

# Usefulness of Omalizumab in Rapid Drug Desensitization in Patients with Severe Anaphylaxis Induced by Carboplatin: Open Questions

**Short title: Omalizumab in rapid drug desensitization**

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Carboplatin is an effective and well-tolerated chemotherapeutic agent used as first-line and subsequent treatment for ovarian cancer. Hypersensitivity reactions (HSRs) to chemotherapy have increased in frequency in the last 20 years, thus preventing the use of first-line therapies and causing a negative impact on patient survival and quality of life [1,2].

Omalizumab is a recombinant humanized anti-IgE monoclonal antibody approved for the treatment of severe allergic asthma and recurrent chronic idiopathic urticaria. It has been studied as an add-on therapy in food allergy, food oral immunotherapy, atopic dermatitis, idiopathic anaphylaxis, and mastocytosis [3].

We present 2 cases of severe anaphylaxis to carboplatin in which omalizumab was used to prevent reactions during rapid drug desensitization (RDD).

#### Case 1

A 57-year-old woman diagnosed with ovarian adenocarcinoma was initially treated with 6 cycles of carboplatin and paclitaxel without complications. A local recurrence developed 1 year later, and the patient started with carboplatin and gemcitabine. During the second cycle of carboplatin (eighth exposure), she developed palmar pruritus and generalized erythematous rash that resolved with dexchlorpheniramine and methylprednisolone. With the following cycle (ninth exposure), she presented palmar pruritus, generalized erythematous rash, nausea, vomiting, and a sense of impending doom. Her blood pressure was 60/30 mmHg and her heart rate was 40 bpm. She was treated with intravenous dexchlorpheniramine, methylprednisolone, and intramuscular epinephrine. At the same time, she

had epigastric pain radiating to the back, with ST segment elevation in leads V1 to V6, and elevated troponin I (0.14 ng/ml), with normal creatinine kinase MB. The patient was asymptomatic after 24 hours without treatment.

She was referred to our department for an allergological work-up. We carried out skin prick testing (SPT) (10 mg/ml in saline solution) and intradermal testing (IDT) (1 and 10 mg/ml) with carboplatin. The result of IDT was positive at 10 mg/ml. Given the severity of the reaction and the positive IDT, we considered RDD with omalizumab as an adjuvant. After giving her informed consent and with the approval of the institutional review board (IRB), the patient received a dose of 300 mg of subcutaneous omalizumab and another dose of 150 mg 7 days later, and every 14 days thereafter. Twenty-four hours after the second dose, we performed a 16-step RDD in the intensive care unit, as previously described [1]. The patient finally tolerated 6 cycles with the same protocol, each without complications.

## Case 2

A 61-year-old woman diagnosed with breast and endometrial cancer previously treated with chemotherapy and radiotherapy, started treatment with carboplatin and paclitaxel for a recurrence. During the third cycle (17th exposure to carboplatin), she experienced general malaise, blurred vision, nausea, hypotension, and severe bronchospasm. The symptoms resolved with treatment.

We performed SPT and IDT with carboplatin, as described in the previous patient. IDT was positive. Omalizumab was prescribed as an adjuvant for RDD using the protocol described above. The patient gave written informed consent and the procedure was approved by the IRB.

We administered 4 cycles of a 16-step RDD protocol, and the patient reacted in all of them. The reactions appeared at steps 12 (1<sup>st</sup> cycle), 14 (2<sup>nd</sup> cycle) and 16 (3<sup>rd</sup> and 4<sup>th</sup> cycles) and all of them involved the skin exclusively, ranging from palmar pruritus and facial erythema to a generalized

rashonly once. All the reactions resolved with intravenous antihistamines and corticosteroids, and the patient was able to finish the 4 cycles.

RDD enables safe re-administration of a drug to which a patient has become allergic. The procedure is usually safe and effective, although there is an inherent risk of a severe or even fatal anaphylactic reaction when a medication to which a patient had presented a severe HSR is re-introduced[1]. Both patients presented severe life threatening reactions with serious cardiovascular involvement. We recommended a 16-steps desensitization with Carboplatin in an intensive care unit. However, both patients and their oncologists refused to receive the drug due to the severity of the previous reactions. Given that Carboplatin is the best drug in patients with ovarian cancer, we decided to administer omalizumab as an adjuvant treatment in order to diminish the risk of a severe reaction during RDD. One patient tolerated RDD without experiencing a reaction, and the other presented mild skin reactions. We do not know whether they would have tolerated the RDD if omalizumab had not been administered as an adjuvant.

To the best of our knowledge there are only 6 publications on the beneficial effect of omalizumab as an adjuvant in desensitization with drugs: one case report with insulin[4], 12 patients with aspirin[5,6], and 3 cases on chemotherapeutic agents [7-9]. The latter together with our two patients are summarized in Table 1.

Omalizumab dosing in allergic asthma is calculated on the basis of patient's weight and total IgE, whereas in urticaria a 300 mg dose is given. All the patients desensitized to aspirin with add-on omalizumab had asthma, and the dose was calculated as for the asthma indication and administered every 2-4 weeks for 16 weeks prior to desensitization [5,6]. However, when clinicians consider the use of omalizumab as an adjuvant in RDD to chemotherapy they do not know what dose to administer, and cannot pre-treat patients for several months, because it is urgent to continue with the chemotherapy regimen. Consequently, the dose given is decided arbitrarily.

In all the cases reported in Table 1 omalizumab was administered every 2 weeks, albeit at variable doses. Ojaimi[7] and Prieto-García [9] administered 300 mg, whereas Cahill[8] administered 150 mg. We administered 300 mg followed 7 days later by 150 mg/2 weeks. The patients described by Ojaimi[7] and Prieto-García [9] and our patient #1 tolerated, all RDD cycles with omalizumab without reactions. In contrast the patient reported by Cahill[8] and our patient #2 presented mild reactions. While more data are needed, it seems that the dose of 300 mg is more effective than 150 mg. The number of doses of omalizumab administered before RDD varies from 1 to 3.

In the light of the currently available data, we can suggest that a dose of omalizumab 300 mg, given every 2 weeks, and with at least one dose given before start of RDD, allows patients with severe anaphylaxis to platinum drugs to receive them safely. Adding omalizumab increases the treatment cost of gynecological cancer, but when platinum-based treatment are avoided, the second line chemotherapeutics seems to be associated with a reduced survival[2].

### **Abbreviations/Acronyms**

RDD: Rapid drug desensitization; HSRs: Hypersensitivity reactions; SPT: skin prick test; IDT: intradermal test; IRB: approval of the institutional review board.

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## Conflicts of interest

Dr. Sánchez-Morillas reports personal fees from the Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clínica, ALK and Stallergens.

Dr. Casado Herráez reports advisory boards of Pharmamar, Lilly, Merck (MSD), Eisai and Roche International; and advisory fees from Pharmamar, Roche and Lilly.

Dr. Rubio Pérez has no conflicts of interest to declare.

Dr. Robledo Echarren reports personal fees from Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clínica and GSK.

Dr. González Gutiérrez reports personal fees from Sociedad Española de Alergología e Inmunología Clínica, GSK and Teva.

Dr. Cimarra reports personal fees from Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clínica, Novartis, ALK.

Dr. Vázquez Cortés reports personal fees from Novartis, Diater, SanofiAventis and Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clínica.

Dr. Cerecedo reports advisory fee from Diater, Leti, ALK and Stallergens; and personal fees from Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clínica

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TABLE 1: Characteristics of patients who received omalizumab as adjuvant therapy during rapid desensitization (RDD) to chemotherapy drugs.

AUTHORS	CASES	PATIENT	DRUG ALLERGY	SYMPTOMS	DOSE OF OMALIZUMAB	NUMBER OF DOSES OF OMALIZUMAB BEFORE RDD	NUMBER OF RDD CYCLES	TOLERANCE
Cahill et al (8)	1	68 years (sex not specified)	Oxaliplatin	Anaphylaxis	150mg/2 weeks	2 doses	4	Mildreaction
Ojaimi et al (7)	1	Female 63 years	Carboplatin	Anaphylaxis	300 mg/2 weeks	3 doses	4	No reaction
Prieto et al (9)	1	Female 61 years	Oxaliplatin	Anaphylaxis	300 mg/2 weeks	1 dose	6	No reaction
Sánchez-Morillas et al	2	Female 57 years	Carboplatin	Anaphylaxis	300 mg once. After 7 days, 150 mg/2 weeks	2 doses	6	No reaction
		Female 61 years	Carboplatin	Anaphylaxis	300 mg once. After 7 days, 150 mg/2 weeks	2 doses	4	Mildreaction