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Case Report

## Oxaliplatin induced laryngospasm: a case series

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### ABSTRACT

Oxaliplatin is a third-generation platinum derivative used as a first-line agent in the treatment of colorectal carcinoma, biliary tract cancer and gastric cancers and can be used as a neoadjuvant/adjuvant in these cancers. The dose limiting toxicity is peripheral neuropathy, others include hypersensitivity reactions, haematological toxicity and pulmonary fibrosis. Hypersensitivity reactions can extend from milder reactions like urticaria, rash to severe symptoms like hypotension and laryngospasm. The laryngospasm due to oxaliplatin is reported to be reversible with corticosteroids, antihistamines and oxygen. This case series suggest that oxaliplatin has a propensity to cause severe hypersensitivity reaction presenting as laryngospasm not with a single dose but with subsequent doses of oxaliplatin. Prompt symptomatic treatment with corticosteroids leads to reversal of symptoms and improvement in the condition of the patient.

**Keywords:** Oxaliplatin, Hypersensitivity, Laryngospasm

### INTRODUCTION

Oxaliplatin is a third generation platinum compound, the other earlier generation platinum compounds being cisplatin and carboplatin.<sup>1</sup> The main indications for oxaliplatin are biliary tract carcinoma, breast carcinoma, colorectal carcinoma, gastric carcinoma, head and neck carcinoma, mesothelioma and non-Hodgkin lymphoma (NHL). It is usually combined with 5-fluorouracil (5-FU), capecitabine, irinotecan, or cyclophosphamide.<sup>2</sup> It is a non-cell cycle specific alkylating agent that causes abnormal crosslinking or cutting of DNA strands and eventually leading to cell death.<sup>3</sup>

The major adverse effects with the platinum compounds may vary from, nephrotoxicity with cisplatin, bone marrow suppression with carboplatin to peripheral neuropathy with oxaliplatin. Acute and chronic neurotoxicity following oxaliplatin is a major constraint, leading to dose reduction, treatment delays and cessation of therapy.<sup>4</sup> Oxidative stress and mitochondrial

dysfunction are said to be the main factors responsible for neuropathy due to platinum compounds. Symptoms most commonly occur with a cumulative dose of 780 mg/m<sup>2</sup>.<sup>4</sup>

The other adverse outcomes include hypersensitivity reactions, haematological toxicity and pulmonary fibrosis. The hypersensitivity reactions can occur either during, or shortly after the infusion of drug. The incidence increases with increase in the number of chemotherapy cycles. Hypersensitivity reactions can vary from mild reactions like rashes to severe reactions, which include laryngospasm, tachycardia, hypotension or hypertension.<sup>5</sup> These hypersensitivity reactions are usually type I in nature. The incidence of laryngospasm is reported to be less compared to the other adverse effects due to drug.<sup>1</sup> Hence, we are reporting a case series of 3 cases of laryngospasm following oxaliplatin combination therapy in various cycles of treatment for various carcinomas from the Department of Radiotherapy, Government Medical College, Kozhikode, Kerala in a period of four months.

## CASE REPORT

### Case 1

A 59 year old female presented with complaints of bleeding per rectum and lower abdominal pain in surgery outpatient department. She was diagnosed with adenocarcinoma rectum after the rectal growth biopsy.

The patient was started on chemotherapy with CapOx regimen (capecitabine and oxaliplatin). First dose of chemotherapy was started on 10<sup>th</sup> December 2018 with injection oxaliplatin 130 mg/m<sup>2</sup> as an intravenous infusion of two hours and tablet capecitabine 675 mg three tablets in the morning and two tablets at night for 14 days. Patient tolerated the first dose well with no adverse reactions reported. The second dose of chemotherapy was administered on 31<sup>st</sup> December with an increased dose of injection oxaliplatin 160 mg/m<sup>2</sup> and tablet capecitabine in the same dose as first chemotherapy, which was also uneventful.

When the third dose of chemotherapy with injection oxaliplatin at a still higher dose of 190 mg/m<sup>2</sup> as two hour infusion with oral capecitabine was administered, the patient developed shivering and breathlessness with stridor immediately after the infusion. She was treated with injection hydrocortisone along with supplemental oxygen and the patient showed an improvement after two hours with an increase in oxygen saturation.

### Case 2

A 60 year old female presented in the surgery outpatient department with a history of increased frequency of bowel movements and blood in stools associated with weight loss. Colonoscopy revealed a neoplasm of sigmoid colon with biopsy confirming the diagnosis of carcinoma sigmoid colon. She was planned on neo adjuvant chemotherapy followed by adjuvant chemotherapy.

She was treated with CapOx regimen with injection oxaliplatin 190 mg/m<sup>2</sup> as an intravenous infusion of two hours and tablet capecitabine 500 mg three tablets in the morning and at night. The first, second and third cycles of neo adjuvant chemotherapy, with the same doses, was tolerated well by the patient. In April 2019, she underwent sigmoidectomy with uretero ureterostomy with duodenal-jejunal stent. The post-operative period was uneventful. Adjuvant chemotherapy was started the same month with the same dose of CapOx which was tolerated well by the patient. In the second cycle of adjuvant chemotherapy with oxaliplatin injection at a dose of 190 mg/m<sup>2</sup>, she developed acute breathlessness with stridor. Evaluation of the patient revealed fall in oxygen saturation and elevated blood pressure. She was immediately managed with supplemental oxygen and injection hydrocortisone and she responded well to the treatment.

### Case 3

A 48 year old female presented with complaints of abdominal pain and blood in stool and was diagnosed histopathologically as a case of rectosigmoid carcinoma. She underwent surgery and was started on adjuvant chemotherapy with 5-FU, leucovorin and oxaliplatin (FOLFOX regime). The first dose of chemotherapy with a dose of oxaliplatin of 85 mg/m<sup>2</sup> was tolerated well by the patient. As she developed allergic skin reactions which was most probably due to 5-FU, the regimen was changed to CapOx with injection oxaliplatin 130 mg/m<sup>2</sup> as two hour intravenous infusion and tablet capecitabine 500 mg twice daily for two weeks. The first dose of CapOx was well tolerated by the patient. During the second dose of CapOx therapy, she developed shivering and breathlessness with stridor immediately after the infusion. This reaction was managed with administration of injection hydrocortisone, pheniramine maleate along with supplemental oxygen and the patient improved with an increase of oxygen saturation to 95%.

## DISCUSSION

Oxaliplatin is administered along with 5-fluorouracil (FOLFOX) and capecitabine (CapOx) for colorectal and sigmoid carcinomas.<sup>6</sup> The CapOx regimen includes administration of injection oxaliplatin as an intravenous infusion on day 1 and oral capecitabine twice daily continued for two weeks. It is given in 8 cycles, each cycle repeated every 21 days. The usually encountered adverse reaction is peripheral neuropathy which can be acute or chronic.<sup>7</sup>

Hypersensitivity reactions to oxaliplatin, which are type I in nature, have been reported in about 10-25% of cases, whereas cases of severe hypersensitivity reported is only 0.5%.<sup>1,7,8</sup> Features of hypersensitivity reactions include minor reactions like rash, urticaria, flushing, itching, abdominal cramps, diarrhoea, and back pain and severe symptoms can manifest as tachycardia, bronchospasm, stridor, dysphonia, hypotension or hypertension and seizures.<sup>9</sup> The incidence of laryngospasm due to oxaliplatin, is less when compared to other adverse effects but can be fatal if not diagnosed and managed early.

Prompt identification and immediate treatment can reverse the symptoms leading to patient improvement and better tolerability of these regimens. Treatment include maintenance of oxygen saturation with supplemental oxygen, suppression of inflammation with parenteral steroids and counteracting the effects of histamine with parenteral antihistamines.<sup>1</sup>

The hypersensitivity reactions can be minimised by increasing the infusion time from two hours to six hours.<sup>5</sup> Administration of intravenous calcium gluconate and magnesium sulphate, 1 g each, just before the oxaliplatin infusion is reported to decrease the incidence of acute

neurotoxicity as well as laryngospasm especially pseudolaryngospasm.<sup>10</sup>

## CONCLUSION

This case series suggest that oxaliplatin has a propensity to cause severe hypersensitivity reactions manifesting as laryngospasm with subsequent doses of infusion and not with a single dose. Prompt recognition of this event and symptomatic treatment with supplemental oxygen and corticosteroids and prolonging the infusion time of oxaliplatin can lead to better patient compliance and lesser hypersensitivity reactions to these regimens.

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