Ribociclib-induced vitíligo-like lesions: a case report and therapeutic considerations

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RESUMEN

La terapia endocrina es el tratamiento estándar para las mujeres con cáncer de mama avanzado con receptores hormonales positivos (HR+) y receptor del factor de crecimiento epidérmico humano 2 (HER2)-negativo, siendo el uso de inhibidores de la quinasa dependiente de ciclina (CDK) 4/6 con inhibidores de la aromatasa el tratamiento de elección. Los tres fármacos disponibles han mostrado resultados de eficacia comparables, con efectos adversos variables pero predecibles y manejables (toxicidad hematológica, diarrea y daños en la función hepática). La toxicidad dermatológica asociada a los inhibidores de la CDK 4/6 es relativamente frecuente, representando hasta el 15% de todos los acontecimientos adversos notificados. Suele ser de intensidad leve a moderada y normalmente no constituye una toxicidad limitante de dosis. Sin embargo, las toxicidades cutáneas más graves son poco frecuentes y constituyen menos del 1% de los acontecimientos adversos notificados. El vitíligo o las lesiones similares al vitíligo son un acontecimiento adverso poco frecuente. El mecanismo exacto del desarrollo de lesiones similares al vitíligo durante el tratamiento con inhibidores de CDK 4/6 sigue siendo desconocido. Este artículo presenta un caso clínico de una paciente con cáncer de mama metastásico avanzado HR+HER2 negativo diagnosticada de lesiones similares al vitíligo tras 7 meses de tratamiento con ribociclib y que requirió un cambio de inhibidor CDK 4/6 debido a toxicidad cutánea de grado 3 con resultado satisfactorio.

Palabras clave: reacción adversa a medicamentos, cáncer de mama, proteínas inhibidoras de la cinasa dependiente de ciclina, ribociclib, vitíligo.

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ABSTRACT

Endocrine therapy is the standard of care for women with advanced breast cancer that is hormone receptor-positive (HR+) and human epidermal growth factor receptor 2 (HER2) –negative, being the use of cyclin-dependent kinase (CDK) 4/6 inhibitors with aromatase inhibitors the preferred first-line treatment. The three available drugs have shown comparable efficacy results, with variable but predictable and manageable adverse effects (hematological toxicity, diarrhea, and liver function damage). Dermatological toxicity associated with CDK 4/6 inhibitors appears to be relatively common, accounting for up to 15% of all reported adverse events. It is usually mild to moderate in intensity and does not normally constitute dose-limiting toxicity. However, more serious skin toxicities are rare and constitute less than 1% of reported adverse events. Vitiligo or vitiligo-like lesions are a rare adverse event. The exact mechanism of the development of vitiligo-like lesions during CDK 4/6 inhibitors treatment is still unknown. This article presents a case report of a patient with advanced metastatic breast cancer HR+HER2 negative diagnosed with vitiligo-like lesions after 7 months of treatment with ribociclib and who required a switching of CDK 4/6 inhibitor due to grade 3 skin toxicity with a positive result.

Keywords: adverse drug reaction, breast cáncer, cyclin-dependent kinase inhibitor proteins, ribociclib, vitíligo.

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INTRODUCTION

Cyclin-dependent kinases 4 and 6 (CDK4/6) in conjunction cyclin D1 regulate cell-cycle progression. The inhibition of the pathway consisting of cyclin-D/CDK4/6 complex blocks the phosphorylation of retinoblastoma protein, thereby preventing cell-cycle progression from G1 to S phase[1]. This is an effective therapeutic strategy for HR-positive advanced breast cancer, both as a first-line option[2] and in patients in whom disease has progressed while they were receiving endocrine therapy.

All three available CDK 4/6 inhibitors - palbociclib, ribociclib and abemaciclib - have shown comparable efficacy results, with variable but predictable and manageable adverse events (AE)[3], including a wide range of cutaneous adverse-effects events, the most common of which is alopecia, followed by rash and pruritus[4]. Pivotal studies of CDK 4/6 inhibitors have shown that the most common cutaneous side effects are mild, with grade 3 rashes only occurring in 0.9% of patients, while the incidence of rashes or the degree of toxicity of CDK 4/6 inhibitors was not shown to have a prognostic impact. Vitiligo-like lesions are a dermatologic AE exceptionally reported with CDK 4/6[5].

We report a case of grade 3 skin toxicity in a patient with metastatic breast cancer who was treated with ribociclib and developed vitiligo-like lesions after treatment.

CASE REPORT

A 42 year-old premenopausal woman was diagnosed in 2005 with invasive lobular, hormone receptor-positive (HR+) and human epidermal growth factor receptor-2-negative (HER2-), stage III breast cancer. She underwent a mastectomy and subsequently received adjuvant chemotherapy, radiotherapy and hormone therapy.

Twelve years after the initial diagnosis, the patient was referred back to our center due to elevated tumor markers. A PET scan revealed peritoneal carcinomatosis as the sole site of disease. In this context, an exploratory laparoscopy was performed, confirming metastatic recurrence of lobular breast cancer with the luminal A subtype. The disease-free interval was 15 years (at age 59). Therefore, based on the results of the MONALEESA-2 clinical trial, the patient began treatment with ribociclib 600 mg/day in combination with letrozole for hormone-sensitive metastatic breast cancer.

After six cycles of treatment, the patient tolerated the treatment well, and a partial response was observed. She did not develop neutropenia but did experience an elevation in transaminase levels, which resolved without incident. During the seventh cycle, the patient started complaining of an erythematous and pruritic rash on sun-exposed areas. Initial treatment with antihistamines was attempted, but the rash worsened, progressing to a generalized form affecting more than 30% of the body surface. Consequently, oral corticosteroids and antihistamines were prescribed, and ribociclib was temporarily discontinued. Twenty-nine days later, ribociclib was reintroduced with dose adjustment of 400 mg/day. Unfortunately, 48 hours later the patient reported scaly lesions on the arms and legs accompanied by intense itching. Given this situation, ribociclib was permanently discontinued due to limiting skin toxicity, and treatment with abemaciclib was started.

The causal association between ribociclib and vitiligo was placed in probable category by assessing causality using both the World Health Organization (WHO) Causality Assessment Scale and the Naranjo Adverse Drug Reaction Probability Scale[6]. She had not experienced any trauma, infections or any other dermatological problems preceding the onset of this symptom.

The patient was referred to the dermatology team for evaluation. She presented with hypopigmented macules and achromic lesions on her upper and lower limbs, as well as on her face. The lesions had a characteristic "confett" appearance due to their poorly defined borders. A diagnosis of ribociclib-induced multifocal vitiligo was made. As topic and sistemic therapy was not improving the lesions, narrowband UVB phototherapy (311 nm) was employed to promote repigmentation. The patient has initiated repigmentation in facial and arm regions, although the affected body surface remains extensive. The patient continues on abemaciclib without new lesions and maintains good clinical condition. She is followed up every 3 months.

DISCUSSION

Vitiligo is an acquired pigmentary autoimmune disorder consisting of developing hypopigmented macules due to the selective loss of melanocytes. Possible mechanisms for the development of vitiligo include autoimmunity, oxidative stress, melanocyte self-destruction, and genetic predisposition. Although, the exact mechanism of the development of viti-

ligo-like lesions during CDK 4/6 inhibitors treatment is still unknown; one hypothesis is that dysregulation of the keratinocyte cell cycle may result in the loss of survival stimuli for neighbouring melanocytes[7]. It has also been proposed that melanocytes, damaged by ultraviolet radiation, may be targets of an increased immune system after CDK 4/6 inhibition due to loss of immune tolerance resulting from reduction of immunosuppressive regulatory T cells and activation of cytotoxic T cells[8]. In addition, it might be interesting further investigations about the immune-mediated mechanism that could explain the irreversible vitiligo-like skin toxicity[7]. Our patient could not have the lesions completely removed and no literature has been found describing the removal of the lesions once they have developed.

The ENCADO (European Network for Cutaneous Adverse event to Oncologic drugs) group reported for the first time cases of vitiligo-like lesions following the use of CDK 4/6 inhibitors in the treatment of 19 patients with metastatic breast cancer at six European university centres[3]. Of these patients, 18 (94.7%) were treated with ribociclib and only one with palbociclib. No cases of abemaciclib-associated vitiligo were reported. All of them were women with a mean age of 63.1 (58-79) years. The mean time on ribociclib treatment until the onset of vitiligo was 5.3 (1-10) months. In most of the cases described, patients were treated with high potency steroid cream and/or calcineurin inhibitors with variable response. Only 5 patients (27.8%) received UVA/UVB phototherapy. Our patient was 59 years old when she started ribociclib and continued for 7 months until it was definitively discontinued due to severe skin toxicity. It should be noted that although it has been reported in the literature that patients were treated with high potency steroid cream, in our case, due to severity, both corticosteroids and systemic antihistamines were required.

A slightly different toxicity profile was described for abemaciclib, probably due to its higher selectivity for CDK4 versus CDK6 (14 times more specific)9. This may explain why the patient did not worsen her skin lesions after switching from ribociclib to abemaciclib.

Cutaneous adverse events are not taken into consideration when choosing what CDK 4/6 inhibitor offer to the patient. Nevertheless, real-world data have shown that skin toxicity could reduce the tolerability of the therapy for the breast cancer patients, leading to a 25% discontinuation rate[10]. Skin toxicities decrease patients' quality of life, which impacts their adherence to treatment and can affect their personal, social, and work relationships, compromising treatment success and patient survival[4]. In our case, the sudden appearance of the lesions caused psychological distress to the patient. This fact, combined with the feeling of anxiety generated by a breast cancer relapse, had a direct impact on our patient's quality of life.

Our case should add to the knowledge gained from existing case reports in the literature. Firstly, because of the development of vitiligo-like lesions induced by ribociclib and, secondly, due to grade 3 skin toxicity, it might be necessary to switch the patient's treatment.

CONCLUSIONS

Ribociclib-induced vitiligo or vitiligo-like lesions are rare adverse events. Lesions can cause psychological distress to patients and affect compliance with treatment. This clinical case highlights the rarity of this adverse event and provides an opportunity to switch to CDK 4/6 inhibitor therapy with a positive outcome.

ETHICAL CONSIDERATIONS

This study was conducted in accordance with the principles outlined in the Helsinki Declaration.

Written informed consent was obtained from the patient for publication of this report and any potentially identificable images or data.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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