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CASE REPORT

Olaparib desensitization using the non-crushable tablet formulation

Dessensibilização ao olaparib utilizando a formulação em comprimido não triturável

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Abstract

Previously reported desensitization protocols for olaparib relied on capsule or tablet suspensions that allowed very low starting doses, which are no longer commercially available in Europe. We describe a 40-year-old female with a pathogenic germline BRCA2 mutation, with triple-negative breast cancer with residual disease after neoadjuvant chemotherapy, who developed immediate cutaneous hypersensitivity after the first dose of adjuvant olaparib. A 2-day, hospital-based desensitization protocol was performed using the currently available non-crushable tablet formulation. A 2-day hospital build-up was performed, achieving a total dose of 400 mg, followed by a single-day build-up 7 days later to a cumulative dose of 600 mg, established as the maintenance regimen. This case supports the feasibility of olaparib desensitization using current tablet formulations and highlights the role of allergy-guided strategies in maintaining access to anticancer guided therapies.

Keywords: *Olaparib. Drug desensitization. Drug allergy. Oncoallergology.*

Resumo

Os protocolos de dessensibilização a olaparib previamente publicados utilizaram suspensões a partir de cápsulas ou comprimidos, permitindo doses muito baixas, atualmente não comercializadas na Europa. Os autores relatam o caso de uma doente do sexo feminino de 40 anos com mutação germinativa BRCA2 patogénica com o diagnóstico de cancro da mama triplo negativo, com doença residual após quimioterapia neoadjuvante, com reação de hipersensibilidade imediata após a primeira dose de olaparib. Foi realizado protocolo de dessensibilização em meio hospitalar, com comprimidos não-trituráveis compreendendo uma fase de indução de dois dias com atingimento de uma dose de 400mg, seguido de um dia de indução, 7 dias depois, com incremento da dose para 600mg, estabelecido como regime de manutenção diária. Este caso apoia a viabilidade da dessensibilização a olaparib utilizando as formulações atuais e sublinha o papel das estratégias guiadas pela Imunoalergologia, para garantir que os doentes mantenham em curso tratamento antineoplásico recomendado.

Palavras-chave: *Olaparib. Dessensibilização a fármacos. Alergia a fármacos. Oncoalergologia.*

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Introduction

Drug allergy accounts for 10-15% of adverse drug reactions.[1] Type I, immunoglobulin E (IgE)-mediated reactions occur within minutes to hours after exposure.[1] Adverse drug reactions are reported in approximately 5% of oncology treatments.[2] Based on presentation, severity, and mediators released, these reactions can be classified according to phenotype and endotype, reflecting the underlying immune pathways (infusion reactions, IgE/non-IgE type I reactions, mixed reactions, cytokine-release syndromes, and types II-IV hypersensitivity reactions).[3,4]

Case report

We report the case of a 40-year-old premenopausal female with a known history of Gilbert syndrome and a recent diagnosis of triple-negative metaplastic breast cancer (cT1cN0M0) with a pathogenic germline BRCA2 mutation. She underwent neoadjuvant chemotherapy (carboplatin, paclitaxel, followed by dose-dense doxorrubicin/cyclophosphamide) and then mastectomy with sentinel lymph node biopsy. The breast specimen revealed residual cancer disease, ypT1aN0, and became eligible for adjuvant olaparib 300 mg bid for 1 year, according to the Olympia trial, which demonstrated significant improvement in overall survival in this setting.[5,6] Two hours after the initial 300 mg oral dose, she developed ocular itching, facial flushing, and a generalized pruritic macular exanthema. Tryptase and interleukin-6 were not measured at the time. Given the pharmacological characteristics of the drug, no skin or *in vitro* tests were feasible, leaving the mechanism of sensitization undetermined. Since adjuvant olaparib prolongs overall survival in this context, drug desensitization was attempted.

A desensitization protocol has previously been reported for this drug; however, it involved olaparib in capsule or tablet suspension form, which enabled lower starting doses.[7-9] As these formulations are no longer commercially available in Europe and olaparib is currently marketed exclusively as 100 mg and 150 mg tablets that cannot be crushed, dissolved, or divided according to the product's regulatory information, this posed a practical challenge requiring protocol adaptation.[2] Pre-medication was tailored to the initial clinical reaction; anti-H1 and anti-H2 antihistamines were used, and acetylsalicylic acid (ASA) was given, the symptoms of flushing and maculopapular rash.[2,4,10]

Desensitization was performed in the hospital setting under continuous monitoring, with 30-min intervals between doses. A 2-day, hospital-based desensitization protocol was performed using the currently available non-crushable tablet formulation. A 2-day hospital build-up was performed, achieving a total dose of 400 mg, followed by a single-day build-up 7 days later to a cumulative dose of 600 mg, established as the maintenance regimen (Table 1).

On day 1, the patient received sequential doses of 100 mg, 100 mg, 100 mg, and 150 mg of olaparib (cumulative dose 450 mg). Twenty-five minutes after the final dose, she developed a pruritic macular exanthema and flushing that resolved with antihistamine treatment. On day 2, olaparib was re-administered at 200 mg twice daily (400 mg cumulative) under premedication (bilastine, famotidine, and ASA) with good tolerance. Seven days later, the dose was escalated to 300 mg twice daily (600 mg/day), which has since been maintained for 16 weeks without breakthrough reactions or hypersensitivity signs (Table 1).

Discussion

Olaparib is a potent poly(ADP-ribose) polymerase (PARP) inhibitor targeting PARP1 and PARP2 that suppresses the growth of selected tumor cell lines and is currently approved for the treatment of patients with breast, ovarian, endometrial, and prostate cancers, usually in the setting of pathogenic BRCA 1/2 mutations.

Desensitization allows patients who experience type I, cytokine-release type, mixed type, or type IV hypersensitivity reactions (except for severe cutaneous adverse reactions) to continue receiving the offending drug when no therapeutically equivalent alternatives exist.[10] It induces a temporary state of tolerance through the gradual administration of subthreshold doses (typically 1/1000-1/100 of the target dose) at fixed intervals, thereby blocking mast cell signaling and mediator release.[2,4]

This adapted protocol enabled the continuation of adjuvant olaparib, despite the initial hypersensitivity reaction. To our knowledge, this is the first successful desensitization using the currently available non-crushable tablet formulation. Our case highlights the feasibility of tailoring desensitization strategies when conventional formulations are unavailable, thereby expanding treatment options for patients requiring uninterrupted therapy.[1,10]

The main limitation of this report is the absence of confirmatory tests (tryptase, basophil activation, or skin testing), which preclude definitive mechanistic

Table 1. Olaparib desensitization protocol using the non-crushable tablet formulation

Day	Step	Time (h:min)	Olaparib tablet dose (mg)	Cumulative daily dose (mg)
1	1	00:00	100	100
	2	00:30	100	200
	3	01:00	150	350
2-6*	1	00:00	200	200
	2*	12:00	200	400
7	1	00:00	300	300
	2*	12:00	300	600

*Outpatient administration.

classification. Nevertheless, the clear temporal relationship, reproducibility of symptoms, and success of desensitization support the diagnosis of a hypersensitivity reaction.

We emphasize the importance of a multidisciplinary team, including allergists, oncologists, nurses, and pharmacists, in the identification and management of potentially severe hypersensitivity reactions that would otherwise limit therapeutic options.

Authors' contributions

L.P. Viegas: conceptualization, study design, protocol development, desensitization procedure, writing – original draft; J. Godinho: patient provision, data analysis, writing – review and editing; M.N. Rosado: pharmacological support, writing – review; L.P. Coelho: writing – review; L.M. Borrego: conceptualization, writing – review and editing.

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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