

Oxaliplatin Allergy is not Always what it Seems. A Case Report

Farzanegan R¹, Borrás J², Busquier I², Castelló JV¹, Torres Gorriz MC¹, Cervera Aznar R¹, Enrique E¹

¹Allergy Department. Castellon University General Hospital. Castellon. Spain.

²Allergy Department. Consortium University Provincial Hospital. Castellon. Spain.

Corresponding author:

Roxana Farzanegan Miñano

Allergy Department, Castellon University General Hospital. Castellon. Spain.

E-mail address: roxana.farzanegan@gmail.com

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Hypersensitivity reactions to chemotherapy agents (HRC) are an increasing problem that limits patients' therapeutic options, needing to change to second line treatments, therefore decreasing quality of life and life expectancy. Fortunately, during the last decade drug desensitization protocols have been developed, allowing patients to receive first line treatment, minimizing risks and increasing life expectancy [1]. Even when patients with severe drug reactions cannot be managed despite adequately modified desensitization protocols, the use of Omalizumab can help to achieve tolerance [2].

Common classification for drug hypersensitivity reactions (HSRs) corresponds to Gell and Coombs classification: Type I (IgE mediated), Type II, (antibody mediated cytotoxicity reactions), Type III (immune complex-mediated reactions), and Type IV for delayed type hypersensitivity [3]. However, this classification does not correlate with actual spectrum of reactions experienced by some patients with HSRs [4,5] reason why a new approach based on precision medicine through phenotypes, endotypes and biomarkers has been proposed [3-7] encompassing the classic HSRs and reactions that do not correspond to this classification [7].

We present the case of a 67-year-old man, with metastatic colon cancer, first treated with oxaliplatin between November 2017 and February 2018 with no incidence, needing oxaliplatin retreatment in May 2019, due to illness relapse.

In June 2019, during second dose of oxaliplatin, at 50ml (27,4mg) dose infusion, the patient started with pruritus, urticarial reaction on thorax and generalized rash. Constants were maintained. Immediately, infusion was stopped and reaction was treated with intravenous (iv) dexchlorpheniramine and hydrocortisone with resolution of pruritus and urticarial lesions but, mild rash persistence. Tryptase determination was performed that same day, once acute symptoms were resolved, not performing IL-6 determination.

That same night our patient attended hospital's emergency room due to high fever (38.5°C). Complementary tests (blood analysis and blood cultures) were done being all normal so he was sent home on a corticosteroid regime.

In the following hours, the residual rash progressively turned into pruritic, micro vesicular lesions distributed on arms, hands and interdigital zone, leaving residual hyperpigmentation 15 days later.

Once seen in the Allergy Department 2 weeks after the reaction, skin test with oxaliplatin were done (prick test: 5mg/ml and intradermal test: 0.5mg/ml and 5mg/ml) being all negative in immediate and late reading. Tryptase during the reaction was $4.2 \mu\text{g/l}$ (corresponding to a normal value).

After overall evaluation, diagnosis of cytokine release syndrome was given [7], indicating next oxaliplatin dose should be administered following desensitization protocol.

In July 2019, 3rd dose of oxaliplatin (154 mg) was programmed following 1st desensitization protocol of 12 steps [3]. Hospital standard premedication was given before start, adding oral acetaminophen 1g. No home premedication was given (Table 1).

Desensitization carried on with no incidence until step 12 (80ml/h, 40ml (24.6mg) passed) moment in which the patient started with mild pruritus on legs and left shoulder. Infusion was stopped and 20mg ebastine was given. Once reaction resolved, infusion continued at 80ml/h, progressively increasing up to 90ml/h and finally 100ml/h, due to posterior good tolerance after 1st stop. When 150ml (92.4mg) had passed, preventive oral acetaminophen 500mg was given, but when 175ml (107.8mg) of infusion was reached, the patient started with chills, vomits, diarrhea and progressively, fever up to 38°, generalized pruritus and exanthema. Infusion was stopped, and successive treatment based upon symptoms was administered. Tryptase and IL-6 determinations were performed. Finally, after more than 4 hours stop, desensitization could not be continued.

Patient was reevaluated 2 weeks later. In this occasion, tryptase and IL-6 determination during reaction were 8.4 µg/l and > 5000 pg/ml respectively. Basal IL-6 level was performed being 3 pg/ml. Tryptase level of 4.2 µg/l obtained during first reaction was taken as a basal level, as it was not elevated, so no new determination was performed. Skin test with oxaliplatin were repeated, being positive at intradermal dose 0.05mg/ml (1/100), with a papule of 11x11mm. After new evaluation, patient was diagnosed of a mixed reaction (IgE-mediated and cytokine release reaction) [7].

2nd desensitization was performed taking account of the new diagnosis. Home standard premedication was added, adding Prednisone 50mg; hospital standard premedication was given, adding prednisone 40mg iv and oral acetaminophen 1g; continuous hydration with saline solution 200ml/h was added too. Total oxaliplatin dose was reduced, administering 75% of total dose needed, and final infusion velocity was 60ml/h, being able to carry out desensitization with no incidences. Successively, 6 more desensitization's could be managed successfully, being able to progressively modify each protocol thanks to good patients' tolerance to previous desensitization. Progressively total dose administration

was reached, shortening of time administration and reduction of premedication was achieved, obtaining good tolerance in all of them (Table).

Finally, patient finished oxaliplatin treatment and actually makes normal life taking oncological follow up.

One of the most immunogenic chemotherapeutic treatments are platins. Reactions to these agents normally present as Type I hypersensitivity reactions, and typically require repeated exposures. Oxaliplatin is an exception to this, as first lifetime exposure reactions have been documented and reactions can be more complex with features including 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].

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 increased HSRs, not being able to calculate its exact prevalence due to the variability of clinical presentations [8].

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

Individual evaluation and risk stratification are needed in patients who suffer HRC. Thanks to the application of the new classification of HSR based on phenotypes, endotypes and biomarkers, a precise medicine can be offered to this patients and chemotherapy treatment can be successfully administered following desensitization protocols.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Table. Consecutive changes made upon successive desensitization protocols

	Home Premedication	Hospital Premedication	Protocol	Target dose of oxaliplatin (%)	Final velocity of infusion reached (ml/h)	Total dose administered (%)
1st Desensitization	No	Hospital standard premedication † + Acetaminophen 1g	12 steps 3 bags	100%	100ml/h	70%
2nd Desensitization	Home standard premedication** + Prednisone 50mg	Hospital standard premedication + Acetaminophen 1g + Prednisone 40mg + Continuous Hydration with saline solution 200ml/h	12 steps 3 bags	75%	60ml/h	100%
3rd Desensitization	Home standard premedication + Prednisone 50mg	Hospital standard premedication + Acetaminophen 1g + Prednisone 40mg + Continuous Hydration with saline solution 200ml/h	12 steps 3 bags	100%	60ml/h	100%
4th Desensitization	Home standard premedication + Prednisone 50mg	Hospital standard premedication + Acetaminophen 1g + Prednisone 40mg + Continuous Hydration with saline solution 200ml/h	12 steps 3 bags	100%	80ml/h	100%
5th Desensitization	Home standard premedication	Hospital standard premedication + Acetaminophen 1g + Continuous Hydration with saline solution 200ml/h	8 steps 2 bags	100%	90ml/h	100%
6th Desensitization	Home standard premedication	Hospital standard premedication + Acetaminophen 1g	8 steps 2 bags	100%	100ml/h	100%
7th and 8th Desensitization	Same as 6th Desensitization					

† ‡ Home standard premedication: (Montelukast 10mg, Ebastine 20mg, Ranitidine 150mg) two days before desensitization, adding Lorazepam 1mg one day before desensitization, and just montelukast 10mg the same morning before desensitization. Acetylsalicylic acid was not administered because our patient was under chronic treatment with dabigatran (anticoagulant oral treatment).