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## Adjuvant Use of Omalizumab in Desensitization to Chemotherapeutics: Beyond IgE-Mediated Reactions

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Drug desensitization is an effective procedure for patients with drug hypersensitivity reactions (HSRs), enabling first-line therapies to be continued. This is particularly relevant in patients with cancer. In some difficult cases, desensitization cannot be completed successfully owing to breakthrough reactions despite adapted 16-step protocols and premedication [1-8].

Omalizumab binds to free serum IgE, thus preventing its ability to bind to FcεRI on the surface of mast cells and basophils and reducing cell signaling and degranulation. In addition to its current approved indications, omalizumab has been used off-label in other conditions, eg, as an adjuvant in induction of food tolerance and venom immunotherapy.

The use of omalizumab as an adjuvant in drug desensitization to chemotherapeutics has been increasingly reported [1-8]. We present 8 patients and review the literature (Supplementary Table) to provide conclusive evidence.

All patients underwent unsuccessful desensitization with a 4-bag, 16-step protocol with premedication (dexchlorpheniramine 5 mg, ranitidine 50 mg, montelukast 10 mg, acetylsalicylic acid 300 mg) 1 hour before starting subcutaneous omalizumab (300 mg per dose) [2,3]. Demographic, clinical features, omalizumab regimens, and outcomes are shown in the Table.

The patients gave their written informed consent for their data to be published.

**Patient 1:** The first rituximab infusion was completed despite urticaria. The second was stopped because of urticaria, profuse sweating, hypotension (60/40 mmHg), and confusion. A first desensitization was not completed, with urticaria appearing 3 times at step 16. Omalizumab was administered 14 and 3 days before the following desensitization, although generalized urticaria appeared at step 16. The patient refused to continue.

**Patient 2:** During the seventh oxaliplatin infusion, the patient developed facial pruritus, dyspnea, oxygen saturation (SpO<sub>2</sub>) 70%, hypotension (70/30 mmHg), altered level of consciousness, and bradycardia requiring intramuscular (IM)

epinephrine. Desensitization was withdrawn after 2 episodes of facial erythema and SpO<sub>2</sub> 88%, once at step 7 and then at step 8 (reaction tryptase, 44.7; basal, 3.2 µg/L). A second attempt at adding omalizumab 6 days before was unsuccessful, and the patient developed the same symptoms as in step 1. Oxaliplatin was withdrawn.

**Patient 3:** During the seventh oxaliplatin infusion, the patient developed palmar and pharyngeal pruritus, erythematous rash, dyspnea, nausea, abdominal pain, diarrhea, and dizziness. Desensitization to oxaliplatin was completed. However, 1 hour later, she experienced nausea, profuse sweating, pallor, abdominal pain, dizziness, hypotension (74/50 mmHg), chills, and fever 38°C. Intensive fluid therapy and meropenem were initiated. Additional tests ruled out infection. The same reaction was recorded 30 minutes later in the following desensitization. Omalizumab was initiated 1 week before the following desensitization, with no further reactions.

**Patient 4:** During the eighth carboplatin infusion, the patient developed itchy throat, cough, dyspnea, SpO<sub>2</sub> 83%, and itchy red palms and face. Desensitization was completed with a cutaneous reaction at step 15. During the following desensitizations, the skin reaction reappeared earlier and was more extensive despite addition or prolongation of protocol steps. It was not possible to complete the infusion. Omalizumab was administered 1 and 14 days before the following, well-tolerated desensitization.

**Patient 5:** During the sixth oxaliplatin infusion, the patient developed palmoplantar pruritus/erythema, dizziness, body pain, malaise, nausea, shivering, and dyspnea. Six desensitizations were completed, with mild intercurrent palmar

pruritus. During the seventh desensitization, at step 12, the patient developed itchy and erythematous palms, abdominal pain, nausea, malaise, and hypotension (88/54 mmHg), requiring intramuscular epinephrine. Omalizumab was administered 1 week before the following cycle, with no further reactions.

**Patient 6:** During the second docetaxel infusion, the patient experienced itchy throat, cough, nausea, tongue and lip edema, and generalized urticaria. Desensitization was attempted, although itchy throat and urticaria developed at steps 10, 12, and 13. Omalizumab was initiated 14 and 7 days before the following desensitization. Infusion was completed, although the patient developed urticaria at steps 14, 15, and 16. An additional desensitization was completed with only 3 small hives lasting 10 minutes at step 14. It was not necessary to stop the infusion.

**Patient 7:** In 2008, the patient experienced shivers during almost all 17 oxaliplatin infusions. These required acetaminophen and corticosteroids, and the protocol was completed. In 2022, FOLFOX-cetuximab was scheduled. The first 12-step desensitization protocol was well tolerated. The patient subsequently experienced a breakthrough cutaneous reaction at steps 11 and 12, and oxaliplatin was stopped. A 16-step protocol was attempted, although the patient experienced a generalized cutaneous reaction and bronchospasm (SpO<sub>2</sub> 90%) at step 13. He received 2 doses of omalizumab before the following desensitization, which was not completed owing to generalized cutaneous reactions at steps 14 and 16. The third dose of omalizumab in 15 days was indicated before the following desensitization, which was successfully

**Table.** Demographic and Clinical Characteristics of the 8 Patients Who Underwent Desensitization to Chemotherapeutics With Adjuvant Use of Omalizumab.

P#	Sex/age	Cancer/ChT	Culprit drug	Severity of IR <sup>a</sup>	Skin tests	Phenotype	OMZ before next DS/ maintenance	Outcome/ tolerated cycles
1	M/78	Lymphoma B-R	Rituximab	Grade 3	+ID 10 mg/mL	Type 1 (IgE)	2 doses/ stopped	Discontinued
2	M/58	Rectal FOLFOX	Oxaliplatin	Grade 3	+ PT 5 mg/mL	Type 1 (IgE)	1 dose/ stopped	Discontinued
3	F/62	Colon FOLFOX	Oxaliplatin	Grade 2	+ ID 5 mg/mL	Mixed	1 dose/ every 2 wk	15 cycles
4	F/47	Ovarian T-C	Carboplatin	Grade 3	+ ID 0.1 mg/mL	Type 1 (IgE)	2 doses/every 4 wk	3 cycles
5	F/50	Colon CAPOX	Oxaliplatin	Grade 2	– (2 years after IR)	Mixed	1 dose/ every 2 wk	3 cycles
6	F/38	Breast D-C	Docetaxel	Grade 2	+ PT 10 mg/mL	Type 1 (IgE)	2 doses/ every 4 wk	2 cycles (MCR at first)
7	M/59	Colorectal FOLFOX-C	Oxaliplatin	Grade 2	+ PT 5 mg/mL	Type 1 (IgE)	2 doses/1st in 2 wk then every 4 wk	5 cycles (MCR at first)
8	F/74	Ovarian C-G	Carboplatin	Grade 3	+ ID 1 mg/mL	Type 1 (IgE)	2 doses/ -	1 cycle (MCR)

Abbreviations: B-R, bendamustine-rituximab; CAPOX, capecitabine-oxaliplatin; ChT, chemotherapy regimen; C-G, carboplatin-gemcitabine; D-C, docetaxel-carboplatin; DS, desensitization; F, female; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOX-C, FOLFOX-cetuximab. ID, intradermal reaction; IR, initial reaction; M, male; MCR, mild cutaneous reaction; OMZ, omalizumab; P#, patient number; PT, prick test; T-C, taxol (paclitaxel)-carboplatin.

<sup>a</sup>Severity of IR according to Brown scale.

completed, with only mild palmar pruritic erythema at step 14. Omalizumab was maintained monthly, and the patient tolerated 4 additional desensitizations.

Patient 8: During the fourth carboplatin infusion, the patient developed intense dizziness, facial flushing, oxygen desaturation, and refractory hypotension requiring intense fluid therapy, 3 doses of intramuscular epinephrine, and admission to the intensive care unit. Desensitization was performed in the intensive care unit. At step 15, the patient developed palmar pruritus and erythema, with chest tightness and diffuse cutaneous erythema lasting 2 hours after treatment, which included intramuscular epinephrine. The infusion was stopped. After 2 doses of omalizumab, the following desensitization was attempted in the intensive care unit. Milder diffused erythema developed at step 15, resolving in 2 hours with antihistamines and corticosteroids. The infusion was resumed and completed with no further reactions. No additional cycles have been needed to date.

We present 8 patients with severe HSRs to chemotherapeutics and unsuccessful desensitizations. Adjuvant omalizumab made it possible to complete desensitization in most cases with mild or no reactions.

Several endotypes and phenotypes have been characterized in HSRs to chemotherapeutics, especially oxaliplatin [9]. Of note, in our series, omalizumab was useful not only in type 1 but also in mixed-phenotype HSRs (cases 3 and 5), preventing cytokine release-related symptoms, as reported elsewhere [1]. This points to a close interaction between IgE-dependent and cytokine release mechanisms in oxaliplatin-induced mixed reactions.

The endotype in each case was based on clinical features, with pain and shivering/fever as indicators of a cytokine release mechanism [9], and on skin-tests results. However, biomarkers such as serum tryptase and IL-6 were not measured in all cases.

Furthermore, with more omalizumab doses given and desensitizations performed, greater efficacy is achieved in tolerance of desensitization, as shown in cases 6 and 7 in our series and in cases reported elsewhere [4,6]. This could be explained by a progressive downregulating effect of omalizumab on FcεRI expression on the surface of the mast cell. Desensitization could potentiate this effect through the involvement of regulatory cytokines such as IL-10 [10].

The number of doses of omalizumab needed to achieve tolerance to desensitization seems to be variable, as shown in our series and in the literature. There is no consensus on dose regimens. Our proposal is to administer 2 doses of omalizumab 300 mg before desensitization, with a maintenance dose every 2-3 weeks (depending on the chemotherapy regimen) if a breakthrough reaction persists. When desensitization is tolerated, the administration interval for omalizumab can be extended to every 4 weeks.

Omalizumab is an effective adjuvant tool in drug desensitization to chemotherapeutics. The dosing regimen could be personalized according to tolerance to desensitization. It is useful not only in type 1 IgE-dependent HSRs, but also in mixed HSRs to oxaliplatin. In addition, effectiveness seems to increase with the number of doses and desensitizations performed. In the absence of clinical trials for this indication of omalizumab, reporting clinical experience is very helpful.

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### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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