

EXPERT OPINION

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Hypersensitivity reactions associated with oxaliplatin and their clinical management

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Introduction: Oxaliplatin, has become an integral part of the medical treatment of colorectal cancer and other malignancies. Increased use of the drug during the last decade, has led to increased occurrence of oxaliplatin-induced hypersensitivity reactions (HSRs), posing a significant challenge for clinicians. This article aims to review the existing literature regarding the incidence, clinical presentation, pathophysiology, risk factors and current management of oxaliplatin-induced HSRs.

Areas covered: A systematic review of the English literature published in PubMed and Medline was undertaken. The clinical manifestations of HSRs were found to be variable and unpredictable. These reactions should be an important concern, as their potential life-threatening risks can force doctors to stop treatment and seek alternatives, which may be less effective, not as well tolerated and/or more expensive. There are a few strategies to prevent these reactions so that patients can still benefit from oxaliplatin. Such strategies include the use of premedication (steroid and antagonists of type I and II histamine receptors), prolonged infusion time and desensitization.

Expert opinion: The presented management strategies as well as novel diagnostic tools including skin/intradermal tests and specific IgE have shown promising results. However, future research and validation are warranted in bigger clinical trials.

Keywords: colorectal cancer, desensitization, hypersensitivity reaction, oxaliplatin

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1. Introduction

Oxaliplatin {1,2-diaminocyclohexane (trans-1) oxalatoplatinum, OXAL (C₈H₁₄N₂O₄)} (Eloxatin; Sanofi-Aventis, Bridgewater, NJ, USA) (Box 1) is a third-generation, platinum-based agent that possesses a 1,2 diaminocyclohexane carrier and an oxalate ligand [1]. Its main mechanism of action is DNA cross-linking, thus inhibiting DNA synthesis and transcription [2]. Oxaliplatin has become an integral part of the medical treatment of colorectal cancer, being approved by the FDA for adjuvant chemotherapy in stage III and for palliative chemotherapy in metastatic colorectal cancer [3]. It is also used in pancreatic, gallbladder and gynecologic cancer therapies [4-6].

Oxaliplatin may cause acute toxicity including neutropenia, thrombocytopenia, nausea, diarrhea, emesis and neuropathy [7,8]. In addition to these adverse effects, patients may also develop hypersensitivity reactions (HSRs).

Hypersensitivity is defined as an unexpected reaction that cannot be explained by the known toxicity profile of the chemotherapeutic agent [9]. HSRs are particularly common with platinum-based drugs, taxanes, asparaginases, monoclonal antibodies, epipodophyllotoxins, doxorubicin and 6-mercaptopurine [9]. These reactions are an important concern, due to their potential life-threatening risks that can

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Box 1. Drug summary.

Drug name	Oxaliplatin
Phase	IV
Indication	Advanced colorectal cancer, pancreatic cancer, adjuvant treatment of colorectal cancer
Pharmacology description	Organoplatinum complex in which the atom of platinum is complexed with 1,2 diaminocyclohexane and with an oxalate ligand as a leaving group
Route of administration	Intravenous
Chemical formula	C ₈ H ₁₄ N ₂ O ₄ Pt
Pivotal trial(s)	[79-81]

Table 1. Incidence of hypersensitivity reactions to oxaliplatin.

Study	No. of patients	No. of patients with HSR (%)	Grade III/IV (%)
Shao <i>et al.</i> (2010) [10]	383	47 (12.3)	9.3
Kim BH <i>et al.</i> (2009) [15]	247	29 (11.7)	1.6
Seki <i>et al.</i> (2011) [16]	108	24 (22.2)	9.3
Suenaga <i>et al.</i> (2008) [17]	272	48 (17.6)	14.6
Siu <i>et al.</i> (2006) [18]	180	27 (15)	2.2
Ichikawa <i>et al.</i> (2009) [19]	105	25 (23.8)	6.7
Kim MY <i>et al.</i> (2012) [20]	393	42 (10.7)	11.9
Parel <i>et al.</i> (2014) [21]	191	17 (8.9)	1.6

HSR: Hypersensitivity reaction.

lead to doctors stopping the treatment and seeking other alternatives, which may be less effective, not as well tolerated and/or more expensive [10].

Since colorectal cancer is the third most common cancer in the world [11], the use of oxaliplatin is gradually increasing and the incidence of HSRs is also likely to further increase. The FDA and Sanofi-Aventis have included a BOX warning for such reactions [12] and it is imperative for clinicians to be aware of the possibility of HSRs when administering oxaliplatin-based therapy and of their clinical management.

2. Incidence

The occurrence of oxaliplatin-related HSRs has increased during the last decade due to the extensive use of oxaliplatin.

Although severe HSRs are rare, the incidence of mild-to-moderate reactions should not be underestimated in the oncology community [13]. In a large Phase III clinical trial (MOSAIC) of oxaliplatin, allergic reactions were present only in 10.6% of the patients, and severe toxicity (grade III/IV) was present in 2.9% of them [14]. More recent data, however, present an HSR incidence ranging from 8.9 to 23.8% (Table 1) [10,15-21], whereas severe anaphylactic reactions are present in a proportion < 2% [13,22-24]. Shao *et al.* [10] reported an incidence of 12.7% with a median of 10 infusions and the median time of onset from the start of infusion was 40 min. Additionally, rechallenge with oxaliplatin led to a high chance of further reactions in up to 71.4% of the patients.

Lee *et al.* [25] presented the results of a retrospective study concerning oxaliplatin-induced HSRs. These reactions occurred at 6.3 ± 0.3 mean chemotherapy cycle. Specifically, HSR occurred at cycle 7.6 ± 0.3 in patients who had never been exposed to oxaliplatin-based chemotherapy, as opposed to 2.6 ± 0.3 in previously exposed patients.

3. Clinical manifestations

The clinical manifestations of HSRs are variable and unpredictable. They include pruritus, urticaria, edema/angioedema, palmar erythema, facial flushing, erythematous rash, dizziness, diarrhea, nausea, back pain, chest discomfort, fever, facial or lingual swelling, and heart rate and blood pressure alterations [26,27]. Although fever alone is not a usual symptom of oxaliplatin-induced hypersensitivity, it has been reported in several cases. In one of these cases, the patient developed fever during the 9th and 10th infusion of oxaliplatin. Despite administration of premedication (promethazine), the patient developed grade III toxicity during the 11th infusion and required admission to the hospital [28]. Another case of a patient presenting with fever, shivering, general malaise and headache as the manifestations of an HSR to oxaliplatin has been recently reported [29]. The symptoms appeared 30 min after the onset of the 10th infusion and recurred in the next 3 infusions despite the prolonged infusion rate and intensified premedication with antipyretics, corticosteroids and antihistamines.

More severe reactions include chest pain, shortness of breath, bronchospasm, anaphylaxis, respiratory arrest and death [18,23]. The severity of HSRs can be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (Table 2).

Severe thrombocytopenia may develop after repeated administrations of oxaliplatin [30-36]. Although most reported cases of thrombocytopenia were self-limited within days, Shao *et al.* [37] reported in 2008 the first fatal case after the 24th course of oxaliplatin-based chemotherapy. The patient deteriorated to deep coma hours after the administration of the drug. The cause of death was intracranial hemorrhage. Notably, five episodes of grade I/II HSRs and mild hemoptysis had occurred during the previous infusions.

Table 2. National Cancer Institute – Common Terminology Criteria for Adverse Events v4.0 (CTCAE) – Clinical severity scale of allergic reactions.

Grade	Description
1	Transient flushing or rash, drug fever < 38°C (< 100.4°F); intervention not indicated
2	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤ 24 h
3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
4	Life-threatening consequences; urgent intervention indicated
5	Death

4. Pathophysiology

The pathophysiology of HSRs to oxaliplatin is not fully elucidated yet. HSRs are generally divided into four types, originally defined by Gell and Coombs (Table 3) [38]. They usually occur after multiple infusions, thus suggesting a type I response. However, HSRs can be caused through other mechanisms as well. Several data support the involvement of type II, type III and type IV reactions.

Type I HSRs, which are the most common, are mediated by IgE immunoglobulin. Degranulation of mast cells and basophils leads to nonimmune mediated histamine and cytokine release [9,39]. The important role of cytokines, especially IL-6, and TNF- α was highlighted by Santini *et al.* [40] who reported a case of a patient who presented elevated IL-6 and TNF- α serum levels following an idiosyncratic HSR. These results were further confirmed by Tonini *et al.* [41] who studied five patients with colorectal cancer and suggested that the observed HSRs could be attributed to a massive release of cytokines. Specifically, it was shown that IL-6 and TNF- α serum levels were significantly decreased following steroid administration, along with the complete regression of clinical symptoms and signs. Similarly, Ulrich-Pur *et al.* [42] reported a case of a patient who developed fever hours after receiving the third infusion of oxaliplatin. A rise in serum levels of IL-6 was observed with 5th and 6th infusion, corresponding to the rise in temperature.

Type II hypersensitivity is implicated in the presentation of hemolysis, thrombocytopenia and Evan's syndrome [43]. These reactions are complement mediated and killer cell activated, with specific IgG and IgM antibodies directed at drug-hapten coated cells. Especially regarding thrombocytopenia, an immunological mechanism has been proposed. There are numerous reports that describe the presence of positive direct

antiglobulin test results [30,31,33,34,37,44]. Immunoglobulin G antibodies against platelets in the presence of oxaliplatin have also been identified [34-36,45]. However, it is still unclear, how oxaliplatin facilitates the reaction between antibodies and platelets.

Chronic urticaria, joint pain, and proteinuria after oxaliplatin regimens have been attributed to type III allergic reactions [19]. The underlying mechanism involves tissue deposition of drug-antibody complexes and activation of complement and inflammatory pathways.

Apart from the aforementioned mechanisms, Masse *et al.* [46] reported a delayed (Type IV) HSR to oxaliplatin. The patient developed a pruritic polymorphous maculopapular rash ~8 h after the beginning of the 7th cycle. The same reaction occurred 2 weeks after this episode, while the patient was receiving his 8th cycle of chemotherapy. Skin tests, which were negative at the immediate reading, became positive about 12 h later for oxaliplatin and docetaxel and 2 days later positive results were also observed for carboplatin and cisplatin. A delayed HSR presenting with hemoptysis and Acute Respiratory Distress Syndrome was also reported by Kobayashi *et al.* [47].

It has also been postulated that oxaliplatin may act as a superantigen on mononuclear cells and may result in the release of cytokines (i.e., IL-6, TNF- α). Other mechanisms that have been suggested include binding of the platinum salts to different peptides of MHC. Human leukocyte antigen phenotype is a significant determinant of occupational sensitization to inhaled hapten of complex platinum salts and the strength of this association varies according to the intensity of exposure [48]. Finally, it has also been suggested that serotonin may be implicated in the observed anaphylactic mechanisms and this could explain the symptoms of hypertension and bronchospasm [23].

5. Risk factors

Multiple factors have been suggested to affect HSR rate to oxaliplatin. Several studies have assessed the presumed risk factors but with heterogeneous results [10,15,18,20,49,50]. A recent study recognized younger age, female sex and use of oxaliplatin as salvage therapy, as putative risk factors [15]. The authors suggested that the association between HSRs and younger age and female gender could be attributed to a potential role of hormonal influences. In another study by Seki *et al.* [16], a higher neutrophil count and a lower monocyte count were reported to be risk factors for grade III/IV HSRs in Japanese patients.

The incidence of HSRs increases in line with the number of cycles. Many studies have reported that patients usually receive an average of between 6 and 10 cycles before the development of HSR. High doses of oxaliplatin have also been associated with a higher risk of developing an HSR, as well as cases where patients receive oxaliplatin as a second line chemotherapy treatment or retreatment after a drug-free period [10,15,49]. In

Table 3. Types of HSRs – Gell and Coombs classification.

Type	Mechanism	Major signs and symptoms	Symptoms described in oxaliplatin-related HSRs
I	Antigen interaction with IgE bound to mast cell membrane causes degranulation Drug binding to mast cell surface causes degranulation Activation of classic or alternative complement pathways Neurogenic release of vasoactive substances	Urticaria, angioedema, rash, hypotension, bronchospasm, agitation, anxiety abdominal cramping, extremity pain	Pruritus, urticaria, edema/angioedema, palmar erythema, facial flushing, erythematous rash, facial or lingual swelling, dizziness, laryngospasm, bronchospasm, chest discomfort, heart rate and blood pressure alterations, chills, malaise, anaphylaxis, dyspnea, sweats, fever, nausea, vomiting, diarrhea, abdominal pain, back pain
II	Antibody reacts with an antigen on a target cell	Autoimmune hemolytic anemia, thrombocytopenia, rheumatic heart disease, goodpasture's syndrome, membranous nephropathy	Hemolytic anemia, thrombocytopenia, Evan's syndrome
III	Antigen-antibody intravascularly form circulating immune complexes that deposit in or on tissues	Serum sickness, arthus reaction, rheumatoid arthritis, post-streptococcal glomerulonephritis, lupus nephritis, systemic lupus erythematosus	Urticaria, joint pain, proteinuria
IV	T lymphocytes react with antigen and release lymphokines	Contact dermatitis, granuloma formation, homograft rejection	Pruritic polymorphous maculopapular rash, hemoptysis, acute respiratory distress

HSR: Hypersensitivity reaction.

a very recent study, Parel *et al.* [21] assessed the incidence and risk factors associated with oxaliplatin-induced HSR. In this study, 191 patients who received the drug from October 2004 to January 2011 were enrolled. Out of this cohort, 8.9% of patients experienced an HSR. Using univariate analysis, HSR was associated with younger age, female gender and prior exposure to platinum. Multivariate analysis only confirmed the higher risk of women. This study presented no increased risk with mean dose or with presence of atopic background. Reintroduction of oxaliplatin was effective in 64.7% of hypersensitive patients using premedication, but no patients who experienced a grade III or IV HSR were rechallenged.

Skin tests have been reported to predict oxaliplatin-induced HSRs. Intradermal tests are more sensitive than prick tests, but since they may be responsible for more side effects, it is recommended to use them in cases that the prick test is negative but the clinical symptoms are highly suggestive of hypersensitivity [51]. However, Garufi *et al.* [52] concluded that negative skin test reaction may be seen in patients who experience HSRs. Similarly, in a study by Meyer *et al.* [53], two of 8 patients with prior HSR had negative skin tests. Leguy-Seguin *et al.* [54] performed patch tests, prick tests and intradermal tests in 21 patients. The authors reported 7 patients with delayed type reactions to platinum salts to have negative skin tests and suggested that the earlier the reaction, the greater the predictive value of prick tests and intradermal tests.

In a recent study by Pagani *et al.* [55], 101 patients under treatment with oxaliplatin, underwent the prick test at a concentration of 1 mg/ml or in case the results were negative, an intradermal injection at a concentration of 0.1 mg/ml was

performed 1 h before each course of oxaliplatin, starting from the second administration. The authors proposed performing tests only in patients who have received at least five courses of oxaliplatin-based therapy. They also concluded that a negative skin test is reliable in predicting HSRs to oxaliplatin.

6. Management

Oxaliplatin induced HSRs represent a significant concern for clinicians and therefore they should be cautious during each administration in case such reactions occur [56]. It is of paramount importance for patients to be closely monitored during and after all infusions. This includes checking of vital signs before and throughout as well as after the administration of the drug [57]. Moreover, since delayed reactions may present hours or even days after the infusion, this possibility should not be overlooked.

When an HSR occurs, the infusion of oxaliplatin should be immediately stopped and replaced by a saline infusion, an intravenous (i.v.) antihistaminic drug, and low-dose corticosteroids administration. In case of more severe reactions, immediate administration of a high dose of steroid may be necessary. After the reaction disappears, oxaliplatin infusion should not be restarted. The clinical status of the patient after the HSR, the potential risk of additional toxicity and the clinical utility of chemotherapy should be taken into consideration before the decision to administer the other scheduled drugs.

In many cases, oxaliplatin treatment is considered fundamental for the patient even after the development of a severe

HSR. Successful reintroduction of oxaliplatin has been reported by implementing few strategies.

6.1 Steroids and antihistamines

In the case of mild reactions, one of the approaches is to use steroids and antihistamines before administration of oxaliplatin. Thomas *et al.* [22] in 2003, reported three patients who developed HSRs to oxaliplatin and were successfully rechallenged after premedication with oral dexamethasone 20 mg, 6 and 12 h before the oxaliplatin infusion, as well as i.v. administration of 125 mg solumedrol, 50 mg of diphenhydramine and 50 mg of cimetidine. In a more recent study, Kidera *et al.* [58] concluded that in patients treated with oxaliplatin-based therapy, increased doses of dexamethasone and antihistamine (diphenhydramine 50 mg orally, followed by dexamethasone 20 mg, granisetron 3 mg and famotidine 20 mg), significantly reduced the incidence of HSRs. Finally, in an interesting study with promising results by Lee *et al.* [59], 96 out of 99 patients with prior HSRs were successfully re-exposed to oxaliplatin after antihistamine and corticosteroid administration with or without prolonged infusion rate, confirming that many of the oxaliplatin-induced HSRs can be controlled by the use of premedication and increase of infusion time. However, it should be highlighted that a more recent publication by the same group, concluded that premedication resulted in a lower success rate in the prevention of HSRs associated with oxaliplatin. Namely, only 71.6% of patients who received premedication had partial or complete prevention of HSRs and were able to continue their treatment [25]. Moreover, Bhargava *et al.* [60] and Brandi *et al.* [13] reported that premedication is not always effective. Bhargava *et al.* [60] presented a patient who developed severe HSR despite the administration of premedication prior to oxaliplatin infusion.

6.2 Prolonged infusion time

Mild HSRs to oxaliplatin can also be ameliorated in some patients by lowering the infusion rate. Brandi *et al.* [13] reported fewer HSRs as the infusion time was increased from standard 2 to 6 h. In this significant retrospective study, 17 patients out of 124 (13.7%) developed hypersensitivity and 6 out of the 17 patients were re-exposed after premedication with steroids and antihistaminic drugs. All except one developed the HSR again. Prolonged infusion rate has been reported in combination with other strategies concerning the successful reintroduction to oxaliplatin.

6.3 Desensitization to oxaliplatin

Desensitization may allow a small number of patients who experienced HSRs to further receive oxaliplatin-based therapy and benefit from the drug. In a very interesting study, Park *et al.* [61] highlighted the high incidence of HSRs after re-exposure to oxaliplatin in patients who had experienced mild HSRs to the drug before and concluded that it may be feasible to continue oxaliplatin without using desensitization.

Desensitization protocols previously developed to manage HSRs caused by other drugs, such as taxanes and other platinum-containing compounds, have also been proven safe and effective in the case of oxaliplatin [62,63]. The success of desensitization protocols depends on the minimum dosage at the start of the protocol, the gradual increases of the dosage and the prolonged administration time. The various oxaliplatin desensitization protocols have been summarized in Table 4. In one of the most important studies, Castells *et al.* [64] developed a standardized 12-step desensitization protocol to achieve desensitization to drug allergens. Out of the 413 performed desensitizations, mild or no reactions were induced in 94% of the cases, whereas no life-threatening HSRs or deaths were reported.

Many cases of successful desensitization of patients with severe HSRs have been reported. Bhargava *et al.* [60] reported a case of a patient who experienced a severe HSR to oxaliplatin before he was successfully desensitized. Nozawa *et al.* [65] also reported a patient who had developed grade III HSR to oxaliplatin during cumulative cycles of FOLFOX and was desensitized using a protocol of an 8-h series of diluted-oxaliplatin infusions. The patient received intensive premedication consisting of oral diphenhydramine 50 mg, domperidone 10 mg, i.v. famotidine 20 mg, and dexamethasone 20 mg, as well as i.v. hydrocortisone 100 mg and granisetron 3 mg during the infusion of oxaliplatin. The patient underwent five additional cycles of desensitization, without experiencing any HSRs.

Syrgiou *et al.* [66] applied the standard protocol for parenteral desensitization to β -lactam antibiotics to three patients who successfully underwent desensitization to oxaliplatin. The treatment was carried out with serial 10-fold dilutions in sufficient volume to administer the total dose. Lim *et al.* [67] reported a patient who underwent desensitization with a fixed-rate 24 h continuous infusion of dilute oxaliplatin, in addition to steroids and H1 antihistamines, whereas Schull *et al.* [68] proposed a 48 h continuous infusion schedule that resulted in much lower peak plasma concentrations of the platinum compound and its metabolites. Similarly, Herrero *et al.* [69] applied a desensitization protocol with increasing concentrations and flow rates that was successfully administered in all five patients.

In a recent study by Cortijo-Cascajares *et al.* [63] a total of 53 desensitization protocols were administered to 21 patients during the study period. Each patient received an average of two desensitization protocols. New mild reactions occurred during six desensitization protocols (11%), but there were no HSRs in the remaining 47 cases (89%). None of these reactions were severe enough to stop the treatment and all patients were able to complete the desensitization protocol. In the annual meeting of the American Academy of Allergy, Asthma and Immunology in 2014, Updegraff *et al.* [70] reported 29 patients who underwent oxaliplatin desensitization. Intravenous diphenhydramine 50 mg, famotidine 20 mg, dexamethasone 50 mg and oral acetaminophen 625 mg were administered 1 h prior, with an additional dose of dexamethasone 50 mg

Table 4. Desensitization protocols for oxaliplatin hypersensitivity.

Study	No. of patients	Presenting features	Premedication	Oxaliplatin dose and dilution	Infusion time
Cortijo-Cascajares <i>et al.</i> (2013) [63]	21	Shortness of breath, hot flushes, bronchial spasms, edema/angioedema, hypotension, erythema, itchiness, hives, rash, maculopapular lesions	Corticosteroids: 1 mg/kg/day; ranitidine: 300 mg/day; cetirizine: 20 mg/day; montelukast: 10 mg/day the night before and 30 min before infusion	Total dose administered in an average of 14 steps	3 – 4 h
Nozawa <i>et al.</i> (2008) [65]	1	Erythema, irritable feeling, difficulty in breathing, burning sensation, palpitations, sweating	Famotidine 20 mg i.v. q.d., dexamethasone 20 mg i.v. q.d., diphenhydramine 50 mg p.o. q.i.d., domperidone 10 mg p.o. q.i.d., hydrocortisone 100 mg i.v. q.d., granisetron 3 mg i.v. q.d.	From 1:10,000 to 1:1 (0.015 – 13.5 mg), 5 steps (total dose 150 mg)	1 h × 4 steps, 4 h for the last step (total 8 h)
Lim <i>et al.</i> (2004) [67]	1	Abdominal distention, heat, flushing, erythema	Diphenhydramine 50 mg p.o. q.i.d., metoclopramide 9 mg i.v. q.d., dexamethasone 5 mg, diphenhydramine 30 mg i.v. q.d.	Fixed-rate, continuous 0.15 mg/ ml	24 h
Schull <i>et al.</i> (2001) [68]	1	Flush, erythema, nausea, hypotension	Ondansetron 8 mg i.v. q.d., Dexamethasone 8 mg i.v. q.d.	Fixed-rate, continuous	48 h
Syrigou <i>et al.</i> (2009) [66]	3	Facial flushing, erythematous rash, back pain, chest discomfort/ pain, pruritus/urticaria, tachycardia, facial swelling, abdominal pain, nausea, hypotension, drug fever, diarrhea, chills	-	Serial 10-fold dilutions (up to 1:100,000) in sufficient volume to administer the total dose	8 h
Wrzesinski <i>et al.</i> (2007) [75]	1	Chest pain, headache, loss of vision, photophobia	Ondansetron 8 mg i.v. b.i.d., magnesium sulfate 1 g i.v. b.i.d., calcium gluconate 1 g i.v. b.i.d., famotidine 20 mg i.v. q.d., dexamethasone 20 mg i.v. q.d., ondansetron 8 mg q.d., diphenhydramine 50 mg i.v. q.d.	From 1:10,000 through 1:1, 5 steps	1 h × 4 steps, 2 h for the last step (total 6 h)
Herrero <i>et al.</i> (2006) [69]	5	Rash, edema, hoarseness, dysphagia, erythema, fever, urticaria, pruritus	-	From 0.003 mg/min through 0.75 mg/min (0.01 – 0.18 mg/ml), several steps	30 – 60 min × several steps (N/S) (total, 5 – 6 h)
Updegraff <i>et al.</i> (2014) [70]	29	N/A	Diphenhydramine 50 mg i.v. q.d., famotidine 20 mg i.v. q.d., dexamethasone 50 mg i.v. b.i.d., acetaminophen 625 mg p.o. q.d.	From 1:1000 through 1:1, 4 steps	1 h × 2 steps, 2 h × 2 last steps (total 6 h)

h: Hour; min: Minute; N/A: Not available; N/S: Not specified.

given prior to the final infusion. The presented results were very interesting, as all but one patient successfully completed the desensitization.

6.4 Calcium and magnesium

Intravenous magnesium sulfate and calcium gluconate have demonstrated some activity in the prophylaxis and treatment

of oxaliplatin-induced neuropathy in advanced stage colorectal cancer patients receiving oxaliplatin, 5-fluorouracil and leucovorin [71-73]. However, a recent Phase III, randomized, placebo-controlled, double-blind study failed to demonstrate any statistically significant difference in the prevention of oxaliplatin-induced sensory neurotoxicity after i.v. calcium and magnesium administration [74]. In a case presented by

Wrzensinski *et al.* [75], a patient who had prior severe HSR to oxaliplatin underwent successful oxaliplatin desensitization, using a four-fold serial dilutions protocol, whereas i.v. magnesium sulfate and calcium gluconate was added to the protocol. The authors suggested that this approach may increase the success rate of desensitization, although premedication was also used.

7. Conclusion

Oxaliplatin, a third-generation platinum compound, is used worldwide for various malignancies. Like almost all chemotherapeutic drugs, it can cause HSRs that may lead to discontinuation of the therapy. There are few strategies to prevent these life-threatening reactions so that the patients can still benefit from oxaliplatin. For patients who experienced mild-to-moderate reactions, administering premedication or prolonging the infusion rate is usually sufficient. If the HSRs are severe, desensitization may be required to continue the therapy. Future research and validation of these strategies are warranted in bigger clinical trials.

8. Expert opinion

Oxaliplatin has become the cornerstone of treatment of early and late colorectal cancer, as well as other malignancies. Although HSRs are not as common as other adverse events of oxaliplatin, such as peripheral neurotoxicity or myelosuppression, this manifestation is certainly of great importance due to its potential life-threatening risks that may result in discontinuation of the drug.

Oxaliplatin is safely administered in the outpatient setting, but HSR can occur anytime during the administration or even after hours as a delayed reaction. The extensive use of oxaliplatin has led to an increase of oxaliplatin-related HSRs during the last decade, with the incidence varying from 8.9 to 23.8% [10,15-18,21]. HSRs usually occur after multiple infusions with the onset, usually between 6 and 10 treatment cycles [10,17,18,50].

The pathophysiology of HSR to oxaliplatin is currently not fully elucidated. Several data support the involvement of type I, II, III and IV allergic reactions. Many cases concerning acute and delayed HSRs have been reported, presenting with a variety of symptoms.

Skin tests have been reported to predict oxaliplatin-induced HSRs. Wong *et al.* [76] reported that a positive skin test was associated with a higher possibility of developing an HSR during subsequent desensitization, whereas Herrero *et al.* [69] concluded that prick and intradermal skin tests are useful in the

diagnosis of HSRs to oxaliplatin. However, negative skin test reaction may be seen in patients who experience HSRs.

Lately, oxaliplatin-specific IgE (sIgE) has been presented as a novel diagnostic tool. In a study by Caiado *et al.* [77], sensitivity and specificity of platin sIgE in patients with HSRs was evaluated. The authors reported that oxaliplatin sIgE is more sensitive (75%) but less specific. However, in a study by Madrigal-Burgaleta *et al.* [57], the test proved to be very specific but less sensitive. The authors recognized that selection bias may have affected the results but concluded that oxaliplatin-specific IgE determination could be helpful.

Successful reintroduction of oxaliplatin after the development of HSR has been reported by implementing few strategies. If the reaction is mild to moderate, patients can be re-exposed to the drug by prolonging the infusion time and after administration of premedication with steroids and antihistamines. Premedication with acetylsalicylic acid and montelukast has also been used during rapid desensitization to platinum chemotherapy in patients who experienced HSRs [57,78], with significantly greater improvement and reduction of symptoms, compared to pretreatment with methylprednisolone [78], but their role in the management of HSR still needs to be further evaluated. In patients who experienced severe HSRs, desensitization may allow them to continue receiving oxaliplatin. Successful desensitizations have been accomplished over the last decade with a variety of protocols applied, but large-scale validation on desensitization strategies are still missing.

The risk of developing HSRs in patients receiving oxaliplatin should not be underestimated. Education of the medical staff to recognize and manage HSRs is critical. Guidelines to optimally re-expose patients to oxaliplatin after HSRs have not been established yet. However, in many cases, oxaliplatin treatment is considered fundamental for the patient even after the development of a severe HSR. Implementing the aforementioned strategies may allow the patient to further receive oxaliplatin-based therapy and benefit from the drug. Future research and validation of these strategies are warranted in bigger clinical trials.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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