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CASE REPORT

Two instances of successful oral desensitisation following hypersensitivity reaction in a patient receiving osimertinib: a case report

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Abstract

Background: Osimertinib is an irreversible epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI) and an available therapy for patients with non-small cell lung cancer (NSCLC) that have an EGFR or T790M mutation. It has become the preferred TKI in this patient group as it is superior to first-generation TKIs; however, osimertinib may be discontinued due to various toxicities or reactions.
Aim: We report two instances of successful osimertinib desensitisation in a 70-year-old woman requiring treatment for NSCLC following two hypersensitivity reactions presenting as angioedema and urticaria.
Clinical details: Osimertinib desensitisation started at 5 mg/day and was gradually increased to 80 mg/day over a period of 30 days.
Outcomes: The patient continued osimertinib 80 mg daily for over a year until treatment was withheld for 4 weeks due to thrombocytopenia and diverticulitis. She restarted osimertinib, completing a second desensitisation to a reduced dose of 40 mg daily without serious adverse effect. The patient continues reduced-dose osimertinib with stable disease.
Conclusion: This case report proposes an osimertinib desensitisation strategy useful for select patients experiencing osimertinib-induced hypersensitivity reactions. It also demonstrates that if there is prolonged disruption to treatment, a second desensitisation can be completed successfully in the same patient so effective treatment in NSCLC may be continued.

Keywords: osimertinib, hypersensitivity, desensitisation, non-small cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR), case report.

INTRODUCTION

Osimertinib is a third-generation irreversible epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI) and an available therapy for patients with non-small cell lung cancer (NSCLC) that have an EGFR or T790M mutation. As osimertinib is superior to first-generation TKIs, it has become the preferred TKI for NSCLC patients; however, it may be discontinued due to various toxicities or reactions. To our knowledge, three case reports published in the literature also summarise osimertinib desensitisation; however, none describes angioedema hypersensitivity reactions.[1–3] This case report describes two instances of successful osimertinib desensitisation in a patient requiring treatment for NSCLC following two hypersensitivity reactions presenting as angioedema and urticaria.

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CASE REPORT

Ethics Statement and Consent

Ethical approval was granted by the Far North Queensland Human Research Ethics Committee (Reference no: 1736 CS). The patient's free, prior, and informed consent for publication was obtained and documented in the Journal of Pharmacy Practice and Research consent form.

Case Presentation

A 70-year-old female patient, who was a former-smoker and had a background of peripheral vascular disease and dyslipidaemia was diagnosed with stage 1 lung

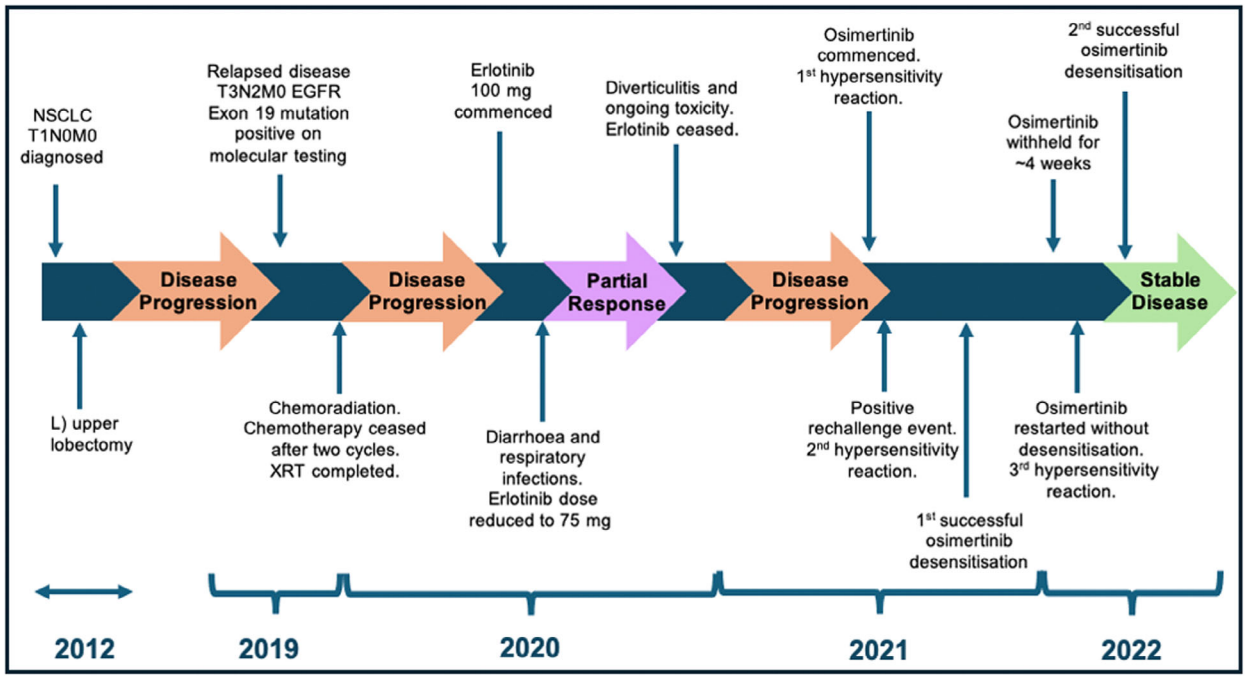

Figure 1 Timeline of patient's clinical course. The figure displays the patient's clinical course incorporating treatment, pathological, and molecular data. EGFR = epidermal growth factor receptor; L = left; NSCLC = non-small cell lung cancer; T1N0M0 = stage 1C lung adenocarcinoma; T3N2M0 = stage 3B; XRT = x-ray telescope.

adenocarcinoma (T1N0M0) in 2012, for which she underwent a left upper lobectomy. Seven years later, she was found to have recurrent stage 3B disease that was EGFR positive and opted for curative intent chemoradiotherapy; however, due to adverse effects, adequate anticancer treatment was not possible. The patient commenced erlotinib 100 mg daily, but this was ceased 3 months later due to severe TKI-induced diarrhoea, diverticulitis, and respiratory infections. The patient was undergoing three-monthly surveillance, which identified evidence of disease progression after 10 months. The decision was made to start osimertinib, a third-generation TKI, as the next line of treatment. She had normal baseline renal and hepatic function.

Clinical Findings

Three days after starting osimertinib 80 mg daily the patient presented with facial swelling, voice changes, throat tightness, and urticaria. Her allergies were recorded as 'sulphur antibiotic – anaphylaxis' on admission. The patient took her first dose of osimertinib around 8 am Tuesday morning. She woke at 5 am on Wednesday morning with mild pruritus and upper lip swelling. She took her second dose of osimertinib at 8 am, then, later that same day, visited her general practitioner, who advised her she was experiencing an allergic reaction and to stop taking osimertinib. The patient woke at 2 am with pruritus but fell back asleep shortly after. Her symptoms worsened into the morning, and at 5 am she had further facial swelling (upper lip, forehead, and periorbital), throat tightness, voice hoarseness, urticarial rash over her face and arms, generalised abdominal pain, and an episode of diarrhoea. She denied any chest tightness, stridor, or breathlessness. The patient was hypertensive (180/98 mmHg), tachycardic (125 bpm), and afebrile. She received one dose of 10 mg loratadine and a 5-day prednisolone course (50 mg per day on days 1 and 2, 37.5 mg on day 3, 25 mg on day 4, 12.5 mg on day 5) to treat her reaction.

Timeline

Diagnostic Assessment

On review, no new allergens (food, medicines, environment, chemicals), prior illness, fevers, or infective symptoms were reported (Figure 1). The patient described her recorded sulphur allergy as swelling and breathing difficulties following an unknown sulphur antibiotic 30 years prior. She reported taking two doses of doxycycline left over from her previous erlotinib treatment when she started to feel unwell; however, these were not effective. The patient had not experienced a reaction to doxycycline previously, but the possibility of allergy

to doxycycline needed to be considered due to the timeline of events.

An inpatient immunology consult concluded that the patient had experienced a delayed but progressive hypersensitivity reaction, and the unusualness of being allergic to osimertinib after the first ever ingestion, unless cross-sensitised by another drug, was acknowledged. A literature search uncovered no reports of similar allergy to osimertinib.

Because the patient had reported sulphur antibiotic allergy, a review of the sulphur-containing mesylate molecule formulated with osimertinib was conducted to determine whether the structure had any cross-reactivity with the most common immunoglobulin E (IgE) epitope of sulfamethoxazole. A pharmacy review, which included consultation with the pharmaceutical company and drug metabolism experts from the Queensland Medicines and Information Advice Service (QMAIS), concluded that the osimertinib molecule and mesylate group did not contain the IgE epitope. Drug metabolism pathways were also explored as this may have explained delayed symptom onset; however, it was concluded that no molecules (active or non-active) created during expected metabolism would contain the IgE epitope.

One month later, the patient was admitted for a planned re-challenge to confirm the reaction to osimertinib. A full dose (80 mg daily) was to be administered and tryptase level taken if any signs of allergy developed. The decision was made to omit pre-medication since the purpose of the re-challenge was to confirm hypersensitivity to osimertinib. The patient took the first dose at 10 am and remained well that day. A second dose was given at 9:30 am the following day, and she remained well until the next morning at 6 am when she experienced pruritus and flushed cheeks. Loratadine 10 mg, hydrocortisone 100 mg intravenous (IV), and Promethazine 12.5 mg IV were given by 7:30 am. A ward call medical review at 8 am noted upper lip and forehead swelling and an urticarial chest rash. A medical oncology review at 9 am noted facial rash and hoarse voice. The patient was hypertensive (175/101 mmHg) and afebrile. Unfortunately, despite the documented plan, no tryptase level was taken. At 10 am, prednisolone 50 mg was administered, and the patient's condition improved throughout the day. The next day, she was discharged after one more dose of 10 mg loratadine and took two more doses of 50 mg prednisolone over the following two days (3-day course in total).

Therapeutic Intervention

A literature review of desensitisation to osimertinib for a similar hypersensitivity reaction was undertaken by the medical oncology and oncology pharmacy team, but no publications were found. Three reports showed successful desensitisation, two relating to hepatotoxicity[1,2] and one for urticarial rash.[3]

The patient was readmitted for a planned desensitisation. She started on osimertinib 5 mg daily as an inpatient and followed the titration plan shown in Figure 2. Education was provided so the patient could safely administer the desensitisation at home to avoid a prolonged hospital stay. Education included supervising the patient disperse osimertinib in water, measure the correct dose using an oral syringe, and administer as per the daily titration plan. After 3 days of education and without further reaction, she was discharged to continue desensitisation as an outpatient. The ward pharmacist provided a daily dosing schedule (Figure 2) for the patient to follow at home. The patient was discharged with loratadine and prednisolone to administer if severe symptoms developed, but she did not require these during the desensitisation period.

Follow Up and Outcomes

The patient continued osimertinib 80 mg daily for 14 months until therapy was withheld due to thrombocytopenia. During the same week, she experienced a severe flare of diverticulitis, which led to an extended treatment break of 4 weeks. After discharge, she restarted osimertinib 80 mg daily without desensitisation. After 2 days, the patient presented to the emergency department with severe nausea and vomiting, which was considered related to her diverticulitis; however, the next morning she had recurrence of pruritus and facial swelling (lips, forehead, and neck). A computed tomography (CT) scan ruled out infective neck collection. The patient received one dose of 10 mg loratadine and four doses of daily IV dexamethasone over 4 days (8 mg on day 1, 8 mg on day 2, 4 mg on day 3, 4 mg on day 4). On discharge, oral dexamethasone was weaned slowly over a 3-week period. The patient was able to complete a second successful desensitisation 2 months later using the same titration schedule to a reduced maximum dose of 40 mg daily to prevent further thrombocytopenia. Her last CT staging scan in December 2023 showed stable disease.

DISCUSSION

Drug hypersensitivity reactions are typically classified into three categories using the Gell-Coombs system (immediate, non-immediate, or delayed). The patient experienced lip angioedema, urticaria, voice hoarseness, and possible gastrointestinal symptoms, which is

Day	Date	Time	Osimertinib (Tagrisso) 80mg in 40mL (=2mg/mL)
Sat	24 Apr 21	0800	5mg (=2.5mL)
Sun	25 Apr 21	0800	5mg (=2.5mL)
Mon	26 Apr 21	0800	8mg (=4mL)
Tue	27 Apr 21	0800	8mg (=4mL)
Wed	28 Apr 21	0800	8mg (=4mL)
Thu	29 Apr 21	0800	10mg (=5mL)
Fri	30 Apr 21	0800	10mg (=5mL)
Sat	01 May 21	0800	10mg (=5mL)
Sun	02 May 21	0800	15mg (=7.5mL)
Mon	03 May 21	0800	15mg (=7.5mL)
Tue	04 May 21	0800	15mg (=7.5mL)
Wed	05 May 21	0800	20mg (=10mL)
Thu	06 May 21	0800	20mg (=10mL)
Fri	07 May 21	0800	20mg (=10mL)
Sat	08 May 21	0800	30mg (=15mL)
Sun	09 May 21	0800	30mg (=15mL)
Mon	10 May 21	0800	30mg (=15mL)
Tue	11 May 21	0800	40mg (=20mL)
Wed	12 May 21	0800	40mg (=20mL)
Thu	13 May 21	0800	40mg (=20mL)
Fri	14 May 21	0800	50mg (=25mL)
Sat	15 May 21	0800	50mg (=25mL)
Sun	16 May 21	0800	50mg (=25mL)
Mon	17 May 21	0800	60mg (=30mL)
Tue	18 May 21	0800	60mg (=30mL)
Wed	19 May 21	0800	60mg (=30mL)
Thu	20 May 21	0800	70mg (=35mL)
Fri	21 May 21	0800	70mg (=35mL)
Sat	22 May 21	0800	70mg (=35mL)
Sun	23 May 21	0800	80mg (=40mL) **Continue this dose ongoing**

Figure 2 Osimertinib desensitisation titration schedule. Solution made daily by dissolving 80 mg tablet in 40 mL water to make a 2 mg/mL solution.

indicative of a moderate–severe hypersensitivity reaction. The planned treatment re-challenge confirmed and helped characterise features of her osimertinib reaction. The timing of the reaction was hard to identify due to limitations of the clinical history and the possibility that the reaction onset occurred while the patient was asleep.

The authors recognise that the reaction presented in this case is unusual and difficult to categorise using conventional classification methods. Given there was no clear airway involvement, the reaction is speculated to be non-immunoglobulin E (non-IgE) mediated.

In people with normal renal and hepatic function, osimertinib and the active metabolites AZ7550 and AZ5104 all have prolonged half-lives of approximately 48 h, 52 h, and 72 h respectively.[4] The suspected mechanism driving this reaction is through direct interaction of osimertinib or its metabolites with mast cells and basophils. Cytochrome P450 3A4 (CYP3A4) is reported to be the major enzyme responsible for osimertinib metabolism, and there can be vast variability of hepatic enzyme levels between individuals. The timeline of these reactions suggests there may be a 'threshold' dose of osimertinib and/or its metabolites due to the prolonged half-lives. The clinical response to antihistamines and steroids suggests a typical urticarial and angioedema reaction with histamine and bradykinin mediators involved, but this does not entirely inform the mechanism.

Learning the patient required repeat desensitisation after an extended treatment break due to a loss of her temporary tolerant state was an important finding. We would recommend repeating desensitisation in patients who have osimertinib hypersensitivity and treatment breaks longer than 6 days (three half-lives).

No detailed clinical data or guidelines have been published for TKI desensitisation. Based on previous successful case reports[1-3] and the speculated mechanism of hypersensitivity, it was decided desensitisation would be appropriate for our patient. Our dosing schedule was developed carefully using the information found in these reports. The reactions in previous case reports were less severe (hepatotoxicity, urticaria) than in our patient, so admission and increased inpatient monitoring were implemented as additional safety measures.

Due to the lack of cross-reactivity between sulfonylarylamine antibiotics and medications containing sulfate groups like mesylate, sulfonamide hypersensitivity was deemed an unlikely mechanism in this case. Although the possibility of unknown metabolites containing immunogenic sulfonylarylamine groups theoretically still exists, it is unlikely based on understood metabolism pathways. Until more is known, patients with serious sulfonylarylamine allergies could be considered for sulfonamide allergen testing on an individual basis if they require treatment with osimertinib.

This case report demonstrates successful osimertinib desensitisation for angioedema hypersensitivity reactions using oral dose titration. It supports the current literature surrounding osimertinib and shows desensitisation can be undertaken on at least two occasions and should be repeated when extended treatment break is required. Osimertinib is the gold standard approach for the treatment of NSCLC, and desensitisation should be recommended to patients experiencing hypersensitivity reactions to allow continuation of treatment.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

AUTHORSHIP STATEMENT

Georgia D. Bennett: Conceptualisation; methodology; writing – original draft; writing – review and editing; visualisation. **Krysti Rosmalen-Brinkley:** Methodology; writing – review and editing. **Kristoffer Johnstone:** Writing – review and editing; supervision. **Genevieve Messina:** Writing – review and editing; supervision.

ETHICS STATEMENT

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PATIENT CONSENT STATEMENT

The patient's free, prior, and informed consent for publication was obtained and documented in the *Journal of Pharmacy Practice and Research* consent form.

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OPEN ACCESS STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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