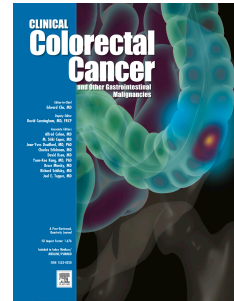


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Immediate and delayed hypersensitivity reactions to a single dose of oxaliplatin

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## **Immediate and delayed hypersensitivity reactions to a single dose of oxaliplatin**

### **Clinical Practice Points**

- Hypersensitivity reactions, occurring during or immediately following oxaliplatin infusions, are well documented and more commonly occur after multiple courses of therapy
- A 69-year old Caucasian woman with stage III colon cancer commenced adjuvant chemotherapy with oxaliplatin and capecitabine. Ten minutes after the completion of the oxaliplatin infusion she experienced a severe hypersensitivity reaction. Following treatment with corticosteroids, anti-histamines and bronchodilators symptoms resolved. Nineteen hours later, a similar reaction occurred.
- A review of the literature found two similar cases of delayed reactions to oxaliplatin occurring 20 and 10 hours after infusion respectively. The first case occurred after the initial dose and again with cycle 2. The second case happened following the sixth infusion.
- This is the first reported case of immediate and delayed hypersensitivity reactions occurring following the initial dose of oxaliplatin.

**Keywords:** Bronchospasm; chemotherapy; hypersensitivity reaction; initial dose; oxaliplatin

### **Introduction**

Oxaliplatin is a third-generation platinum compound widely used in combination with fluoropyrimidine agents in the treatment of colorectal cancer and a variety of other malignancies. Like other platinum agents, oxaliplatin is associated with hypersensitivity

reactions (HSR). The overall incidence of HSR is 13%, with the rate of severe reactions approximately 0.5%.<sup>1</sup> HSR following oxaliplatin may occur within minutes of its administration and with any cycle of therapy. The incidence increases with multiple courses of therapy, indicating that prolonged exposure to oxaliplatin has a role in patient sensitization.<sup>2</sup> In a recent case series analysis, life-threatening severe anaphylactic reactions (SAR) to oxaliplatin were defined as side effects including symptomatic bronchospasm, allergy-related edema/angioedema, hypotension or anaphylaxis requiring hospitalization and medical intervention.<sup>3</sup> In addition to the 8 patients from this case series, a literature review of 23 English language retrospective studies from 1997 to 2011, identified 59 further cases.<sup>3</sup> The median cycles of oxaliplatin given before SAR developed was 10 (range, 2-29). Three fatalities (4.5%) were reported. We wish to report an unusual presentation of hypersensitivity to the initial dose of oxaliplatin, consisting of severe respiratory symptoms which occurred immediately after completion of the infusion and recurred again 19 hours later.

### **Case Report**

A 69-year old Caucasian woman underwent a left hemicolectomy for a non-obstructing mass in the caecum. Histology showed a moderately differentiated adenocarcinoma extending through the bowel wall into the sub-serosa. Two of 9 sampled lymph nodes contained metastatic carcinoma. There was no evidence of metastatic disease on staging. Medical history included asthma, osteoarthritis and anxiety. Her only medications were salbutamol and temazepam, both only as required. There was no history of allergies. Adjuvant chemotherapy for Stage III disease was commenced with XELOX (oxaliplatin 130 mg/m<sup>2</sup> IV and capecitabine 1000 mg/m<sup>2</sup> given orally twice a day for 14 days); repeated every 3 weeks. Ondansetron and dexamethasone were prescribed for 3 days as anti-emetics. Ten minutes after completion of the 2 hour infusion of oxaliplatin, the patient complained of tightness in the throat and severe shortness of breath. Stridor and swelling of the lips were observed.

Blood pressure was slightly elevated. Bronchospasm and laryngeal spasm were diagnosed and immediate treatment with hydrocortisone 100 mg IV given. Following promethazine 12.5 mg IV and a further 100mg IV of hydrocortisone, symptoms quickly resolved. Nebulized salbutamol and ipratropium were administered. No potential precipitating factors, such as cold drinks, were noted. The patient was admitted overnight for observation. Next morning, 19 hours after completion of the oxaliplatin infusion, a similar, though less severe, episode occurred. Symptoms included difficulty in breathing, hoarse voice and swelling of the tongue. Following treatment with IV promethazine, symptoms resolved. Dexamethasone, for prevention of nausea, and nebulized ipratropium had been given several hours before and these may have contributed to the less severe presentation. The only other medication taken was a single dose of capecitabine given 4 hours prior to the HSR. Standard haematological and biochemical blood tests taken following the reactions showed no abnormalities. Unfortunately IgE and tryptase levels were not measured at the time of the reactions. She recovered well with no subsequent problems. The patient refused further treatment with oxaliplatin and declined all other adjuvant chemotherapy options.

### **Discussion**

HSR to oxaliplatin are rarely seen following the first administration of the drug. In a retrospective review of 1224 patients exposed to oxaliplatin-containing chemotherapy regimens, Polyzos et al reported 308 cases of hypersensitivity, with 113 termed severe.<sup>4</sup> Only 5 patients (0.4%) developed an acute severe reaction during the first three courses of treatment.

Two similar cases of HSR, with a delayed presentation after oxaliplatin administration, have been reported in the literature. An 81-year old Caucasian woman was treated with XELOX for metastatic colorectal cancer. Twenty hours after the first infusion of oxaliplatin, she acutely developed serious dyspnoea with an inspiratory stridor and peripheral

cyanosis.<sup>5</sup> Following pre-medication with dexamethasone and anti-histamines, a second cycle of oxaliplatin was administered over 6 hours without incident. However, 20 hours later the same reaction with dyspnoea and stridor again occurred. Further treatment with oxaliplatin was discontinued. A 46-year old man with metastatic colorectal cancer received five courses of combination chemotherapy with oxaliplatin without incident. However, following the sixth dose he experienced a delayed severe HSR reaction.<sup>6</sup> Ten hours after oxaliplatin administration, the patient developed dysesthesia and laryngeal spasm. Symptoms progressively regressed without treatment. Successful re-challenge with oxaliplatin was achieved with an increase in dilution and infusion time.

Because HSR reactions to platinum compounds are usually seen after multiple cycles, the mechanism is thought to be due to a Type I response, mediated by IgE.<sup>3,7</sup> Immune-mediated thrombocytopenia and haemolytic anemia have also been reported with oxaliplatin indicating a Type II hypersensitivity mediated by IgG and IgM.<sup>7-10</sup> IgG mediated Type III reactions, resulting in symptoms such as chronic uricaria and fever, have been documented<sup>7</sup>. Delayed reactions which can occur hours or even days after an oxaliplatin infusion have been reported. These are Type IV HSR mediated through T-cells and can present as contact dermatitis.<sup>12</sup>

The exact mechanism of our patient's reaction is unclear, but may involve immune-mediated and non-immunologic mechanisms possibly including Type I and Type IV HSR.<sup>7,8</sup> Prick and intradermal skin tests have been beneficial in detecting drug-specific IgE with platinum salts.<sup>8</sup> Skin testing was deemed unnecessary in our patient as we didn't intend to continue oxaliplatin therapy and the possible risk of anaphylaxis which has been reported following skin testing.<sup>14</sup> It has also been postulated that excess serotonin may play a role in inducing bronchospasm through serotonin receptors I and II.<sup>15</sup>

Strategies such as premedication with corticosteroids and antihistamines and prolongation of the infusion rate have been used to prevent SAR after oxaliplatin use.<sup>3,16</sup> Desensitization protocols have also been employed successfully.<sup>16-18</sup> However, despite these interventions, reactions have still occurred. Prior to making her decision to cease adjuvant chemotherapy, our patient was made fully aware of the options for continuing oxaliplatin-based chemotherapy and the potential risk of further serious and even fatal HSR even with preventative strategies. She was also given the option of continuing chemotherapy without oxaliplatin using single agent treatment with capecitabine or infusional fluorouracil and understood the potential survival benefits.

### **Conclusion**

This is the first reported case of an immediate acute HSR with the initial dose of oxaliplatin followed by a similar delayed reaction 19 hours later. Due to the increasing clinical use of oxaliplatin in the adjuvant and metastatic settings, clinicians should be aware of this unusual, potentially life-threatening HSR presentation.

### **References**

1. Lee C, Gianos M, Klaustermeyer WB. Diagnosis and management of hypersensitivity reactions related to common chemotherapy agents. *Ann Allergy Asthma Immunol* 2009; 102:179-87.
2. Syrigou E, Syrigos K, Saif MW. Hypersensitivity reactions to oxaliplatin and other antineoplastic agents. *Curr Allergy Asthma Rep* 2008; 8:56-62.
3. Wang JH, King Tm, Chang MC, Hsu CW. Oxaliplatin-induced severe anaphylactic reactions in metastatic colorectal cancer: Case series analysis. *World J Gastroenterol* 2012; 18:5427-33.



4. Polyzos A, Tsavaris N, Gogas H et al. Clinical features of hypersensitivity reactions to oxaliplatin: a 10-year experience. *Oncology* 2009; 76:36-41.
5. De Vries RS, Mattijssen EJ, van Sorge AA. Serious delayed hypersensitivity reaction to oxaliplatin. *Ann Oncol* 2006; 17:1723-4.
6. Potenza S, Nasti G, Alessandro O, Filipelli A, Rossi F, Capuano. Severe respiratory symptoms to oxaliplatin infusion: a case report of delayed hypersensitivity reaction. *Invest New Drugs* 2010; 28:185-6.
7. Makrilia N, Syrigou E, Kaklamanos I, Manolopoulos L, Saif MW. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. *Met-Based Drugs* 2010; 2010:20708.
8. Pagani M. The complex clinical picture of presumably allergic side effects to cytostatic drugs: Symptoms, pathomechanism, reexposure and desensitization. *Med Clin North Am* 2010; 94: 835-52.
9. Maindault-Goebel F, Andre T, Tournigand C et al. Allergic-type reactions to oxaliplatin: retrospective analysis of 42 patients. *Eur J Cancer* 2005; 41: 2262-7.
10. Bautista MA, Stevens WT, Chen CS, Curtis BR, Aster RH, Hsueh CT. Hypersensitivity reaction and immune-mediated thrombocytopenia from oxaliplatin: two case reports and a review of the literature. *J Hematol Oncol* 2010; 3: 12.
11. Cobo F, De Celis G, Pereira A, Latorre X, Pujadas J, Albiol S. Oxaliplatin-induced immune hemolytic anemia: a case report and review of the literature. *Anticancer Drugs* 2007; 18: 973-6.
12. Ichikawa Y, Goto S, Hirokawa S et al. Allergic reactions to oxaliplatin in a single Institute in Japan. *Japan J Clin Oncol* 2009; 39; 616-20.
13. Vilee C, Tennstedt D, Marot L, Goossens A, Baeck M. Delayed urticarial with oxaliplatin. *Contact Derm* 2010; 63: 50-3.

14. Martin-Lazaro J, Firvida JL, Berges-Gimeno P. Anaphylaxis after oxaliplatin allergy skin testing. *J Investig Allergol Clin Immunol* 2014; 24: 267-85.
15. Lee MY, Yang MH, Liu JH et al. Severe anaphylactic reactions in patients receiving oxaliplatin therapy: a rare but potentially fatal complication. *Support Care Cancer* 2007; 15:89-93.
16. Lee SY, Kang HR, Song WJ, Lee KH, Han SW, Cho SH. Overcoming oxaliplatin hypersensitivity: different strategies are needed according to the severity and previous exposure. *Cancer Chemother Pharmacol* 2014; 73: 1021-9.
17. Syrigou E, Karapanaagiotou EM, Alamara CV, Boura PG, Saif MW, Syrigos KN. Hypersensitivity reactions to oxaliplatin: a retrospective study and the development of a desensitization protocol. *Clin Colorectal Cancer* 2009; 8:106-9.
18. Cortijo-Cascajares S, Nacle-Lopez I, Garcia-Escobar I et al. Effectiveness of oxaliplatin desensitization protocols. *Clin Transl Oncol* 2013; 15:219-25.