



Atypical presentation of fever as hypersensitivity reaction to oxaliplatin

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Abstract

Oxaliplatin, a third-generation, platinum-based agent is widely used, most commonly in the FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) regimen, which is the first-line therapy in metastatic colorectal adenocarcinoma and adjuvant chemotherapy in stage III colorectal cancer. Platinum-based products are well known for causing hypersensitivity reactions. Fever associated with oxaliplatin-hypersensitivity reactions typically follows a specific pattern. It usually starts during the oxaliplatin infusion or immediately after (within hours instead of days) and happens after several administrations (mean 2–25) with unpredictable clinical presentations. We report a case of oxaliplatin-induced hypersensitivity reaction manifesting as fever but with unusual presentation than the aforementioned features.

Keywords

Oxaliplatin, hypersensitivity reaction, fever

Introduction

Oxaliplatin, a third-generation, platinum-based agent that possesses 1,2-diaminocyclohexane carrier and oxalate ligand¹ is widely used, most commonly in the FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) regimen, which is the first-line therapy in metastatic colorectal adenocarcinoma and adjuvant chemotherapy in stage III colorectal cancer.² It is also part of XELOX³ (capecitabine and oxaliplatin) regimen for the treatment of metastatic gastric and colorectal cancers. More recently, oxaliplatin has shown benefits in local colorectal carcinoma, gynecological and other gastrointestinal malignancies like pancreatic and gall bladder carcinomas.^{4,5}

Platinum-based products are notorious for causing hypersensitivity reactions (HSR). HSR is defined as an unexpected reaction that cannot be explained by known toxicity profile of chemotherapy agent.⁶ It can happen either during (acute reaction) or following (delayed reaction) administration of the drug. The incidence of HSR to oxaliplatin ranges between 10% and 23.8%,^{7–15} although very few of these are severe (grade 3–4 reactions) cases (0.5–2%).^{16–18} HSR to oxaliplatin in patients with colorectal cancer include facial flushing, burning sensation, weakness, vomiting, edema,

dizziness, tongue swelling, dyspnea, hives/rashes and fever/chills.^{19,20} Fever associated with oxaliplatin-HSR typically follows a specific pattern.^{19–21} These reactions especially in platinum-containing agents are thought to be mediated by immunoglobulin E (IgE) and other directly released vasoactive mediators. The fever usually starts during the oxaliplatin infusion or immediately after (within hours instead of days) and happens after several administrations (mean 2–25)^{20,22,23} with unpredictable clinical presentations.²⁴ The HSR is self-limiting (<48 h), and not typically associated with symptoms of immediate hypersensitivity such as angioedema, wheals, hypotension and bronchospasm. It also does not respond well to

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antipyretics, and no clinical or laboratory signs of infection accompanies the fever. Finally, re-exposure to oxaliplatin triggers fever even with the use of pre-medication regimens. We report a case of oxaliplatin-induced HSR manifested as fever but with unusual presentation than the aforementioned features.

Case report

The patient is a 70-year-old Caucasian male with T3N1M0 (stage III): adenocarcinoma status post laparoscopic sigmoid colectomy who was initiated on an oxaliplatin-based regimen (mFOLFOX6) in the adjuvant setting. The patient's tumor was found to be $5 \times 5 \times 1$ cm in size, with one of the 20 lymph nodes excised found to be positive for metastasis. It was well-differentiated infiltrating adenocarcinoma of sigmoid colon with evidence of lymphovascular invasion and minimal inflammatory response. During his first infusion with oxaliplatin (85 mg/m^2), 30 minutes into it the patient had adverse reactions including nausea, vomiting, extreme dehydration and near-syncopal event for which patient required intravenous fluids and anti-emetics. Following the patient's second infusion, he developed high-grade fevers of up to 40°C – 40.5°C . This fever was noted to be on second day after the infusion and was associated with other symptoms like chills, nausea, vomiting, headache, and weakness. He was admitted to the hospital for this fever and had extensive work up done to rule out the source of fever along with treatment with broad-spectrum empiric antibiotics. His other medical history included hypercholesterolemia and constipation. Prior surgical procedures included sigmoid colectomy, tonsillectomy and a port-a-catheter placement prior to initiation of chemotherapy. Patient had no significant medication, seasonal or food allergies and no significant family history. The patient had no history of tobacco, alcohol or recreational drug use. On examination during admission, vital signs were significant for temperature of 40°C and 40.5°C on first and second days, heart rate of 98–110 beats per min, blood pressure of 106/56–110/60 mm Hg, respiratory rate 18–22/min and oxygen saturation of 94–96% on room air; remainder of the examination was unremarkable. The patient's work-up for infectious process was negative including leukocytosis, blood cultures, chest X-ray, and urine analysis and culture. The antibiotics were discontinued after 48 h of blood cultures being negative and the fevers self-resolved in 36 h, with two repeat values of 39.4°C and 38.8°C . The patient was subsequently discharged home only to return with similar complaints after the third infusion. This time again, the fever occurred two days after the infusion and resolved within 48 h without any other identifiable source of fever. Oxaliplatin was held during

the fourth and fifth infusions and patient had no evidence of fevers but still demonstrated associated nausea and vomiting, which were well tolerated with symptomatic management and pre-medications. Discussion was held with the patient regarding desensitization protocols given the importance of oxaliplatin in the regimen but the patient opted to continue chemotherapy without oxaliplatin and completed nine more cycles of adjuvant 5-fluorouracil and leucovorin, for a total of 12 cycles (six months) of adjuvant chemotherapy. Six months following completion of adjuvant therapy, he is disease-free.

Discussion

Chemotherapeutic agents are well known to cause HSRs, which in some cases can lead to cessation of medication if severe. Certain groups that are found to have high incidence of HSR are platinum-based drugs (cisplatin, carboplatin and oxaliplatin), taxanes (paclitaxel and docetaxel), asparaginases, monoclonal antibodies and epipodophyllotoxins.²⁵ Increasing use of oxaliplatin is leading to increase in the incidence of HSR.^{16–18} Comparison of characteristics of HSR of oxaliplatin with other platinum-containing agents has been elucidated^{6,20,22,24,26–28} (Table 1). Even though all the platinum agents are implicated in causing HSR, they do differ in incidence, features and timing of the reaction. So far many desensitization protocols have been developed and are in use for different platinum agents.^{30–34} No one protocol suggests better efficacy over other and so far data is also limited, as no randomized trials exist even though comparisons have been made.^{31,32,34}

HSRs typically are graded based on the US National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE). The previous version of CTCAE, version 3, graded HSR with specific differentiation for fever below or above 38°C , whereas the most recent version (v4.03) has been revised to specify what interventions are needed and response to treatment³⁵ (Table 2). Four types of HSR exist. Type I reactions are mediated by IgE/mast cells and are immediate in nature due to release of histamine/other directly released vasoactive agents. These type I HSRs do, however, require prior sensitization and hence manifest after several exposures to the inciting agent. Type II HSRs are antibody-mediated (immunoglobulin G (IgG), immunoglobulin M (IgM)) cytotoxicity caused by activation of complement system and killer cells, leading to hemolysis and thrombocytopenia. Type III HSRs are due to formation of soluble antigen–antibody immune complex and its deposition in vascular walls of organs leading to fever, chronic urticarial, proteinuria, and vasculitis. Type IV HSRs are

Table 1. Characteristics of HSR in platinum agents.

Characteristic	Cisplatin ^{27,29}	Carboplatin ^{27,28}	Oxaliplatin ^{6,20,22,24,26,28}
Incidence	5–20%	16%	10–23.8%
Number of cycles for onset	Unknown	6 cycles (range 2–12)	7 cycles (range 2–25)
Duration after infusion	Minutes	Minutes to days	Minutes to hours
Presentation	Fever, anxiety, cough, angioedema, dyspnea, vomiting, bronchospasm, diaphoresis, hypotension, rash and pruritus	Itching, rash, chest tightness, blood pressure changes, facial edema	Dyspnea, heart rate changes, back pain, fever, pruritus, erythema, nausea, rash
Reintroduction feasible?	Not studied	Can be done with slowing infusion rate	Can be done, premedication, slowing infusion rate, and/or desensitization

Table 2. US National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Grading of allergic reactions.³⁴

	Version 3.0	Version 4.0
Grade	Allergic reaction/hypersensitivity reaction	Allergic reaction
1	Transient flushing or rash Drug fever <38°C	Transient flushing or rash, drug fever <38°C; intervention not needed
2	Rash Flushing Urticaria Dyspnea Drug fever >38°C	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤ 24 hr
3	Symptomatic bronchospasm with or without urticaria Parenteral medication or medications indicated Allergy related edema/angioedema Hypotension	Prolonged reaction not rapidly responsive to symptomatic medication and/or brief interruption of infusion. Recurrence of symptoms following initial improvement Hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)
4	Anaphylaxis	Life-threatening consequences with urgent intervention indicated
5	Death	Death

delayed-type HSR, mediated through T-cells and resulting in contact dermatitis or granuloma formation.³⁶

Oxaliplatin HSR-related fever can vary in severity (i.e., > or <38°C) and as mentioned earlier has specific characteristics. It typically occurs after several infusions and is immediate during or few hours after the infusion's completion. The development of oxaliplatin-HSR-induced fever occurs most commonly after six to 10 courses,^{7,8,26,37–40} and in most cases is accompanied by marked discomfort, which can lead to discontinuation of the treatment, jeopardizing the prognosis for the patient.

The pathophysiology of oxaliplatin-HSRs is not yet fully understood. Different hypotheses exist, with the most common one being IgE-mediated (Type I) hypersensitivity.^{20,40–42} However, case

reports have been published describing all four types of HSRs in patients receiving oxaliplatin.^{20,41–43} Given the fact that oxaliplatin HSRs most commonly occur after several treatments and tend to be immediate in nature with regard to timing of the infusion in most patients, type 1 HSR seems the most appropriate mechanism for this type of HSR as sensitization must take place beforehand.¹⁷ The cause of fever following oxaliplatin infusions was postulated by Ulrich-Pur et al.²¹ to be a result of transient elevations in interleukin-6 (IL-6). Whether increased IL-6 levels is a bystander effect or a direct effect of oxaliplatin is unknown.

HSR with oxaliplatin is shown to be more prevalent in certain populations. Age and female gender are well-known risk factors.^{9,10,13} Kim et al.¹⁰ suggested association between younger age and female gender to HSR

by hormonal influences. In a univariate analysis of 191 patients, Parel et al.¹⁴ demonstrated a mean age of 56.2 ± 10.5 years in patients with observed HSR to 62.6 ± 12 years as those without it. Similarly, the incidence of HSR in women was 94%, which has been highest so far reported in a study, although it did have significant proportion of women (89%) with a previous exposure to platinum salts. Previous exposure hence appears to be another risk factor for HSR. The effect of platinum free interval as risk factor on incidence and severity of HSR is still a matter of debate⁹ and needs further evaluation.

Our patient presented with atypical features of fever, with the occurrence seen in second and third infusions (rather than after six to ten infusions) along with delayed onset of one to two days after the completions of infusion (rather than during or immediately following the infusion). We applied the Naranjo Nomogram⁴⁴ for assessment of probability of adverse drug reaction, and the score was calculated as eight, which is high probability. Based on the severity of fever in this patient and its other characteristics, this HSR would suffice as grade 2 reaction using NCI CTCAE version 3.0 and 4.0³⁵ (see Table 2 for details). Our patient differed in presentation, as he did not have the typical risk factors for development of platinum-related HSR of young age, female gender or previous exposure to platinum salts. Although most oxaliplatin-induced fevers occur after six to ten infusions, one previous report by Ulrich-Pur et al. indicated an onset of fever with the second oxaliplatin infusion. However, in that patient, the onset of fever began 2 h after the oxaliplatin infusion. In our patient, the onset of fever occurred >24 h after the infusion, which is unusual. The fever was typical in some of its features such as, it did not respond to the common therapies of antipyretics, anti histamines and steroids; it was self limiting within 36–48 h, and it did have a worse grade 2 reaction on repeat infusion compared with the first infusion.

Management of HSR in patients with oxaliplatin has been well studied. Numerous studies on desensitization protocols and pre-medication protocols have been documented.^{19,20,22,23,26,32,33,45–47} Common interventions include, slowing the rate of infusion²⁶ in grade 1 and 2 type reactions along with premedication with antihistamines, antipyretics, and steroids. The present patient was offered slowing the infusion rate along with desensitization to drug, but the patient preferred to omit the oxaliplatin infusions and ensue chemotherapy with only 5-fluorouracil and leucovorin.

Conclusion

HSR is a common manifestation of platinum-based drugs, and its incidence is rising as a result of its

increasing clinical use. Fever, albeit uncommon, can present as either sole or initial manifestation of HSR. Recognition and timely intervention is necessary to prevent serious, high-grade HSRs. Features of fever and other HSR are very typical in majority of cases but atypical presentation requires high index of suspicion and thorough work up for management. Desensitization strategies may be considered to successfully continue the use of drug and improve prognosis in patients.

Author contributions

All authors participated in the conception, design, analysis, interpretation, writing, revising, and approval of this article.

Declaration of Conflicting Interests

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References

1. Kelland L. The resurgence of platinum-based cancer chemotherapy. *Nat Rev Cancer* 2007; 7: 573–584.
2. Benson AB 3rd, Venook AP, Bekaii-Saab T, et al. Colon cancer, version 3.2014. *J Natl Compr Canc Netw* 2014; 12: 1028–1059.
3. Rothenberg ML, Oza AM, Bigelow RH, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. *J Clin Oncol* 2003; 21: 2059–2069.
4. Lorgis V, Chauffert B, Gentil J, et al. Influence of localization of primary tumor on effectiveness of 5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) in patients with metastatic pancreatic adenocarcinoma: a retrospective study. *Anticancer Res* 2012; 32: 4125–4130.
5. Muggia FM. Recent updates in the clinical use of platinum compounds for the treatment of gynecologic cancers. *Semin Oncol* 2004; 31: 17–24.
6. Shepherd GM. Hypersensitivity reactions to chemotherapeutic drugs. *Clin Rev Allergy Immunol* 2003; 24: 253–262.
7. Shao YY, Hu FC, Liang JT, et al. Characteristics and risk factors of oxaliplatin-related hypersensitivity reactions. *J Formos Med Assoc* 2010; 109: 362–368.
8. Siu SW, Chan RT and Au GK. Hypersensitivity reactions to oxaliplatin: experience in a single institute. *Ann Oncol* 2006; 17: 259–261.
9. Mori Y, Nishimura T, Kitano T, et al. Oxaliplatin-free interval as a risk factor for hypersensitivity reaction among colorectal cancer patients treated with FOLFOX. *Oncology* 2010; 79: 136–143.

10. Kim BH, Bradley T, Tai J, et al. Hypersensitivity to oxaliplatin: an investigation of incidence and risk factors, and literature review. *Oncology* 2009; 76: 231–238.
11. Lee KH, Park YJ, Kim ES, et al. Hypersensitivity reactions to oxaliplatin. *Cancer Res Treat* 2006; 38: 240–241.
12. Ichikawa Y, Goto A, Hirokawa S, et al. Allergic reactions to oxaliplatin in a single institute in Japan. *Jpn J Clin Oncol* 2009; 39: 616–620.
13. Seki K, Senzaki K, Tsuduki Y, et al. Risk factors for oxaliplatin-induced hypersensitivity reactions in Japanese patients with advanced colorectal cancer. *Int J Med Sci* 2011; 8: 210–215.
14. Parel M, Ranchon F, Nosbaum A, et al. Hypersensitivity to oxaliplatin: clinical features and risk factors. *BMC Pharmacol Toxicol* 2014; 15: 1.
15. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; 350: 2343–2351.
16. Lee C, Gianos M and Klaustermeyer WB. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. *Ann Allergy Asthma Immunol* 2009; 102: 179–187. (quiz 187–179, 222.17).
17. Syrigou E, Syrigos K and Saif MW. Hypersensitivity reactions to oxaliplatin and other antineoplastic agents. *Curr Allergy Asthma Rep* 2008; 8: 56–62.
18. 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: 835–852, xiii.
19. Saif M, Roy S, Ledbetter L, et al. Fever as the only manifestation of hypersensitivity reactions associated with oxaliplatin in a patient with colorectal cancer oxaliplatin-induced hypersensitivity reaction. *World J Gastroenterol* 2007; 13: 5277–5281.
20. Thomas RR, Quinn MG, Schuler B, et al. Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer* 2003; 97: 2301–2307.
21. Ulrich-Pur H, Penz M, Fiebiger WC, et al. Oxaliplatin-induced fever and release of IL-6. *Oncology* 2000; 59: 187–189.
22. Meyer L, Zuberbier T, Worm M, et al. Hypersensitivity reactions to oxaliplatin: cross-reactivity to carboplatin and the introduction of a desensitization schedule. *J Clin Oncol* 2002; 20: 1146–1147.
23. Bhargava P, Gammon D and McCormick MJ. Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer* 2004; 100: 211–212.
24. Saif MW. Hypersensitivity reactions associated with oxaliplatin. *Expert Opin Drug Saf* 2006; 5: 687–694.
25. Gobel BH. Chemotherapy-induced hypersensitivity reactions. *Oncol Nurs Forum* 2005; 32: 1027–1035.
26. Brandi G, Pantaleo MA, Galli C, et al. Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer* 2003; 89: 477–481.
27. Basu R, Rajkumar A and Datta NR. Anaphylaxis to cisplatin following nine previous uncomplicated cycles. *Int J Clin Oncol* 2002; 7: 365–367.
28. Robinson JB, Singh D, Bodurka-Bervers DC, et al. Hypersensitivity reactions and the utility of oral and intravenous desensitization in patients with gynecologic malignancies. *Gynecol Oncol* 2001; 82: 550–558.
29. Koren C, Yerushalmi R, Katz A, et al. Hypersensitivity reaction to cisplatin during chemoradiation therapy for gynecologic malignancy. *Am J Clin Oncol* 2002; 25: 625–626.
30. Confino-Cohen R, Fishman A, Altaras M, et al. Successful carboplatin desensitization in patients with proven carboplatin allergy. *Cancer* 2005; 104: 640–643.
31. Keat K, Harnett P and Fulcher DA. Carboplatin desensitization. *Ann Allergy Asthma Immunol* 2007; 99: 468–469.
32. Cortijo-Cascajares S, Nacle-Lopez I, Garcia-Escobar I, et al. Effectiveness of oxaliplatin desensitization protocols. *Clin Transl Oncol* 2013; 15: 219–225.
33. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, et al. Desensitizing oxaliplatin-induced fever: a case report. *J Investig Allergol Clin Immunol* 2013; 23: 435–436.
34. Gastaminza G, de la Borbolla JM, Goikoetxea MJ, et al. A new rapid desensitization protocol for chemotherapy agents. *J Investig Allergol Clin Immunol* 2011; 21: 108–112.
35. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Washington, DC: National Institutes of Health, <http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf> (2009).
36. Gell PGH, Coombs RRA and Lachmann PJ. *Clinical aspects of immunology*, 3rd ed. Oxford Philadelphia: Blackwell Scientific Publications, 1975.
37. Shibata Y, Ariyama H, Baba E, et al. Oxaliplatin-induced allergic reaction in patients with colorectal cancer in Japan. *Int J Clin Oncol* 2009; 14: 397–401.
38. Suenaga M, Mizunuma N, Shinozaki E, et al. Management of allergic reactions to oxaliplatin in colorectal cancer patients. *J Support Oncol* 2008; 6: 373–378.
39. Polyzos A, Tsavaris N, Gogas H, et al. Clinical features of hypersensitivity reactions to oxaliplatin: a 10-year experience. *Oncology* 2009; 76: 36–41.
40. Stahl M, Koster W and Wilke H. Reaction after oxaliplatin—prevention with corticosteroids? *Ann Oncol* 2001; 12: 874.
41. Santini D, Tonini G, Salerno A, et al. Idiosyncratic reaction after oxaliplatin infusion. *Ann Oncol* 2001; 12: 132–133.
42. Tonini G, Santini D, Vincenzi B, et al. Oxaliplatin may induce cytokine-release syndrome in colorectal cancer patients. *J Biol Regul Homeost Agents* 2002; 16: 105–109.
43. Maindrault-Goebel F, Andre T, Tournigand C, et al. Allergic-type reactions to oxaliplatin: retrospective analysis of 42 patients. *Eur J Cancer* 2005; 41: 2262–2267.
44. Lanctot KL and Naranjo CA. Comparison of the Bayesian approach and a simple algorithm for assessment of adverse drug events. *Clin Pharmacol Ther* 1995; 58: 692–698.

45. Lee SY, Kang HR, Song WJ, et al. Overcoming oxaliplatin hypersensitivity: different strategies are needed according to the severity and previous exposure. *Cancer Chemother Pharmacol* 2014; 73: 1021–1029.
46. Mis L, Fernando NH, Hurwitz HI, et al. Successful desensitization to oxaliplatin. *Ann Pharmacother* 2005; 39: 966–969.
47. Lim KH, Huang MJ, Lin HC, et al. Hypersensitivity reactions to oxaliplatin: a case report and the success of a continuous infusional desensitization schedule. *Anticancer Drugs* 2004; 15: 605–607.