Adyuvant 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 (HSR), enabling to continue first-line therapies, which is particularly relevant in patients with cancer. In some difficult cases, it cannot be successfully completed, due to breakthrough reactions despite adapted 16-step-protocols and all premedications [1-8].

Omalizumab binds to free serum-IgE preventing its linking to FcεRI on mast-cell and basophil surface, reducing cell-signaling and degranulation. In addition to its current approved indications, omalizumab has been used off-label in other conditions such as an adjuvant in food tolerance induction and venom immunotherapy.

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

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

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CASE 1: First rituximab infusion was completed despite urticaria. Second was withdrawn due to urticaria, profuse sweating, hypotension (60/40 mmHg) and confusion. A first desensitization was not completed, appearing urticaria three times at step-16. Omalizumab was administered 14 and 3 days before following desensitization but generalized urticaria appeared at step-16. The patient refused to continue.

CASE 2: During 7th oxaliplatin infusion facial pruritus, dyspnea, oxygen saturation (SpO2) 70%, hypotension 70/30 mmHg, obnubilation and bradycardia appeared, requiring intramuscular (im) epinephrine. Desensitization was withdrawn after suffering facial erythema and SpO2 88% twice, at steps-7 and 8 (reaction tryptase 44.7; basal 3.2 mcg/L). A second attempt adding omalizumab 6 days before was unsuccessful developing same symptoms at step-1. Oxaliplatin was withdrawn.

CASE 3: At 7th oxaliplatin infusion, palmar/pharyngeal pruritus, erythematous rash, dyspnea, nausea, abdominal pain, diarrhea, and dizziness developed. Oxaliplatin desensitization was completed, but one hour later, she suffered nausea, profuse sweating, pallor, abdominal pain, dizziness, hypotension 74/50 mmHg, chills and fever 38ºC. Intensive fluid-therapy and meropenem were initiated. Complementary studies discarded infection. Next desensitization resulted in same reaction 30 minutes later. Omalizumab was initiated one week before next desensitization, and no reaction appeared afterwards.

CASE 4: Within 8th carboplatin infusion, the patient developed itchy throat, cough, dyspnea, SpO2 83%, itchy red palms and face. Desensitization was completed with cutaneous reaction at step-15. During next desensitizations skin reaction reappeared earlier and more extensive despite

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adding/prolonging protocol-steps, and finally precluding infusion completion. Omalizumab was administered 1 and 14 days before well-tolerated next desensitization.

CASE 5: During 6th oxaliplatin infusion the patient presented palmoplantar pruritus/erythema, dizziness, body pain, malaise, nausea, shivering and dyspnea. Six desensitizations were completed with mild intercurrent palmar pruritus. During 7th desensitization, at step-12 itchy/erythematous palms, abdominal pain, nausea, malaise, and hypotension 88/54 mmHg developed, requiring im epinephrine. Omalizumab was administered, one week before next cycle with no further reaction.

CASE 6: During 2nd docetaxel infusion, the patient suffered itchy throat, cough, nausea, tongue/lip edema and generalized urticaria. Desensitization was attempted but itchy throat and urticaria developed at steps 10-12-13. Omalizumab was initiated, 14/7 days before next desensitization. Infusion was completed although urticaria developed at steps 14-15-16. An additional desensitization was completed with only 3 small hives at step-14 lasting 10 minutes without stopping infusion.

CASE 7: in 2008 the patient suffered shivers during almost all 17 oxaliplatin infusions requiring acetaminophen and corticosteroids to complete them. In 2022, FOLFOX-cetuximab was scheduled. First 12-step desensitization protocol was well tolerated. Next, resulted in breakthrough cutaneous reaction at steps 11/12, stopping oxaliplatin administration. A 16-step protocol was attempted but generalized cutaneous reaction and bronchospasm (SpO2 90%)

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developed at step-13. He received 2 doses of omalizumab before next desensitization which was not completed due to generalized cutaneous reactions at steps-14 and 16.

Third dose of omalizumab in 15 days was indicated before next desensitization, which was successfully completed, with only mild palmar pruritic erythema at step-14.

Omalizumab was maintained monthly, tolerating 4 additional desensitizations.

CASE 8: During 4th carboplatin infusion intense dizziness, facial flushing, oxygen desaturation and refractory hypotension developed, requiring intense fluid therapy, 3 doses of im epinephrin and MICU admission. Desensitization was performed at MICU. At step-15, palmar pruritus and erythema started, with chest tightness and diffuse cutaneous erythema lasting 2 hours after treatment, including im epinephrin. Infusion was withdrawn. After 2 doses of omalizumab, next desensitization was attempted at MICU. Milder diffused erythema developed at step-15, resolving in 2 hours with antihistamine and corticosteroid. Infusion was resumed and completed with no further reaction. No more cycles were needed so far.

DISCUSSION

We present 8 patients with severe HSR to chemotherapeutics and unsuccessful desensitizations. Adjuvant omalizumab enable to complete desensitization in most of them with milder or no reaction.

Different endotypes/phenotypes have been characterized in chemotherapeutics HSR, particularly for oxaliplatin [9]. Of note, in our series, omalizumab was useful not only in type-1 but also in mixed-phenotype HSR (cases 3, 5), preventing cytokine-release related symptoms, as shown in

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another case reported [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-released mechanism [9], and on skin-tests results. However, biomarkers as serum-tryptase and IL6 were not measured in all cases.

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

The number of doses of omalizumab needed to achieve desensitization tolerance seems to be variable, as shown in our series and in the literature. No consensus about dose regimen exists. Our proposal is to give 2 doses of omalizumab 300 mg before desensitization, maintaining a dose every 2-3 weeks (depending on chemotherapy regimen) if a breakthrough reaction persists. When desensitization tolerance is achieved, omalizumab could be spaced out to every-4-weeks.

Omalizumab is an effective adjuvant tool in drug desensitization to chemotherapeutics. Dose regimen could be personalized according to desensitization tolerance. It is useful in Type-1 IgE-dependent but also in mixed HSR to oxaliplatin, and effectiveness seems to increase with the number of doses and desensitizations performed. In the absence of clinical trials for this indication of omalizumab, to report clinical experience is of major help.

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Conflict of Interest

Authors disclose any financial relationship with a pharmaceutical manufacturer for this study.

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Table 1. Demographic and clinical characteristics of the 8 patients who underwent desensitization to chemotherapeutics with adjuvant use of omalizumab. * IR severity according to Brown scale.

P #	Gender / age	Cancer/ ChT	Culprit drug	*IR severity	Skin tests	Pheno -type	OMZ before next DS/ manteinance	Outcome/ tolerated cycles
1	M/78	Lymphoma B-R	Rituximab	Grade 3	+ID 10 mg/ml	Type I (IgE)	2 doses/ stopped	Discontinued
2	M/58	Rectal FOLFOX	Oxaliplatin	Grade 3	+ PT 5 mg/ml	Type I (IgE)	1 dose/ stopped	Discontinued
3	F/62	Colon FOLFOX	Oxaliplatin	Grade 2	+ ID 5 mg/ml	Mixed	1 dose/ every 2w	15 cycles
4	F/47	Ovarian T-C	Carboplatin	Grade 3	+ ID 0.1 mg/ml	Type I (IgE)	2 doses/ every 4w	3 cycles
5	F/50	Colon CAPOX	Oxaliplatin	Grade 2	- (2 years after IR)	Mixed	1 dose/ every 2w	3 cycles
6	F/38	Breast D-C	Docetaxel	Grade 2	+ PT 10 mg/ml	Type I (IgE)	2 doses/ every 4w	2 cycles (MCR at 1st)
7	M/59	Colorectal FOLFOX-C	Oxaliplatin	Grade 2	+ PT 5 mg/ml	Type I (IgE)	2 doses/1st in 2w then every 4w	5 cycles (MCR at 1st)
8	F/74	Ovarian C-G	Carboplatin	Grade 3	+ ID 1 mg/ml	Type I (IgE)	2 doses/ -	1 cycle (MCR)

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:** intradermoreaction; **IR:** initial reaction; **M:** male; **MCR:** mild cutaneous reaction; **OMZ:** omalizumab; **P#:** patient number; **PT:** prick-test; **T-C:** taxol (paclitaxel)-carboplatin. **W:** week.