

Successful desensitization to oxaliplatin after a single initial dose of omalizumab in a patient with elevated IgE levels

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Omalizumab, an anti-IgE monoclonal antibody, is used as an adjuvant in hymenoptera venom immunotherapy and in induction of oral tolerance in food allergy [1,2]. Few cases of its use in platinum desensitizations have been reported, and each one employs a different regimen [3-5]. We present a case of successful oxaliplatin desensitization achieved after a single initial dose of omalizumab, in a patient with elevated IgE levels upon oxaliplatin reintroduction, and after severe hypersensitivity reactions (HSRs) during previous desensitization attempts.

A 57-year-old patient diagnosed with metastatic sigmoid adenocarcinoma was initially treated in 2014 with nine cycles of folinate, oxaliplatin and 5-fluorouracil. In 2016 he received eight cycles of folinate, irinotecan and 5-fluorouracil. Later that year his treatment was substituted for gemcitabine, oxaliplatin and bevacizumab. He tolerated one cycle of this regimen. During the second cycle, after receiving gemcitabine and while receiving oxaliplatin, he experienced generalized erythema, cough, dyspnea and oxygen desaturation. Intradermal testing to oxaliplatin (0.5 mg/ml) was positive (negative prick test, 5 mg/ml). Prick (38 mg/mL) and intradermal (0.38 mg/ml) tests to gemcitabine were negative. Oxaliplatin was substituted with irinotecan while maintaining gemcitabine and bevacizumab. He tolerated 3 cycles of this new regimen. During the fourth cycle, however, while receiving irinotecan, he presented with anaphylaxis (facial erythema, dyspnea and pharyngeal pruritus). Intradermal testing to irinotecan (2 mg/ml) was positive (negative prick test, 20 mg/mL).

In 2018, due to cancer progression, the patient was assigned treatment with folinate, oxaliplatin, 5-fluorouracil and bevacizumab. A first 12-step desensitization [6]

to oxaliplatin was completed without adverse symptoms. Premedication with acetylsalicylic acid (ASA) was avoided for this desensitization, due to a history of angioedema possibly related to this drug (he tolerated other nonsteroidal anti-inflammatory drugs). He received oral premedication with 10-mg montelukast two days before administration, and with 10-mg montelukast and 300-mg ranitidine on the day of administration. The oncology department added intravenous premedication with 20-mg dexamethasone and 5-mg dexchlorpheniramine, and 1-g oral acetaminophen.

During the second desensitization, however, the patient experienced facial erythema, wheezing, dyspnea, oxygen desaturation (89%), tachycardia (110 bpm), and hypotension (80/50 mmHg) during step 10 (7-mg threshold dose). Forty-eight hours later, a new, 16-step attempt failed due to facial erythema, cough and oxygen desaturation (89%) during step 14 (7-mg threshold).

Retrospectively analyzed serum samples from 24 hours before and immediately after the first unsuccessful desensitization showed total IgE levels of 6900 and 7410 kU/L, respectively. Serum tryptase samples were drawn immediately after the 12-step desensitization (2.03 ug/L), and immediately and 2 hours after the 16-step desensitization (<1.00 ug/L in both cases). Baseline tryptase levels were of 1.37 ug/L, and eosinophil counts were normal. Skin testing to a standard allergen battery and stool parasites tests were negative. He reported no previous history of allergic disease (atopic dermatitis, rhinoconjunctivitis, asthma), alcohol intake or tuberculosis. A provocation test with 300mg of ASA was completed without adverse symptoms.

We administered a single, 300 mg dose of subcutaneous omalizumab 19 days before re-attempting desensitization. We employed an 18-step protocol, and 300 mg of ASA were added to the premedication regimen. He experienced facial and upper-extremity erythema during the fifteenth step (cumulative oxaliplatin dose: 7.2 mg) that

responded quickly to intravenous dexchlorpheniramine. Desensitization was re-started 30 minutes later by repeating the previous step and resuming the protocol. There were no new symptoms. This procedure was repeated every two weeks for four subsequent cycles, using 300 mg of omalizumab two weeks before each cycle. No new hypersensitivity events occurred, and the patient achieved clinical stability of cancer. Variation in total IgE levels is shown in Figure 1.

The use of anti-IgE treatment as an adjuvant for desensitization in cases of refractory platinum hypersensitivity was first described in 2012 by Cahill et al. in a patient with previous failed desensitizations to oxaliplatin [3], and later in 2014 by Ojaimi et al. in a case of carboplatin desensitization [4]. Cahill et al. used two doses of 150 mg, one every two weeks, followed by a 16-step protocol [3]. Ojaimi et al. used three doses of 300 mg, one every two weeks, prior to desensitization [4]. Recently, Prieto-García et al. (2019) employed a single 300 mg dose of omalizumab one week before desensitization [5].

To the best of our knowledge, initial total IgE levels in these reports were not elevated. In our case, however, total IgE levels were consistently high before the first severe HSR, after re-exposure to oxaliplatin. We cannot confirm whether this IgE profile occurred due to specific IgE against oxaliplatin or to underlying systemic causes, but it defined our patient as a challenging case for desensitization. Regardless, omalizumab was effective as an adjuvant after a single dose, and repeated use resulted in tolerance of all subsequent cycles. Considering this may prove useful when developing omalizumab protocols in such situations.

It is important to mention that, in our case, factors other than omalizumab may have led to a favorable outcome. Protocol extension and ASA were added concomitantly to omalizumab. The use of longer protocols has been described as a

means to achieve desensitization tolerance [7], and this may have aided in the final result. Breslow et al. described the efficacy of pretreatment with ASA and montelukast in lessening the severity and the frequency of HSRs to chemotherapy during desensitization [8]. There is little further evidence proving this guarding effect, but we cannot rule out its contribution in our patient. Further studies are necessary in patients with a history of failed desensitizations despite protocol modification and complete premedication regimens.

Our patient's total IgE profile, however, leads us to believe that tolerance without anti-IgE treatment would have been difficult. Observed variations in total IgE levels are worth noting (Figure 1). Prior to receiving anti-IgE treatment, levels had declined from 7410 to 4690 kU/L in a two-week period without significant interventions, possibly in part due to intra-test variation [9]. Three weeks after the initial dose of omalizumab, we observed a further decline in total IgE from 4690 to 2664 kU/L, similar to that observed by Ojaimi et al.⁴ Finally, total IgE levels had descended to 575 kU/L five months after receiving the last dose of omalizumab. This clear reduction may partially explain the observed oxaliplatin desensitization [10].

In cases of advanced cancer where delay in treatment may impair prognosis, time-sparing solutions after unsuccessful desensitizations are clearly beneficial. We report a case of successful platin desensitization after a single dose of omalizumab, in a patient with a challenging IgE profile. Our outcome may indicate that the use of single-dose anti-IgE regimens -along with protocol modification- could be as effective as regimens that employ multiple doses before reattempting desensitization. This seems to be true even in patients with elevated total IgE and a history of repeatedly failed desensitization attempts.

Disclosures

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FIGURE 1: Patient Evolution and IgE Levels upon Re-Exposure to Oxaliplatin

*During this desensitization 300 mg acetylsalicylic acid (ASA) were added to the rest of the patient's premedication.

**At this point the patient had received a total of 3 doses of omalizumab (300mg each). The sample was taken on the day of the 3rd 18-step desensitization.

***This sample was taken 5 and a half months after the last dose of omalizumab was administered, and 6 months after the 5th and last 18-step desensitization.

