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CASE REPORT

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Successful Rapid Desensitization in a Patient with Osimertinib-Induced Immediate-Type Hypersensitivity Reaction

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ABSTRACT

Osimertinib is an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) drug effective in patients with non-small cell lung cancer (NSCLC) harboring EGFR-TKI sensitivity and T790M resistance mutations. However, it is associated with hypersensitivity reactions like skin rash and urticaria. While slow desensitization protocols are documented in the literature, to our knowledge there are no reports of rapid desensitization with osimertinib.

We present successful rapid desensitization with osimertinib in a 64-year-old female with lung adenocarcinoma. She was diagnosed seven years ago and after six cycles of chemotherapy and six years on gefitinib, disease progression led to a repeat biopsy, revealing the EGFR 790M mutation. She started osimertinib at a dose of 80 mg, and on the fourth day of treatment, approximately 3-4 hours after drug administration, she developed urticaria on her arms and legs. Despite continuing treatment with methylprednisolone and an antihistamine, the urticarial rash persisted, leading to the discontinuation of osimertinib. Symptoms persisted for about a week before resolving. No alternative treatment options were available because the patient declined chemotherapy. A prick-to-prick test with osimertinib tablets was negative. To prevent treatment interruption, a six-step rapid desensitization protocol with osimertinib, adapted from crizotinib desensitization protocols, was used with bilastine premedication. No reaction occurred during desensitization. The patient continued osimertinib without any issues for six months.

Antineoplastic drug hypersensitivities are of paramount importance because alternative treatment options with equivalent efficacy are often unavailable. Desensitization to these drugs is crucial in the absence of alternative effective treatments and can be lifesaving.

Keywords: Rapid desensitization, osimertinib, NSCLC, EGFR-TKI

INTRODUCTION

First- and second-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) provide higher overall response rates and longer disease-free survival than initial platinum-based doublet chemotherapy and have therefore become the standard of care. The identification of acquired resistance mechanisms to EGFR-TKIs led to the development of third-generation EGFR-TKIs, such as rociletinib and osimertinib (1). Osimertinib is selective for non-small cell lung cancer (NSCLC) patients harboring both EGFR-TKI-sensitizing mutations and the T790M resistance mutation (2).

Osimertinib is associated with various hypersensitivity reactions, including skin rash and urticeria. In a case reported by Makimoto et al., a female patient who had previously received erlotinib and gefitinib developed urticaria

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on the second day after switching to osimertinib therapy. The cutaneous manifestations resolved following discontinuation of the drug and recurred on the third day after reinitiation of treatment. In another reported case, involving a patient with no prior exposure to EGFR-TKI therapy, urticaria developed on the fourth day of osimertinib treatment, approximately 20 hours after the last administered dose (3, 4). In drug hypersensitivity reactions, desensitization is of critical importance in patient management when no alternative drug is available or when alternative therapies are less effective. According to the position paper of the European Academy of Allergy and Clinical Immunology (EAACI) Drug Allergy Interest Group, rapid desensitization is recommended for immediate-type drug hypersensitivity reactions as well as for uncomplicated, non-severe, mild delayed drug reactions (5). Although successful slow desensitization protocols have been reported in the literature, to the best of our knowledge and based on our literature review, rapid desensitization to osimertinib has not previously been described.

Here, we present a patient with immediate type hypersensitivity reaction due to osimertinib who was successfully and rapidly desensitized, allowing continuation of therapy in the absence of alternative treatment options.

CASE REPORT

A 64-year-old female patient was diagnosed with lung adenocarcinoma seven years ago. After completing six cycles of carboplatin-paclitaxel chemotherapy and being found to have a positive EGFR L858R mutation, she was treated with gefitinib for six years. In 2024, while continuing gefitinib treatment, the patient underwent a repeat biopsy due to disease progression and was diagnosed with the EGFR 790M mutation. The patient was started on osimertinib at a dose of 80 mg and tolerated the treatment without any adverse effects for the first three days. On the fourth day, erythematous, edematous wheals were observed on the arms and legs within 3-4 hours after administration of osimertinib (Figure 1). The patient was started on methylprednisolone and antihistamines by her physician, and osimertinib was continued for approximately one week.

During this period, the urticarial lesions persisted, leading to discontinuation of osimertinib. The lesions

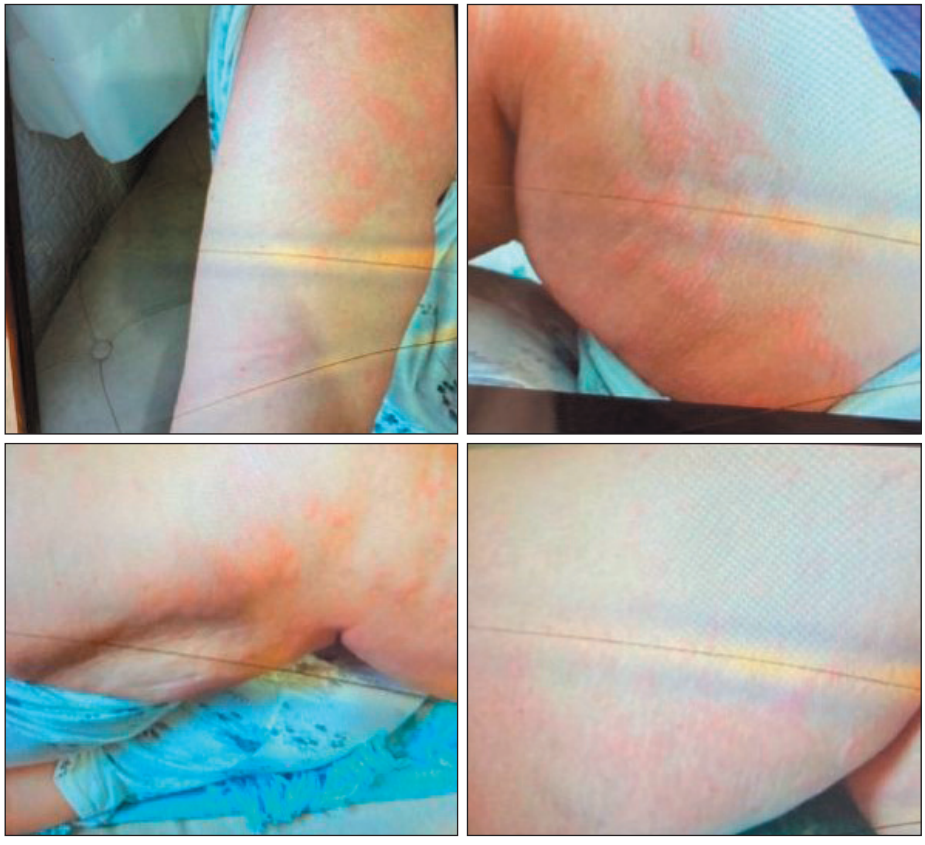

Figure 1: Urticaria developing on the extremities 3-4 hours after osimertinib administration.

completely resolved within the following week. The patient's urticaria was not accompanied by any additional systemic findings. An oncologist was consulted regarding alternative treatment options, and as the patient declined chemotherapy, no alternative treatment was available. Laboratory investigations revealed no abnormalities that could account for the urticaria. A prick-to-prick test with an osimertinib tablet was performed and yielded negative results (positive control: 10 × 12 mm). The patient subsequently underwent a six-step rapid desensitization protocol under bilastine prophylaxis, with 30-minute intervals between each step and a cumulative osimertinib dose of 80 mg (Table I). The solutions were prepared by dissolving the osimertinib tablet in distilled water at 55 °C, without crushing or shaking the tablet. The desensitization procedure was performed under emergency care conditions in our outpatient allergy clinic, including continuous vital sign monitoring, established intravenous access, and the availability of adrenaline for use if required, and was conducted by experienced medical staff. In the event of clinical necessity, an intensive care unit equipped with mechanical ventilation support is available at our institution to ensure the continuation of advanced monitoring and therapeutic management. The patient's vital signs were recorded between each step of the protocol. The patient was observed for two hours after completion of the protocol. No adverse reactions occurred during the procedure, and desensitization was deemed successful. The patient continued osimertinib therapy for a total of six months without complications. Chemotherapy was later resumed due to disease progression. Written informed consent and the permission to publish case report was obtained from the patient.

Table I: Rapid desensitization steps with osimertinib

Step	Dose	Cumulative dose
1	1 ml Solution-B	1 mg
2	3 ml Solution-B	4 mg
3	6 ml Solution-B	10 mg
4	1 ml Solution-A	20 mg
5	2 ml Solution-A	40 mg
6	4 ml Solution-A	80 mg

*Each step was administered sequentially at 30-minute intervals. The solutions were prepared for oral administration. Solution-A: 10 mg/ml (80 mg osimertinib tablet + 8 ml distilled water) Solution-B: 1 mg/ml (1 ml Solution-A + 9 ml distilled water)

DISCUSSION

Most drugs are low-molecular-weight compounds with simple chemical structures and are not readily recognized by cells of the immune system. Due to their small size, they are insufficient to effectively engage immune receptors and activate T and B lymphocytes. Consequently, the majority of drugs are not immunogenic in their native form. Currently, three principal models have been proposed to explain how low-molecular-weight drugs interact with immune receptors to initiate T-cell responses. These include the hapten-prohapten model, the altered peptide repertoire model, and the pharmacological interaction (p-i) model. According to the hapten-prohapten model, small-molecule drugs or their reactive metabolites are incapable of eliciting an immune response on their own; instead, they become immunogenic only after forming covalent bonds with endogenous proteins, thereby generating a novel antigenic determinant capable of triggering immune activation. Accordingly, skin testing may not provide sufficient diagnostic value in confirming the diagnosis. Moreover, a negative skin test result cannot definitively rule out an IgE-mediated hypersensitivity reaction (6, 7). Furthermore, immediate-type hypersensitivity reactions associated with pharmacologic agents may be mediated by IgE antibodies or may arise through non-IgE-dependent mechanisms. Although IgE-mediated reactions necessitate a prior sensitization phase, the clinical manifestations of IgE- and non-IgE-mediated reactions are largely indistinguishable; consequently, delineating the underlying immunopathogenic mechanism is frequently challenging in clinical practice. EGFR-TKIs are also associated with prominent dermatologic adverse events, the most common of which is a papulopustular acneiform eruption (8). As our patient experienced urticaria 3-4 hours after taking osimertinib an immediate type hypersensitivity reaction was considered and she is successfully and rapidly desensitized, allowing continuation of osimertinib therapy.

Few cases of osimertinib desensitization have been reported in the literature, and to our knowledge, none of these involved rapid desensitization.

Makimoto et al. described the implementation of a desensitization protocol for a patient experiencing osimertinib-induced urticaria, which was assessed as a delayed-type hypersensitivity reaction, with a targeted dose of 40 mg. Desensitization was initiated at a starting dose of 0.1 mg/day, with the dose doubled daily, and the protocol was completed over a two-week period (3). In another report,

Solak et al. applied a slow desensitization protocol based on Makimoto et al.'s protocol in a case of osimertinib-induced urticaria, achieving a target dose of 80 mg over 50 days (4). In another case, following the initiation of osimertinib at a daily dose of 80 mg, pruritus and lip angioedema developed approximately 20 hours after the first dose. Subsequently, about 21 hours after the second dose, the patient experienced facial edema, hoarseness, generalized urticaria, abdominal pain, and diarrhea. A successful 30-day desensitization protocol was implemented, beginning with an initial dose of 5 mg/day; the first three days were conducted under inpatient supervision, and the remainder was completed on an outpatient basis at home (9). In contrast, in our case, an immediate-type hypersensitivity reaction was suspected and a rapid desensitization protocol was implemented and successfully completed.

Hirabayashi et al. reported a two-week desensitization protocol with a target dose of 40 mg in a case of osimertinib-induced fever and hepatotoxicity, noting that neither fever nor hepatotoxicity recurred during treatment (10). Watanabe et al. described successful slow desensitization over 16 days in two patients who developed pruritus and toxic erythema associated with osimertinib; however, the details of the desensitization protocol were not provided in their report (11).

Given that our patient developed immediate-type urticarial reaction attributable to osimertinib and rapid desensitization to osimertinib was planned under ongoing antihistamine therapy, a six-step rapid desensitization protocol was applied, adapted from a previously published protocol for crizotinib, another EGFR tyrosine kinase inhibitor (12). Bilastine was chosen as premedication because of its favorable safety and tolerability profile, minimal drug-drug interaction potential, and low incidence of adverse effects (13). To ensure preservation of drug activity during preparation, previously described administration methods for patients receiving osimertinib via a nasogastric tube were reviewed, and the drug solution was prepared according to the technique reported by Takeda et al., by dissolving the tablet in sterile water at 55 °C without crushing it (14).

CONCLUSION

To our knowledge, this is the first case report of successful rapid desensitization with osimertinib in the literature. Antineoplastic drug hypersensitivities are of paramount importance because alternative treatment options with equivalent efficacy are often unavailable. Rapid desensitization with osimertinib may allow continuation of the drug in immediate-type hypersensitivity reactions in appropriate clinical circumstances.

Conflict of Interest

The authors have no relevant financial interests to disclose.

Author Contributions

All authors contributed equally to this article.

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