

Oxaliplatin Hypersensitivity: Case Report and Successful Repeat Desensitization

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Introduction: Oxaliplatin is a third generation organoplatinum complex used as an antineoplastic agent in combination with fluorouracil and leucovorin for colorectal carcinoma. Hypersensitivity reactions are commonly observed to oxaliplatin, with an incidence of 12% to 16%. Desensitization protocols for oxaliplatin with premedication using steroids or antihistamines have been previously reported. We present a patient who underwent successful repeat desensitization without premedication.

Case Summary: A 43-year-old Asian male with metastatic rectal adenocarcinoma was started on chemotherapy with oxaliplatin and leucovorin followed by fluorouracil. Three hours after the first infusion of oxaliplatin, he developed generalized urticaria, which resolved with Benadryl. Similar symptoms developed after the second cycle. A desensitization protocol, without premedication, was developed for the third oxaliplatin cycle starting at 1:10,000 of the therapeutic dose followed by doubling doses thereafter until a cumulative goal dose of 175 mg was administered. Fluorouracil and leucovorin were then infused at the usual rates. Skin prick testing, before the procedure, using 5 mg/mL oxaliplatin was negative. Intracutaneous testing using dilutions of 1:1000, 1:100, and 1:10 were also negative. The patient was observed for 2 hours after the procedure without evidence of a hypersensitivity reaction. Two weeks later, the same protocol was successfully implemented for completion of his fourth cycle of chemotherapy and continued biweekly for a total of 11 cycles. Follow-up revealed tumor remission.

Conclusion: A desensitization protocol without premedication may be considered in those patients with a history of oxaliplatin hypersensitivity reactions with avoidance of the cumulative exposure to pretreatment medications.

Keywords: oxaliplatin, desensitization, allergy, hypersensitivity, skin test

INTRODUCTION

Hypersensitivity reactions tend to occur in association with several chemotherapeutic agents. These agents include paclitaxel, docetaxel, doxorubicin, teniposide, etoposide, asparaginase, procarbazine, cisplatin,

carboplatin, and oxaliplatin. These hypersensitivity reactions include flushing, hypotension, shortness of breath, urticarial rashes, erythema, pruritus, and bronchospasm. Oxaliplatin is a newer organoplatinum complex antineoplastic agent approved in 2002 for the treatment of colorectal carcinoma and is commonly used in combination with fluorouracil and leucovorin for the treatment of metastatic disease.^{1,2} It is well recognized that platinum-containing agents are associated with hypersensitivity reactions including rash, urticaria, angioedema, erythema, pruritus, hypotension, and bronchospasm, with a reported incidence approaching 12% to 16%.^{1,3,4}

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Successful oxaliplatin desensitization protocols have been previously reported using pretreatment with steroids or antihistamines.^{2,5-7} We present an oxaliplatin desensitization protocol that was developed without the use of premedication such as antihistamines and corticosteroids. We sought to spare the patient of long-term corticosteroid exposure because this chemotherapeutic regimen would be used for at least 11 cycles, with the possibility of repeated courses in the future, pending clinical response.

CASE REPORT

A 43-year-old Asian male with metastatic rectal adenocarcinoma was started on chemotherapy with oxaliplatin (85 mg/m²), fluorouracil, and leucovorin every 2 weeks. Three hours after the first infusion of oxaliplatin, fluorouracil, and leucovorin, he developed a generalized pruritic urticarial rash. The rash was not associated with angioedema, hypotension, or bronchospasm. Antihistamines were administered followed by prompt resolution the rash. Two weeks later, a second infusion was performed, and the rash occurred again within 3 hours. He was administered prednisone 30 mg with a short taper and Benadryl 25 mg every 6 hours as needed. The allergy service was consulted to devise and implement an oxaliplatin desensitization protocol. On the basis of the published data regarding hypersensitivity reactions and platinum containing compounds, oxaliplatin appeared to be the likely drug causing the rash.

A desensitization protocol, without premedication, was developed for the third oxaliplatin cycle starting at 1:10,000 of the therapeutic dose followed by doubling doses thereafter until a cumulative goal dose of 175 mg was administered. Fluorouracil and leucovorin were then infused at the usual rates. Skin prick testing, before the procedure, using 5 mg/mL oxaliplatin was negative. Intradermal testing using dilutions of 1:1000, 1:100, and 1:10 were also negative. In vitro anti-oxaliplatin specific immunoglobulin (Ig)E testing using the drug and the patient's serum was negative. The desensitization procedure was performed in a monitored environment in a hospital chemotherapy infusion clinic with appropriate resuscitation equipment for the treatment of anaphylaxis at the bedside.

The preparation and administration of the oxaliplatin was performed as outlined in Table 1. Each of the first 5 doses was administered by intravenous (IV) push over 5 minutes. Doses 6 to 9 were infused over 15 minutes, and doses 10, 11 were infused over 30 minutes, with the last dose over 1 hour. There were a total of 12 doses, with a total infusion time of 3.5 hours.

Table 1. Protocol for Intravenous Desensitization with Oxaliplatin*

Oxaliplatin conc. (mg/mL)	Dose no. [†]	Amount given (mL)	Infusion time (min)	Dose given (mg)
0.05	1	0.36	5	0.018
	2	0.7	5	0.035
	3	3.5	5	0.175
0.5	4	0.6	5	0.3
	5	1.2	5	0.6
	6	2	15	1
5.0	7	0.6	15	3
	8	1.2	15	6
	9	2.4	15	12
	10	4.8	30	24
	11	9.6	30	48
	12	16	60	80
		Totals	205	175

*Oxaliplatin dose: 85 mg/m².

[†]15-20 minutes between doses.

The patient tolerated the desensitization and subsequently received oxaliplatin by way of this protocol every 2 weeks for a total of 13 cycles (2 standard infusions and 11 by way of desensitization protocol) with induction of clinical tumor remission. However, the patient received dexamethasone 12 mg orally in cycles 10 and 11 for nausea. Follow-up revealed tumor remission.

DISCUSSION

This case report demonstrates the utility of desensitization protocols in the setting of a documented hypersensitivity reaction. Previously reported desensitization protocols use intensive premedication regimens using antihistamines and oral steroids. We sought to develop a protocol without premedication for 2 reasons. First, the routine and regular use of high-dose oral steroids is not without side effects. Second, according to Lowery et al.⁸ minimal and easily treated reactions can be identified earlier in the course of the protocol, thereby avoiding progressive serious reactions.

Hypersensitivity reactions are relatively common with platinum-based compounds. Symptoms may occur within minutes to hours and often occur after 4 to 6 doses.⁷ The exact mechanism is unclear; however, both IgE and non-IgE mechanisms are likely involved. We were unable to identify oxaliplatin-specific IgE using an enzyme-linked immunosorbent assay. Furthermore, percutaneous and intracutaneous testing with oxaliplatin was negative. Some authors, however, have found evidence for IgE by demonstrating positive skin tests.⁹ This may be consistent with the spectrum

of hypersensitivity reactions observed with this drug. Garufi et al.⁹ reported 4 positive intradermal skin tests in 5 patients with hypersensitivity reactions associated with oxaliplatin administration. However, rechallenge of the patient with a negative skin test failed. In addition, intradermal testing was negative in 15 patients without hypersensitivity to oxaliplatin. Meyer et al.¹⁰ reported positive skin tests in 6 of 8 patients with prior hypersensitivity reactions. Thomas et al.¹¹ reported positive skin tests in 2 of 3 patients with hypersensitivity. Rechallenge of the patient with a negative skin test failed. Thus, a positive skin test may be helpful, whereas a negative test should be interpreted with caution.

Various desensitization protocols have been reported, varying in length of time and protocol pretreatment regimens. Lim et al.⁶ reported a successful 24 hour desensitization in combination with histamine blockade and IV steroids. Mis et al.² reported a successful desensitization using IV steroids and histamine blockade followed by an 8 hour desensitization. Markman et al.³ reported a successful carboplatin desensitization that entailed the use of a multidrug premedication protocol including antihistamines (H1 and H2), leukotriene modifiers, nonsteroidal anti-inflammatory, oral and IV steroids, and oral beta-agonists. Last, Confino-Cohen et al.¹² reported the successful implementation of a carboplatin desensitization protocol using IV steroids immediately followed by a 6 hour desensitization. This protocol was successful in 20 of 23 patients with a positive skin test to carboplatin.

The desensitization protocol presented is different than those previously reported. First, premedication was not used as to avoid masking the initial signs and symptoms of a hypersensitivity reaction. Second, although this protocol started with a 1:10,000 dilution, doubling doses were administered thereafter. This is in contrast with those reported in which the subsequent doses were increased 10 fold. Third, the rate of infusion was faster with the initial dilutions and slower with the later dilutions.

CONCLUSION

Hypersensitivity reactions to platinum-based chemotherapeutic compounds are commonly observed. Such

hypersensitivity reactions may be IgE or non-IgE mediated. In this report, we present a successful oxaliplatin desensitization protocol, used without premedication, which allowed numerous additional cycles of the drug to be administered with subsequent completion of the chemotherapeutic regimen.

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