

Hypersensitivity Reactions to Oxaliplatin: A Retrospective Study and the Development of a Desensitization Protocol

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Abstract

Background: We recorded the epidemiologic and clinical features of hypersensitivity reactions (HSRs) to oxaliplatin in colorectal cancer (CRC) patients in order to provide information on the management of these patients. We also developed a desensitization protocol and evaluated its clinical application. For these reasons, we analyzed retrospectively the records of 215 CRC patients treated with oxaliplatin-containing regimens either as an adjuvant, first-line, second-line, or more. **Patients and Methods:** Data from 52 patients with HSRs were analyzed according to the Common Toxicity Criteria for Adverse Events (CTCAE), v3.0. Three patients were chosen for the desensitization protocol. After determining the starting point for desensitization, we applied the standard protocol for parenteral desensitization to b-lactam antibiotics. Oxaliplatin treatment was then carried out with serial 10-fold dilutions in sufficient volume to administer the total dose. A total of 52 patients (24.2%) were recorded as having an allergic reaction to oxaliplatin. **Results:** Hypersensitivity reactions were recorded after a mean of 6.5 (SD $\pm$ 4.5) cycles. Only 4 patients (4 of 215; 1.8%) developed CTCAE grade 3/4 HSRs. Hypersensitivity reactions were seen more likely in patients receiving second-line or more of chemotherapy compared with chemotherapy-naïve patients. No other correlations were seen (the presence of atopic disease, positive skin prick test). The 3 patients, having completed the parenteral desensitization protocol, completed their treatment uneventfully as well. **Conclusion:** Hypersensitivity reactions from oxaliplatin respond quickly to the discontinuation of the drug and appropriate support. Premedication and an increased infusion time could allow for readministration. The desensitization protocol we developed can provide a reliable alternative to permanent discontinuation of oxaliplatin.

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Introduction

Platinum-containing agents (cisplatin, carboplatin, oxaliplatin) are regarded as a high risk for the development of hypersensitivity reactions.¹ Oxaliplatin is a third-generation organoplatinum compound in which the platinum atom is complexed with diamminocyclohexane and with an oxalate ligand.¹ The drug has been approved for both second-line and first-line treatment of metastatic colorectal cancer (mCRC) in combination with 5-fluorouracil (5-

FU) and leucovorin (LV),² and also for the adjuvant treatment of stage III CRC.³ Oxaliplatin in combination with capecitabine has also been used in a trial setting as preoperative chemoradiation in locally advanced rectal cancer.³ Oxaliplatin is active in other malignancies, including gastric and pancreatic carcinomas. Its administration is especially convenient for patients and oncology departments because it is safely given in the outpatient setting. Widely used in a great variety of indications with various combinations of 5-FU/LV and capecitabine-based regimens, oxaliplatin is also combined with bevacizumab, an antineovascularization monoclonal antibody (MoAb) that binds to vascular endothelial growth factor.^{2,4} The use of oxaliplatin has shown to have mild side effects ranging from reversible neurotoxicity and vomiting to manageable neutropenia and leukopenia. However, a significant percentage of patients receiving this chemotherapeutic agent might present idiosyncratic or hypersensitivity reactions (HSRs).

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Hypersensitivity is defined as an unforeseen reaction that cannot be explained by the known toxicity profile of the chemotherapeutic agent (Table 1).⁵ Hypersensitivity reactions have been observed with the use of a number of antineoplastic agents, including the taxanes (paclitaxel, docetaxel), asparaginase, the epipodophyllotoxins, procarbazine, doxorubicin, 6-mercaptopurine, and the MoAbs (cetuximab, trastuzumab, rituximab, and bevacizumab).⁵ Acute onset and delayed reactions have all been described that consist of flushing, pruritus, urticaria/rash, erythema, hypotension, dyspnea, bronchospasm, nausea, back pain, and drug fever.⁶

The aim of this study was to record the epidemiologic and clinical features of hypersensitivity reactions to oxaliplatin in CRC patients treated with this agent, in order to provide some useful clinical information for the management of patients receiving oxaliplatin infusion. In addition, we developed a desensitization protocol and evaluated its clinical application.

Patients and Methods

In this study, we analyzed retrospectively the records of 215 CRC patients consecutively treated with oxaliplatin-containing regimens at the Oncology Department of Sotiria General Hospital, Athens Medical School. We included 92 patients (42.8%) receiving adjuvant treatment, 85 patients (39.5%) receiving first-line treatment for metastatic disease, and 38 patients (17.7%) receiving chemotherapy as second-line or more. Of these, we identified 52 patients (24.2%) that were “labeled” as having developed HSRs. These patients were analyzed according to the Common Toxicity Criteria for Adverse Events (CTCAE), v3.0, and their characteristics and management were recorded. Of these 52 patients, 17 were receiving adjuvant treatment, whereas 24 and 11 patients were treated for metastatic disease (first-line and second-line plus, respectively).

Results

The characteristics of the 52 patients recorded as having an HSR to oxaliplatin are shown in Table 2. Being diagnosed with CRC, none had received in the past any other platinum component (cisplatin or carboplatin). According to our findings, the HSRs were recorded after a mean ($\pm$ SD) of 6.5 ($\pm$ 4.5) cycles (median, 7 cycles; range, 1-16 cycles). Of the total number of patients studied, only 4 patients (4 of 215; 1.8%) developed CTCAE grade 3/4 HSRs. Patients receiving second-line or more of chemotherapy and were in the past exposed to other cytotoxic agents were more likely to develop HSRs, compared with chemotherapy-naïve patients in the adjuvant setting.

All 52 patients responded to a validated questionnaire, which inquired about the presence or not of atopic disease. Atopic status was evaluated by the presence of a positive skin prick test to one or more common environmental aeroallergens (*Dermatophagoides pteronyssinus*, *D. farinae*, cat dander, *Alternaria* Alt, *Cladosporium*,

Table 1 Hypersensitivity Reactions According to CTCAE, v3.0

HSR/Grade	Description
1	Transient flushing or rash, drug fever < 38°C (< 100.4°F)
2	Rash, flushing, urticaria, dyspnea, drug fever $\geq$ 38°C ($\geq$ 100.4°F)
3	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension
4	Anaphylaxis
5	Death

Abbreviations: CTCAE = Common Toxicity Criteria for Adverse Events; HSR = hypersensitivity reaction

Aspergillus fumigatus, grasses mix, *Olea europaea*, *Parietaria officinalis*, and latex [ALK Company]). The presence of atopic disease or positive skin prick test did not correlate with the development of HSRs to oxaliplatin.

Also, patients' sex, age, site of primary tumor, degree of differentiation, stage at diagnosis, and number and sites of metastatic lesions did not correlate with the development of HSRs. In addition, the existence of common comorbidities (medical history of diabetes mellitus, chronic obstructive pulmonary disease, hypertension, and coronary artery disease) did not correlate with the development of HSRs to oxaliplatin. Table 3 summarizes the various presentations of HSRs.

With regard to management, we rechallenged with oxaliplatin 32/48 (67%) patients who developed grade 1/2 HSRs. The reasons for not attempting to readminister oxaliplatin in the remaining 16 of 48 (33%) patients were therapeutic availability of other oxaliplatin-free chemotherapy schemes (n = 9), individuals' preference (n = 4), and the completion of chemotherapy without the substitution of oxaliplatin (n = 3). The 32 patients were rechallenged one week later, after they had received the following premedication: ranitidine 150 mg, methylprednisone 1 mg/kg (maximum 60 mg), and cetirizine 10 mg at 13, 7, and 1 hours before oxaliplatin administration. Premedication was successful in only 12 of 32 (37.5%) patients, who successfully completed their oxaliplatin-containing treatment. The remaining 20/32 (62.5%)—despite premedication administration—developed HSRs when rechallenged. In 3 patients, a desensitization protocol was performed, either because the patient insisted on exploiting all the possibilities receiving this drug (n = 1) or because there was no other alternative therapeutic solution besides oxaliplatin (n = 2). All 3 patients consented to participate according to this protocol.

Allergy Tests and Desensitization Protocol

Skin tests were performed in the 3 patients chosen for the application of the desensitization protocol as well as in 5 control subjects

Table 2 Characteristics of the 52 Patients Recorded as “Hypersensitive” to Oxaliplatin

Age, Years		Sex, n		Cycles of Chemotherapy			Line of Chemotherapy (%)		
Mean	Range	Male	Female	Mean	Range	Median	Adjuvant	First-Line	$\geq$ Second-Line
63.4	43-72	34	18	6.5	1-16	7	17 (33)	24 (46)	11 (21)

Clinical Symptoms	Ratio of Patients (%)
Facial Flushing	48/52 (92.3)
Erythematous Rash	37/52 (71.2)
Back Pain	30/52 (57.7)
Chest Discomfort/Pain	22/52 (42.3)
Pruritus/Urticaria	22/52 (42.3)
Tachycardia	16/52 (30.8)
Facial Swelling	11/52 (21.2)
Abdominal Pain	11/52 (21.2)
Nausea	6/52 (11.5)
Hypotension	5/52 (9.6)
Drug Fever	3/52 (5.8)
Diarrhea	2/52 (3.8)
Chills	1/52 (1.9)

who had previously been treated with oxaliplatin, without having any allergic reactions. Skin prick test was performed with oxaliplatin solution at concentrations of 0.01, 0.1, 1, and 10 mg/mL, and histamine 10 mg/mL and normal saline solution 0.9% were used as positive and negative controls, respectively. A positive skin test was considered as any wheal > 3 mm from the negative control.

One out of 3 patients had positive reaction at 1 mg/mL and the other 2 at 10 mg/mL, whereas all control subjects had negative skin prick test to all concentrations examined.

Intradermal tests were performed in all 8 individuals, after the skin prick test, with oxaliplatin at concentrations 0.001, 0.01, 0.1, and 1 mg/mL, with intent to determine the best concentration to start the desensitization and to examine whether any concentration caused irritations to the control subjects. One out of 3 patients (the same patient who had a positive skin prick test at 1 mg/mL) had a positive reaction at 0.001 mg/mL and the other 2 had a positive reaction at 0.1 mg/mL. All intradermal tests were negative in all control individuals.

Desensitization Protocol

We applied the standard protocol for parenteral desensitization to b-lactam antibiotics in patients with b-lactam allergy, with minor modifications. Oxaliplatin treatment was carried out with serial 10-fold dilutions (up to 1:100,000) in sufficient volume to administer the total dose. Patients were monitored for blood pressure, heart rate, and oxygen saturation changes every 15 minutes. Intramuscular epinephrine (1:1000), diphenhydramine, and methylprednisolone (125 mg) were placed at bedside. The possibility of intubation was available on-call, if needed, and the allergist was on site to answer questions regarding the desensitization and modify the protocol, and one set of intubation was available in the case of patient need intubation. The parenteral desensitization protocol was performed in an outpatient setting because 8 hours were needed for its completion.

Table 4 demonstrates the dilutions and total dose of one patient. All 3 patients completed the parenteral desensitization protocol with success

Solution of Oxaliplatin, mg/mL	Volume, mL	Oxaliplatin Dose, mg
0.00001	1	0.00001
0.0001	1	0.0001
0.001	1	0.001
0.01	1	0.01
0.1	1	0.1
1	1	1
1	2	2
1	4	4
10	0.8	8
10	1.6	16
10	3.2	32
10	3.5	35
10	6.4	64

and were able to continue their treatment until completion, with the same protocol of desensitization performed each time uneventfully.

Discussion

The incidence of HSRs to oxaliplatin is rising as a consequence of its growing clinical use in both adjuvant and metastatic treatments of CRC and other malignancies. Hypersensitivity reactions following oxaliplatin exposure might arise within minutes after infusion and at any time within a cycle of therapy. In any case, the occurrence increases with multiple courses of therapy^{6,7} and indeed signifies that prolonged drug exposure has a role in patients' sensitization. Although it has been reported to occur in a minority of patients (2%-12%) who receive oxaliplatin, < 0.5% of them develop grade 3/4 reactions.⁶⁻¹⁰ In the largest clinical trial (MOSAIC) of oxaliplatin, allergic reactions were present only in 10.6% of the enrollments, and severe toxicity (grade 3/4) was present only in 2.9% of them.¹¹ In a retrospective analysis of hypersensitivity reactions to oxaliplatin, 42 patients with CRC were recognized as having allergic reactions, of which only 3 were severe, escalating into anaphylactic shock.¹² In a recent report of 180 patients, only 15% were labeled as having an allergy to oxaliplatin.¹³ However, the proportion was higher among those receiving oxaliplatin in a palliative second-line (or more) setting (19.6%) than in an adjuvant or palliative first-line settings (10.2%). On the whole, 2.2% developed grade 3/4 reactions.¹⁴ When re-exposure to oxaliplatin occurred, 28.6% of the 14 patients resulted in HSRs with 14.3% reactions of grade 3/4 intensity.¹⁴

In our study, the allergic reactions appeared in 24% of the patients studied (1.8% with severe, grade 3/4 HSRs) after a median of 7 cycles of chemotherapy—findings that are in agreement with the literature.^{7,9} According to our results, chemotherapeutic combinations, as well as clinical and pathologic parameters of the patients, did not correlate with the development of HSRs. With regard to the line of treatment, patients in second-line of chemotherapy are more prone to develop HSRs.

Although the pathophysiology of HSRs to oxaliplatin is unclear, several mechanisms have been suggested. These reactions usually appear after multiple infusions, suggesting the need for sensitization. They can be described as type I allergic reactions, which result from the degranulation of mast cells and basophils following immunoglobulin E binding. Histamine and other cytokines (leukotrienes, prostaglandins), which have prominent inflammatory potential, are then released, leading to the constriction of the smooth muscles and the dilation of capillaries. Early onset of symptoms during oxaliplatin administration further supports the above explanation.^{14,15} Both type II complement-mediated killer cells activated reactions (with thrombocytopenia, hemolysis, and Evan's syndrome) and type III delayed (vasculitic urticaria) might also be observed following oxaliplatin administration.^{7,16,17}

Conclusion

According to our findings, premedication was successful in only 37.5% of the patients, whereas the application of a desensitization protocol was successful in all 3 patients. Unfortunately, this is a time-consuming procedure that adds to the inconvenience of the patient and the burden of the oncology departments. It is important to note that risk and benefit must be weighed before offering desensitization procedure to a patient because of potential risks affiliated with it. For example, such a procedure can be offered to a CRC patient who is receiving oxaliplatin in the adjuvant therapy, whereas desensitization should not be offered to a mCRC patient who has other treatment options or a pancreatic cancer patient.

Disclosures

The authors have no relevant relationships to disclose.

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