Oxaliplatin Allergy Is Not Always What It Seems: A Case Report

Farzanegan R[1], Borrás J[2], Busquier I[3], Castelló JV[1], Torres Gorriz MC[1], Cervera Aznar R[1], Enrique E[1]
[1]*Allergy Department, Castellon University General Hospital, Castellon, Spain*
[2]*Allergy Department, Consortium University Provincial Hospital, Castellon, Spain*
[3]*Oncology Department, Consortium University Provincial Hospital, Castellon, Spain*

J Investig Allergol Clin Immunol 2021; Vol. 31(5): 446-448
doi: 10.18176/jiaci.0655

Key words: Desensitization. Oxaliplatin. Mixed reactions.

Palabras clave: Desensibilización. Oxaliplatino. Reacciones mixtas.

Hypersensitivity reactions to chemotherapy agents are an increasingly common problem that limits patients' therapeutic options, necessitating a switch to second-line treatments and therefore decreasing quality of life and life expectancy. Fortunately, drug desensitization protocols developed during the last decade enable patients to receive first-line treatment, thus minimizing risks and increasing life expectancy [1]. Omalizumab can help to achieve tolerance, even in cases where severe drug reactions cannot be managed despite adequately modified desensitization protocols [2].

According to the widely used Gell and Coombs classification, drug hypersensitivity reactions (DHRs) are divided into 4 types: Type I, IgE-mediated reactions; Type II, antibody-mediated cytotoxicity reactions; Type III, immune complex–mediated reactions; and Type IV, delayed-type hypersensitivity reactions [3]. However, since this classification does not correlate with the actual spectrum of reactions experienced by some patients with HSRs [4,5], a new precision medicine approach based on phenotypes, endotypes, and biomarkers has been proposed [3-7]. This approach encompasses classic DHRs and reactions that do not fit with the classification [7].

We present the case of a 67-year-old man with metastatic colon cancer who was first treated with oxaliplatin between November 2017 and February 2018 with no complications. He required retreatment with oxaliplatin in May 2019 because of a recurrence.

In June 2019, during the second infusion of oxaliplatin (50 mL [27.4 mg]), the patient developed pruritus, urticaria on the thorax, and generalized rash. His vital signs were unaffected. The infusion was stopped immediately, and the reaction was treated with intravenous dexchlorpheniramine and hydrocortisone. The pruritus and urticarial lesions resolved, although mild rash persisted. Tryptase was determined on the same day once acute symptoms had resolved. IL-6 was not determined.

In the evening, the patient came to our emergency department with high fever (38.5°C). Additional tests (blood analysis and blood cultures) yielded normal results, and the patient was sent home with a corticosteroid regimen.

During the following hours, the residual rash progressed to pruritic, microvesicular lesions on the arms, hands, and interdigital area, with residual hyperpigmentation 15 days later.

Skin tests were performed with oxaliplatin in the allergy department 2 weeks after the reaction (prick test, 5 mg/mL; and intradermal test, 0.5 mg/mL and 5 mg/mL) and yielded negative results in both the immediate and the late readings. Tryptase during the reaction was normal (4.2 µg/L).

A general evaluation led to a diagnosis of cytokine release syndrome [7], and the patient was recommended to receive his next oxaliplatin dose following a desensitization protocol.

The third dose of oxaliplatin (154 mg) was programmed for July 2019 following a first 12-step desensitization protocol [3]. Standard hospital premedication was given before starting, with addition of oral aacetaminophen 1 g. No home premedication was given (Table).

No complications were observed until step 12 (80 mL/h, 40 mL [24.6 mg]), when the patient developed mild pruritus on his legs and left shoulder. The infusion was stopped, and 20 mg of ebastine was administered. Once the reaction had resolved, the infusion continued at 80 mL/h, increasing progressively to 90 mL/h and finally to 100 mL/h, owing to good tolerance after the first interruption. When 150 mL (92.4 mg) had been administered, the patient was given preventive oral acetaminophen 500 mg. However, at 175 mL (107.8 mg), he developed chills, vomiting, diarrhea, and, eventually, fever (38°C), with generalized pruritus and exanthema. The infusion was stopped, and treatment was subsequently administered based on symptoms. Tryptase and IL-6 were determined. After discontinuation for more than 4 hours, the desensitization protocol was stopped.

The patient was re-evaluated 2 weeks later, when tryptase and IL-6 during the reaction were 8.4 µg/L and >5000 pg/mL, respectively. Baseline IL-6 was 3 pg/mL. A tryptase level of 4.2 µg/L obtained during the first reaction was taken as baseline, since it was not elevated; consequently, no new determination was performed. Skin tests with oxaliplatin were repeated and proved to be positive at an intradermal dose of 0.05 mg/mL (1/100), with a wheal of 11 × 11 mm. After a new evaluation, the patient was diagnosed with a mixed reaction (IgE-mediated and cytokine release syndrome) [7].

The second desensitization was performed taking the new diagnosis into account. Standard home premedication

was added (prednisone 50 mg), and standard hospital premedication was given (intravenous prednisone 40 mg and oral acetaminophen 1 g). The patient also received continuous hydration with saline solution 200 mL/h. The total oxaliplatin dose was reduced, with 75% of the total necessary dose administered. The final infusion velocity was 60 mL/h, and the desensitization protocol was completed without complications. A further 6 desensitizations were successful, and the protocol could be modified gradually owing to the patient's good tolerance to previous desensitization. The total dose was eventually reached, with shortening of administration time and reduction in premedication. The patient tolerated each stage of the protocol (Table).

The patient completed his treatment with oxaliplatin and is currently in standard follow-up for his disease.

Platins are one of the most immunogenic chemotherapeutic treatments. Reactions to these agents normally present as Type I hypersensitivity reactions and typically require repeated exposures. Oxaliplatin is an exception, in that first lifetime exposure reactions have been documented and reactions can be complicated by factors such as typical IgE-mediated symptoms and atypical symptoms such as back and pelvic pain and cytokine-mediated fever and chills [7-10]. Antibody-mediated thrombocytopenia and immune complex–mediated syndromes with urticaria and proteinuria have also been observed [4,8].

Table. Consecutive Changes Made in Successive Desensitization Protocols

	Home premedication	Hospital premedication	Protocol	Target dose of oxaliplatin, %	Final velocity of infusion reached, mL/h	Total dose administered, %
First desensitization	No	Hospital standard premedication[a] + acetaminophen 1 g	12 steps 3 bags	100%	100 mL/h	70%
Second desensitization	Home standard premedication[b] + prednisone 50 mg	Hospital standard premedication + acetaminophen 1g + prednisone 40 mg + continuous hydration with saline solution 200 mL/h	12 steps 3 bags	75%	60 mL/h	100%
Third desensitization	Home standard premedication + prednisone 50 mg	Hospital standard premedication + acetaminophen 1 g + prednisone 40 mg + continuous hydration with saline solution 200 mL/h	12 steps 3 bags	100%	60 mL/h	100%
Fourth desensitization	Home standard premedication + prednisone 50 mg	Hospital standard premedication + acetaminophen 1 g + prednisone 40 mg + continuous hydration with saline solution 200 mL/h	12 steps 3 bags	100%	80 mL/h	100%
Fifth desensitization	Home standard premedication	Hospital standard premedication + acetaminophen 1 g + continuous hydration with saline solution 200 mL/h	8 steps 2 bags	100%	90 mL/h	100%
Sixth desensitization	Home standard premedication	Hospital standard premedication + acetaminophen 1 g	8 steps 2 bags	100%	100 mL/h	100%
Seventh and eighth desensitizations	Same as sixth desensitization					

[a]Hospital standard premedication: intravenous ranitidine, intravenous dexchlorpheniramine, sublingual diazepam.
[b]Home standard premedication: montelukast 10 mg, ebastine 20 mg, ranitidine 150 mg 2 days before desensitization, adding lorazepam 1 mg 1 day before desensitization, and only montelukast 10 mg the same morning before desensitization. Acetylsalicylic acid was not administered because the patient was receiving long-term treatment with dabigatran (oral anticoagulant treatment).

Colorectal cancer is currently the third most common cancer in western countries, and because oxaliplatin is a key chemotherapeutic agent, its increasing use leads to more frequent DHRs. However, it is difficult to calculate the exact prevalence of these DHRs owing to variability in their clinical presentations [8].

We report a mixed reaction to oxaliplatin. Mixed reactions present as an overlap in the symptoms of Type I reactions and cytokine release reaction, thus making it difficult to differentiate between them [7]. In this type of reaction, both tryptase and IL-6 can be elevated [4].

Personalized evaluation and risk stratification are needed in patients who experience DHRs. Thanks to the application of the new classification based on phenotypes, endotypes, and biomarkers, treatment can be tailored, and chemotherapy can be successfully administered following desensitization protocols.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Berges-Gimeno MP, Carpio-Escalona LV, Longo-Muñoz F, Bernal-Rubio L, Lopez-Gonzalez P, Gehlhaar P, et al. Does Rapid Drug Desensitization to Chemotherapy Affect Survival Outcomes? J Investig Allergol Clin Immunol. 2020;30(4):254-63.
2. Prieto-García A, Noguerado B, Rojas P, Torrado I, Rodríguez-Fernández A, Tornero P. Unexpected Anaphylaxis After Completing a Desensitization Protocol to Oxaliplatin: Successful Adjuvant Use of Omalizumab. J Investig Allergol Clin Immunol. 2019;29(1):53-5.
3. De las Vecillas Sánchez L, Alenazy L, Garcia Neuer M, Castells M. Drug Hypersensitivity and Desensitizations: Mechanisms and New Approaches. Int J Mol Sci. 2017;18(6):1316.
4. Castells M. Drug Hypersensitivity and Anaphylaxis in Cancer and Chronic Inflammatory Diseases: The Role of Desensitizations. Front Immunol. 2017;8:1472.
5. Isabwe GA, Garcia Neuer M, De las Vecillas Sanchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes. J Allergy Clin Immunol. 2018;142(1):159-70.
6. Muraro A, Lemanske Jr RF, Castells M, Torres MJ, Khan D, Simon H-U, et al. Precision medicine in allergic disease-food allergy, drug allergy, and anaphylaxis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology. Allergy. 2017;72(7):1006-21.
7. Wilfox Jimenez-Rodriguez T, Garcia Neuer M, Alenazy L, Castells M. Anaphylaxis in the 21st century: phenotypes, endotypes, and biomarkers. J Asthma Allergy. 2018;11:121-42.
8. Caiado J, Castells M. Presentation and Diagnosis of Hypersensitivity to Platinum Drugs. Curr Allergy Asthma Rep. 2015;15(4):15.
9. T Wong J, Ling M, Patil S, Banerji A, Long A. Oxaliplatin Hypersensitivity: Evaluation, Implications of Skin Testing, and Desensitization. J Allergy Clin Immunol Pract. 2014;2(1):40-5.
10. Silver J, Garcia-Neuer M, Lynch DM, Pasaoglu G, Sloane DE, Castells M. Endophenotyping Oxaliplatin Hypersensitivity: Personalizing Desensitization to the Atypical Platin. J Allergy Clin Immunol Pract. 2020;8(5):1668-80.

Manuscript received August 2, 2020; accepted for publication November 23, 2020.

Farzanegan R
Allergy Department
Castellon University General Hospital
Castellon
Spain
E-mail: roxana.farzanegan@gmail.com