exposure. Drug-induced photosensitivity can be seen in patients treated with all kinds of oncology treatments, including chemotherapeutic agents, targeted anticancer therapies, and immune checkpoint inhibitors.

Case outline We present a case of a patient with metastatic hormone receptor positive and $HER2^-$ metastatic breast cancer who developed phototoxic skin changes during the treatment with ribociclib/letrozole. During the treatment, the patient developed mild redness of the skin in a strict photosensitive distribution and rash changed to erythematous confluent plaques on the neck and upper part of the chest, face, and forearms. After treatment cessation the skin changes did not reappear.

Conclusion As the observed cutaneous adverse effect subsided after the treatment cessation and did not reappear after the initiation of palbociclib/letrozole treatment, it can be concluded that the adverse effects were the consequence of ribociclib action. Management of cutaneous adverse effects is different depending mostly of grade of cutaneous adverse effect and its severity.

Keywords: ribociclib; breast cancer; phototoxicity

INTRODUCTION

Ribociclib belongs to the family of cyclin-dependent kinases 4/6 inhibitors (along with palbociclib and abemaciclib). It is administered orally and it operates by preventing oncogene retinoblastoma phosphorylation, thus blocking cell division [1]. Ribociclib has been approved in 2017 for the treatment of patients with hormone receptor-positive (ER^+) and human epidermal growth factor receptor 2-negative ($HER2^-$) advanced breast cancer. The approval of ribociclib was supported by Phase III of the Mammary Oncology Assessment of LEE011's Efficacy and Safety – NCT01958021 (MONALEESA-2) study, where its benefits both in progression-free survival and in overall survival were demonstrated [2]. More specifically, when administered together with the aromatase inhibitor letrozole, ribociclib achieved a 30% or greater reduction in tumor size in more than 53% of patients with measurable disease in comparison to letrozole monotherapy [2].

The most common adverse reactions of ribociclib, observed in 20% or more of patients, are neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache, and back pain. Also, hypersensitivity of the patient to the active substance or to peanuts and soy is a contraindication for the drug use [2]. Ribociclib may provoke several cutaneous adverse effects including rashes, vitiligo, and bullous dermatitis [3]. Also, one case erythema dyschromicum perstans was reported after the use of ribociclib [4].

As an adverse effect, skin photosensitivity can be observed in patients treated with all kinds of oncology treatments, including chemotherapeutic agents, targeted anticancer therapies and immune checkpoint inhibitors [5]. Recently, one case of ribociclib-induced phototoxicity was documented in a woman that received ribociclib (600 mg) for seven months. It initially manifested as dyschromia over sun-exposed forearms and neck and subsequently as bullae formation [6]. Since the varieties of ribociclib-provoked skin photosensitivity have been rarely documented, we present this case report to add to the list of possible strong adverse effects that include development of rash and erythematous confluent plaques on sun-exposed body parts.

CASE REPORT

The initial treatment of the left breast cancer started in February 2022, when partial resection of the left breast was done and the diagnosis of infiltrating ductal cancer (hormone receptor

Received • Примљено: September 25, 2024
Revised • Ревизија: December 8, 2024
Accepted • Прихваћено: December 9, 2024
Online first: December 10, 2024

Correspondence to:
Simonida BOBIĆ
Institute for Oncology and Radiology of Serbia
Pasterova 14
11000 Belgrade
Serbia
simonidapupovac@yahoo.com

positive, HER2 negative) was confirmed. Postoperative radiotherapy was next performed and patient was on adjuvant hormonal therapy, oral tamoxifen, from April 2022 until January 2023. At this point, computed tomography scan revealed multiple liver metastases. The treatment with letrozole and ribociclib has started from March of 2023. Laboratory findings were all in normal ranges. Ribociclib was introduced in a dose of 600 mg orally once a day, and letrozole of 2.5 mg, once a day.

The patient exhibited an atopic constitution and because of the already established allergy to one or several types of pollen she received antihistaminic treatment during the first cycle of ribociclib-letrozole (21 days). However, the patient stopped antihistaminic treatment around day 15. During the break from ribociclib (that lasts for seven days, from days 21–28), she developed mild redness of the skin in a strict photosensitive distribution (face, neck and upper part of the chest) on day 26. She started with second cycle of ribociclib/letrozole from day 28 and on day 2 (during second cycle) rash changed to erythematous confluent plaques on the neck and upper part of the chest (Figure 1), face (Figure 2) and rash on the forearms (Figure 3). The treatment with ribociclib/letrozole was discontinued.

After all skin changes subsided and completely disappeared, in May of 2023 (around day 30 from the last treatment), the treatment continued with a different cyclin-dependent kinases 4 and 6 (CDK4/6) drug – palbociclib, along with letrozol, and the further treatment was without complications.

The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved.

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal.

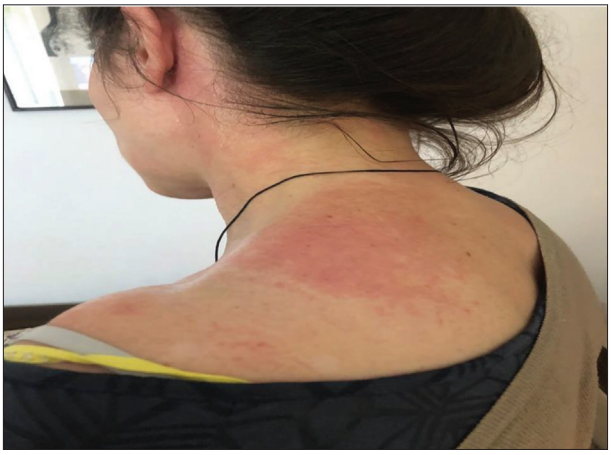

Figure 1. Erythematous confluent plaques on the neck and upper part of the chest

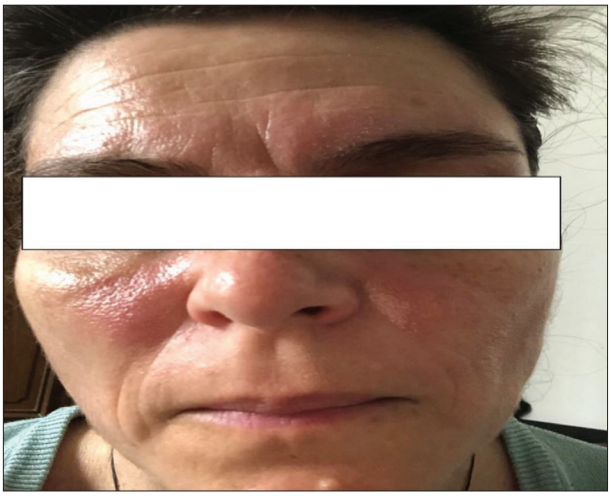

Figure 2. Erythematous confluent plaques on the face

DISCUSSION

Drug-induced photosensitivity can be classified as either phototoxic or photoallergic reactions based on the underlying pathophysiological mechanism [5, 7]. Phototoxicity is a nonimmune-mediated response to cytotoxic damage caused by UV-induced generation of reactive oxygen species [5]. It is typically manifested as an exaggerated sunburn response with clearly demarcated erythema and edema occurring on sun-exposed skin. The main feature of phototoxicity as that it starts rapid, within hours of exposure to the agent and UV radiation, and progressively develops to localized or more diffuse hyperpigmentation [5, 7]. The personalization of therapies in breast cancer has favored the introduction of new molecular-targeted therapies into clinical practice. Among them, CDK4/6 inhibitors have acquired increasing importance, with the approval in recent years of palbociclib, ribociclib, and abemaciclib in combination with endocrine therapy (ET) [8]. MONALEESA-2 is a phase III randomized, double-blind, placebo-controlled study of ribociclib combined with letrozole for the treatment of postmenopausal women with $HR^+/HER2^-$ advanced breast cancer who received no prior therapy for advanced disease [9]. In this study, adverse event of any grade that occurred in at least 35% of the patients in either group were neutropenia, nausea, infections, fatigue, and diarrhea [10]. MONALEESA-3 is a phase III randomized, double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for treating postmenopausal women and men with $HR^+/HER2^-$ advanced breast cancer who have received no or only one line of ET for advanced breast cancer [11], and in this study neutropenia, nausea, and tiredness were the most prevalent of all-grade adverse events observed in 30% of patients [12].

Ribociclib-induced phototoxicity was already documented as dyschromia over sun-exposed forearms and neck and subsequent bullae formation [6]. On the other hand, the cutaneous manifestations observed in this case study (rash and erythematous confluent plaques) are likely photoallergic as the rash occurred after a few days of starting the drug and was gradually progressive. This is in line with the literature evidence as the most common clinical presentation of photoallergy, eczematous eruption, appears usually 24–72 hours after sunlight exposure and treatment

Figure 3. The rash on the forearm

with causative agent. Symptoms tend to worsen and peak 48–72 hours after onset and mostly resolves after removal of the causative agent and sun avoidance [5, 7].

Photoallergic drug reactions are mediated by a T cell-mediated immune mechanism, resulting in a delayed type IV hypersensitivity response, so they manifest only in presensitized individuals and are much more rare than phototoxic drug reactions [5, 7]. Having in mind the atopic constitution of the patient, it is reasonable to assume that the observed cutaneous changes can be driven by the exaggerated immune reaction.

In general, CDK4/6 inhibitors can provoke rash as a side effect (data obtained from meta-analysis evaluating toxicity end points), but further details on the type of rash were not available [13]. Specifically, for ribociclib, conclusions drawn from the phase I trial performed to determine dose-limiting toxicity and maximum-tolerated dose of ribociclib (performed on 21 patients), suggest that the rash is a common side effect as it presented in 52% of patients along with oral mucositis. Again, further details on rash type were not available [14].

In 2024, a retrospective cohort study of all patients with $HR^+/HER2^-$ advanced breast cancer treated with ribociclib at Humanitas Cancer Center between June 2017 and December 2022 was conducted and 14.3% of all patients experienced treatment-related cutaneous adverse events. The most frequent cutaneous adverse events were eczematous dermatitis (53.8%) and maculo-papular reaction (15.4%) [15]. Another study compared adverse events associated with CDK4/6 inhibitors based on FDA's adverse event reporting system and reported that different skin toxicities were observed in all three CDK4/6 inhibitors used [16].

The patient presented in this case report received a combination therapy (ribociclib/letrozole), and therefore, the possibility that photoallergy was initiated by letrozole action has to be taken into consideration. Letrozole is an aromatase inhibitor and is known to have cutaneous side effects. In phase 2 of a randomized study in postmenopausal women with breast cancer, receiving letrozole, skin rash was noted as a side effect in 23 out of 125 (18.4%) patients. The type of skin lesions was described as exfoliative, nodular, follicular, generalized, maculo-papular, and others [17]. However, no such cutaneous effects were observed after the treatment of the same patient with palbociclib/letrozole suggesting that the observed side effects were provoked by the action of ribociclib.

Establishing a diagnosis of photosensitive reactions induced by anticancer agents can be challenging and requires close evaluation of the clinical presentation and medication history of the patient. Also, these patients are often treated in combination with a range of other therapies that may be potentially involved in the occurrence of photosensitive reactions, and it can be very challenging to identify the most likely causative agent [7].

The involvement of ribociclib in the observed cutaneous adverse effect is straight-forward as the symptoms subsided after the treatment cessation, and they did not appear again when the treatment option was changed. Letrozole was a part of both treatment options, and therefore the impact of this drug on the cutaneous adverse effects can be excluded. Although photoallergic dermatitis is a rare side effect of ribociclib, strict photoprotection should be advised to these patients while prescribing this medication. As different dermatologic adverse events can lead to dose modifications and interruption or discontinuation of anticancer treatments in severe cases, the prophylactic behavior of the patient is strongly encouraged. In cases where preventative measures fail and photosensitivity occurs, symptomatic treatment with topical or systemic corticosteroids may help to reduce the impact of the photosensitive eruptions on patient quality of life and allow potentially life-saving cancer therapies to be continued without dose modification.

Recently, Abemaciclib [18] and Ribociclib [19] demonstrated to significantly improve the invasive disease free survival in intermediate and high risk populations of early $HR^+/HER2^-$ breast cancer patients so the treatment with CDK4/6 inhibitors is being implemented in treatment of breast cancer patients with early breast cancer, as well as metastatic breast cancer, so the understanding and management of all side effects is crucial.

Conflict of interest: None declared.

REFERENCES

1. Kim S, Tiedt R, Loo A, Horn T, Delach S, Kovats S, et al. The potent and selective cyclin-dependent kinases 4 and 6 inhibitor ribociclib (LEE011) is a versatile combination partner in preclinical cancer models. Oncotarget. 2018;9(81):35226–40. [DOI: 10.18632/oncotarget.26215] [PMID: 30443290]
2. Shah A, Bloomquist E, Tang S, Fu W, Bi Y, Liu Q, et al. FDA Approval: Ribociclib for the Treatment of Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Advanced or Metastatic Breast Cancer. Clin Cancer Res. 2018;24(13):2999–3004. [DOI: 10.1158/1078-0432.CCR-17-2369] [PMID: 29437768]
3. Raschi E, Fusaroli M, La Placa M, Ardizzoni A, Zamagni C, Poluzzi E, et al. Skin Toxicities with Cyclin-Dependent Kinase 4/6 Inhibitors in Breast Cancer: Signals from Disproportionality Analysis of the FDA Adverse Event Reporting System. Am J Clin Dermatol. 2022;23(2):247–55. [DOI: 10.1007/s40257-021-00645-0] [PMID: 34699032]
4. Mariano M, Donati P, Cameli N, Pigliacelli F, Morrone A, Cristaudo A. Ribociclib-Induced Erythema Dyschromicum Perstans (Ashy Dermatosis)-Like Pigmentation in a Metastatic Breast Cancer Patient. J Breast Cancer. 2021;24(1):117–21. [DOI: 10.4048/jbc.2021.24.e1] [PMID: 33634626]
5. Sibaud V. Anticancer treatments and photosensitivity. J Eur Acad Dermatol Venereol. 2022;36 Suppl 6(Suppl 6):51–8. [DOI: 10.1111/jdv.18200] [PMID: 35738806]
6. Jhan JY, Wang WE, Chu SC, Cheng CH, Chang CH. Case Report: Ribociclib-induced phototoxicity presented as dyschromia with subsequent bullae formation. Front Oncol. 2023;13:1184738. [DOI: 10.3389/fonc.2023.1184738] [PMID: 37692847]
7. Hofmann GA, Weber B. Drug-induced photosensitivity: culprit drugs, potential mechanisms and clinical consequences. J Dtsch Dermatol Ges. 2021;19(1):19–29. [DOI: 10.1111/ddg.14314] [PMID: 33491908]
8. Vieira C, Piperis MN, Sagkriotis A, Cottu P. Systemic treatment for hormone receptor-positive/HER2-negative advanced/metastatic breast cancer: A review of European real-world evidence studies. Crit Rev Oncol Hematol. 2022;180:103866. [DOI: 10.1016/j.critrevonc.2022.103866] [PMID: 36336168]
9. Novartis Pharmaceuticals. A Randomized Double-Blind, Placebo-Controlled Study of LEE011 in Combination With Letrozole for the Treatment of Postmenopausal Women With Hormone Receptor Positive, HER2 Negative, Advanced Breast Cancer Who Received no Prior Therapy for Advanced Disease. 2023. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT02941926
10. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(18):1738–48. [DOI: 10.1056/NEJMoa1609709]. Erratum in: N Engl J Med. 2018;379(26):2582. [DOI: 10.1056/NEJMx180043] [PMID: 27717303]
11. Novartis Pharmaceuticals. A Randomized Double-Blind, Placebo-Controlled Study of Ribociclib in Combination With Fulvestrant for the Treatment of Men and Postmenopausal Women With Hormone Receptor Positive, HER2-Negative, Advanced Breast Cancer Who Have Received no or Only One Line of Prior Endocrine Treatment. 2023. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT02422615
12. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018;36(24):2465–72. [DOI: 10.1200/JCO.2018.78.9909] [PMID: 29860922]
13. Costa R, Costa RB, Talamantes SM, Helenowski I, Peterson J, Kaplan J, et al. Meta-analysis of selected toxicity endpoints of CDK4/6 inhibitors: Palbociclib and ribociclib. Breast. 2017;35:1–7. [DOI: 10.1016/j.breast.2017.05.016] [PMID: 28618307]
14. Seront E, Schmitz S, Papier M, van Maanen A, Henry S, Lonchay C, et al. Phase 1 Study Evaluating the Association of the Cyclin-Dependent Kinase 4/6 Inhibitor Ribociclib and Cetuximab in Recurrent/Metastatic p16-Negative Squamous Cell Carcinoma of the Head and Neck. Front Oncol. 2019;9:155. [DOI: 10.3389/fonc.2019.00155] [PMID: 30941307]
15. Borroni RG, Bartolini M, Gaudio M, Jacobs F, Benvenuti C, Gerosa R, et al. Ribociclib-Induced Cutaneous Adverse Events in Metastatic HR+/HER2- Breast Cancer: Incidence, Multidisciplinary Management, and Prognostic Implication. Oncologist. 2024;29(6):484–92. [DOI: 10.1093/oncolo/oyae004] [PMID: 38242689]
16. Lin W, Zeng Y, Weng L, Yang J, Zhuang W. Comparative analysis of adverse events associated with CDK4/6 inhibitors based on FDA's adverse event reporting system: a case control pharmacovigilance study. BMC Pharmacol Toxicol. 2024;25(1):47. [DOI: 10.1186/s40360-024-00770-6] [PMID: 39123221]
17. Mayer IA, Prat A, Egle D, Blau S, Fidalgo JAP, Gnant M, et al. A Phase II Randomized Study of Neoadjuvant Letrozole Plus Alpelisib for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer (NEO-ORB). Clin Cancer Res. 2019;25(10):2975–87. [DOI: 10.1158/1078-0432.CCR-18-3160] [PMID: 30723140]
18. Johnston SRD, Toi M, O'Shaughnessy J, Rastogi P, Campone M, Neven P, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol. 2023;24(1):77–90. [DOI: 10.1016/S1470-2045(22)00694-5] [PMID: 36493792]
19. Slamon D. Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2– early breast cancer: Primary results from the phase III NATALEE trial. LBA500. J Clin Oncol. 2023. [DOI: 10.1200/JCO.2023.41.17_suppl.LBA500]

Рибоциклибом индукована фототоксичност – ера нових лекова и нових токсичности

Симонида Бобић[1], Бојана Попарић-Банђур[1], Милана Матовић[1], Лидија Павловић[1], Маријана Миловић-Ковачевић[1,2]

[1]Институт за онкологију и радиологију Србије, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод Рибоциклиб припада породици инхибитора киназа зависних од циклина 4/6 и одобрен је 2017. године за лечење болесница са узнапредовалим карциномом дојке позитивним на хормонски рецептор ($ЕР^+$) и негативним на рецептор за хумани епидермални фактор раста 2 ($ХЕР2^-$). Пошто се рибоциклиб за лечење рака дојке користи само последњих неколико година, његови ретки нежељени ефекти описани су кроз различите приказе случајева. Кожна фотосензитивност обухвата широк спектар дерматолошких стања узрокованих или погоршаних током излагања сунцу. Фотосензитивност изазвана лековима може да се испољи код онколошких болесника који се лече свим модалитетима системске терапије: хемиотерапеутицима, циљаном терапијом и имунолошком терапијом.

Приказ болесника Приказујемо случај болеснице са метастатским карциномом дојке позитивним на хормонски рецептор и негативним на рецептор за хумани епидермални фактор раста, код које се јавила кожна фототоксичност током примене терапије рибоциклибом/летрозолом. Током третмана појавило се благо црвенило коже у строго фотосензитивној дистрибуцији и осип се променио у еритематозне спојене плакове на врату и горњем делу грудног коша, лица и подлактица. После прекида примене лека промене на кожи се нису поново појавиле.

Закључак Пошто се испољено кожно нежељено дејство повукло после прекида терапије и није се поново јављало после примене терапије палбоциклибом/летрозолом, може се закључити да је нежељено дејство последица примене рибоциклиба. Лечење кожних нежељених ефеката је различито, углавном у зависности од степена кожних нежељених ефеката и његове тежине.

Кључне речи: рибоциклиб; карцином дојке; фототоксичност