A case report of an adverse drug reaction with a combination of oxaliplatin and perindopril

Christina Okello

ABSTRACT

Introduction: Oxaliplatin is a third-generation platinum compound that is used as a single agent and in combination with fluorouracil (5-FU) to treat a variety of solid organ cancers. Patients treated with Oxaliplatin may develop hypersensitivity reactions. Angiotensin-converting enzyme inhibitors (ACEI) are established to have multiple cardiovascular benefits. Recent studies also suggest that ACEI may have a role in preventing Oxaliplatin-induced peripheral neuropathy.

Case Report: We present a case of a patient who presented with adverse reactions on two separate occasions. At the time of the first reaction he had been on an ACEI (Perindopril), which he had used for four years for management of hypertension and was within hours of receiving the seventh cycle of adjuvant modified Fluorouracil, Leucovorin, Oxaliplatin (FOLFOX-6) for ypT3N0 rectal adenocarcinoma. On the second episode, he presented with a reaction before his eighth cycle of chemotherapy, while still taking the ACEI. Determination of the cause of the reactions was challenging and management involved switching from Perindopril to a calcium channel blocker (Amlodipine) and Oxaliplatin desensitization. The patient was able to complete chemotherapy treatment with no further reactions.

Conclusion: The combination of Perindopril with Oxaliplatin could increase the risk of adverse reactions. These adverse reactions could be managed by substituting Perindopril with a calcium channel blocker and use of an Oxaliplatin desensitization protocol.

Keywords: Adverse drug reactions, Oxaliplatin and ACEI, Oxaliplatin hypersensitivity

INTRODUCTION

Colorectal cancer is the third most common cancer in the world [1] and Oxaliplatin represents a key chemotherapeutic agent in its management. Oxaliplatin is a third-generation platinum compound with a 1,2 diamino cyclohexane carrier ligand, and is used as a single agent or in combination with fluorouracil (5-FU) to treat several cancers.

Its acute toxicities include myelosuppression, peripheral sensory neuropathy and hypersensitivity reaction [2]. Hypersensitivity reactions (HSRs) are a very rare adverse effect of Oxaliplatin, but the incidence increases with multiple cycles of therapy [3]. With improved outcomes in cancer care, longer patient survival and extended treatment courses, patients are exposed to drugs for longer periods, increasing the risk of sensitization and of HSRs [4].

Angiotensin-converting enzyme inhibitors are well known for their cardiovascular benefits. A recent study has shown that they may also have a role in preventing Oxaliplatin-induced peripheral neuropathy [5]. These inhibitors have been described as augmenting factors in anaphylactic reactions according to several studies [6–9]. Most reactions to ACEI occur within the first week or month of initial therapy and often within hours of the initial dose [10]. However, some cases may occur years after therapy has begun [11, 12].
CASE REPORT

We report about a 54-year-old male patient who had a background of ypT3N0 rectal adenocarcinoma on first line adjuvant chemotherapy with modified FOLFOX-6 who was also on perindopril daily for four years for management of hypertension. He presented having spontaneous onset facial swelling that began within one to two hours following cycle 7 of chemotherapy.

This episode began spontaneously and manifested as marked swelling of the lips and the face with minimal involvement of the tongue lasting about 12 hours (Figure 1). He had no rashes or itching. He had previously tolerated other cycles of chemotherapy reasonably well and mainly reported fatigue, diarrhea, and grade 1 intermittent peripheral neuropathy. He had no history of exposure to platinum agents. His only regular medication was Perindopril which he had used for four years without any side effects. He had no known allergies to medications but reacted to bee stings. He reported 3–4 lifetime episodes of localized reactions after bee stings. The last reaction was two years prior and responded to intramuscular antihistamines.

His observations were stable. An impression of acute Oxaliplatin hypersensitivity was made. This episode resolved spontaneously with dexamethasone.

An extensive discussion was held between the patient and the oncologist at an outpatient review regarding the risks of severe anaphylaxis and the benefits of continuing treatment and a decision was made for immunological evaluation and possible Oxaliplatin desensitization.

There was a slight delay in commencement of the eighth cycle of chemotherapy two weeks later, as the patient had an upper respiratory tract infection.

He presented to the emergency department with sudden onset tongue swelling two and a half weeks after the 7th cycle of chemotherapy. The tongue swelling began spontaneously and rapidly progressed over a duration of thirty minutes. He denied any shortness of breath or chest tightness but had dysphagia and hoarseness of voice. He had no associated fever, rash or itch and denied any new potential allergen exposure or medication changes. He reported being only on Perindopril for hypertension.

His observations were stable. On examination he was noted to have marked unilateral left lip and tongue swelling (Figure 2), a hoarse voice and coated tongue. Adrenaline, antihistamines, and steroids were administered with complete resolution of symptoms. The patient was admitted overnight for observation. Perindopril was switched to amlodipine due to suspected ACEI angioedema.

Blood tests requested for follow up revealed a normal level of C1 esterase inhibitor, mildly elevated level of C3 (199), C4 (0.4), and fibrinogen (5.9). His C-reactive protein (CRP) was 13 suggestive of an acute phase reaction. The rest of his blood tests were unremarkable. He was discharged with two Epinephrine autoinjector pens and an anaphylactic action plan in case of recurrence.

At this stage the patient and oncology team revisited the potential causes of angioedema, the unpredictable nature of these episodes, the risks and benefits and the patient was still keen to proceed with chemotherapy in a monitored setting with a view to discontinue in case of further reactions.

He was commenced on the eighth cycle of chemotherapy/Oxaliplatin (88.6364 mg/m²) desensitization a week later in an inpatient setting.

Oxaliplatin was given as per the desensitization protocol and antihistamines and steroids included as part of premedication. He had no other reactions and successfully completed 12 cycles of chemotherapy.
DISCUSSION

Our patient was a 58-year-old male receiving the seventh cycle of first line adjuvant chemotherapy for colorectal cancer who initially developed an adverse reaction within hours of an Oxaliplatin infusion. According to various studies hypersensitivity to Oxaliplatin is more common in certain populations such as women, younger patients (mean age, 56.2 years) and patients who had experienced a prior exposure to platinum salts [4, 13].

Incidence rates for Oxaliplatin hypersensitivity reactions have been reported to vary from 2–25%, and some reports indicate hypersensitivity treatment discontinuation rates up to 21% [14]. Oxaliplatin causes a wider variety of immediate hypersensitivity reactions than do other platinum-based chemotherapeutics. Some resemble type 1 reactions and respond to desensitization, as in this case. Others are atypical, possibly mast cell-independent cytokine release reactions refractory to desensitization [15].

Oxaliplatin allergy can manifest as a skin rash, itching, swelling of the lips, face or throat, breathing difficulties, fever and chills [16]. Hypersensitivity reactions typically result from an immunoglobulin E (IgE)/mast cell-mediated action [14]. Moreover they are IgE mediated. Oxaliplatin HSRs occur only after repeated exposure to the drug with some studies citing the highest risk being after six prior infusions of Oxaliplatin [14, 17]. In this case, our patient developed swelling of the lips after the seventh course of treatment and was suspected to be related possibly to Oxaliplatin hypersensitivity.

He had a history of allergy to bee stings responsive to anti-histamines. A study showed that patients with a history of atopy and an initial type 1 reaction respond to desensitization with antihistamine pre-medications, whereas non-atopic patients with the same initial reaction phenotype are more likely to convert to a cytokine release or mixed reaction during desensitization [15]. In this case, antihistamines were included as part of the desensitization protocol with a good outcome.

Interestingly, our patient re-presented with tongue swelling two and a half weeks later suspected to be related to ACEI/Perindopril angioedema. The symptoms responded to adrenaline, antihistamines, and steroids. He had been on Perindopril for four years with no reactions. The pathophysiology of ACEI-induced angioedema involves inhibition of bradykinin and substance P degradation by ACE (kinase II) leading to vasodilator and plasma extravasation [18]. Angioedema can involve any area of the body. It is usually a benign condition, but can cause respiratory distress and death if severe laryngeal edema occurs [19].

The presentation of both reactions in this patient presented a diagnostic challenge as the patient was on both treatments concurrently. We were able to rule out an acquired C1 esterase deficiency by laboratory testing. However, due to the overlap of presentation of allergy symptoms after using both treatments it was difficult to conclusively determine what the primary trigger was. Therefore, a decision was made to adjust both treatments. After switching from Perindopril to Amlodipine and putting the patient on an Oxaliplatin desensitization protocol there were no more adverse events. Angiotensin-converting enzyme inhibitors (ACEI) have been described as augmenting factors in anaphylactic reactions [6] and therefore avoiding them in patients on Oxaliplatin may be one way of reducing the incidence of adverse reactions.

CONCLUSION

The combination of Perindopril and Oxaliplatin could increase the risk of adverse events in patients. These adverse reactions could be managed by substituting Perindopril with a calcium channel blocker and use of an Oxaliplatin desensitization protocol.

REFERENCES

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Author Contributions
Christina Okello – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Author declares no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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