sIgE/sIgG4 profile in platinum desensitization: is there immunological tolerance?

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To the Editor,

Hypersensitivity reactions (HSR) to platinum drugs have significantly increased worldwide[1,2]. Drug desensitization (DD) is safe and effective, enabling a temporary state of tolerance to the implicated drug[3]. It remains to be understood if, similarly to allergen immunotherapy[4-5], successive DD could be accompanied by an immunological shift, allowing progressive simplification of DD protocols in the long-term. We aimed to assess for the first-time platinum specific IgE/IgG4 (sIgE/sIgG4) profile along multiple and consecutive DD.

Prospective cohort study including oncologic patients >18years-old with HSR to platinum drugs initiating DD in our Allergy & Clinical Immunology Unit from January 2021 to June 2022. HSR diagnosis was considered in the presence of suggestive HSR symptoms and, when possible, confirmed with skin test (ST) with the culprit drug 2-4 weeks after the reaction. Patients were enrolled in the DD program when there were no

therapeutic alternatives. ST with platinum drugs and the 12-step DD protocol were performed in our Unit[6]. Control group included oncologic patients treated at the Oncology Unit receiving at least 7 infusions of platinum drugs with tolerance. The study was approved by the hospital's ethics committee (532/19) and all patients signed an informed consent.

Demographic and clinical data were obtained in the first interview and registered anonymously. Brown's grading system[7] was used to classify HSR's severity.

A blood sample (~5ml) was collected before platinum infusion, in the first DD and then every two DD for the patients included, and before the 8th and 12th treatments for controls. Samples were analyzed in the Research Institute for Medicines. sIgE and sIgG4 were determined for platinum drugs in all patients using a Bovine Serum Albumin (BSA) standard binding method. The platinum salts were conjugated to human serum albumin by mixing an excess of the drugs in phosphate buffer at pH 7.4 and then by incubating for 24 hours followed by a second conjugation procedure using the same conditions. After conjugation, the excess drug was separated by dialysis, and the drug conjugates were immobilized by PureProteome Albumin Magnetic Beads. The PureProteome Albumin Magnetic Beads are conjugated to an antibody specific for human serum albumin. These magnetic beads provide a rapid, scalable, and reproducible means to bind >98% of albumin from serum and plasma samples, facilitating the detection and analysis of proteins of interest. A cut-off of 0.10kUA/L was used for negative in vitro testing.

A total of 7 patients fulfilled criteria to enroll the study, although 3 were excluded due to discontinuation of platinum therapy. Control group was represented by 3 patients. Of the 4 patients with HSR, 3 were women, median age 68.5 years [45-78 years]. Two patients had positive intradermal ST in the concentrations of 0.5mg/ml and 0.05mg/ml, both with HSR grade II, the other 2 did not undergo skin testing due to urgent need of platinum desensitization (Table I). There were no breakthrough HSR during desensitizations.

Regarding sIgE/sIgG4 profile (Figure 1, Supplementary Table I), a progressive reduction in sIgE was observed for all patients, with an initial median of 2.86kU/L [1.31-3.29kU/L] decreasing to 0.12kU/L [0.11-0.18kU/L] in the last DD (Figure 1A). In parallel, an increase in sIgG4 was found, with an initial median of 0.38logAU/mL [0.18-0.81logAU/mL] rising to 2.43logAU/mL [1.85-3.14logAU/mL] at the last DD (Figure 1B). The present study reports for the first time a trend in favor of an immunological shift along multiple and consecutive platinum DD, resembling the tolerance mechanisms induced by allergen immunotherapy.

Data on long-term tolerance in subsequent desensitization protocols is sparce. Tüzer et al[8] noticed a decrease in the frequency and severity of reactions with repeated DD protocols, demonstrating a possible role of IL-10 in the temporary tolerance induced by DD[8], with an increase during DD procedures and a decrease between treatments.

It remains unknown if the cytokine profile along multiple DD, similarly to the sIgE/sIgG4 profile hereby demonstrated, favors a long-lasting immunological tolerance. In fact, sIgE could be of interest, not only for the diagnosis, as previously demonstrated by our group[9], but also for risk stratification. As for sIgG4 antibodies, their precise role is controversial. They are still considered to demonstrate a response to immunotherapy, although levels of allergen-specific IgG do not predict or correlate with a clinical response to immunotherapy[5].

Despite the study's main limitations, namely the short sample and the absence of breakthrough HSR during DD not allowing to document different immunological DD profiles, this first report has an important adding value in fulfilling the gap knowledge on the immunological profile along DD treatments.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Contributions

RB, JC: study design; RB, JC: data collection; JG, CA, AGS: data analysis; RB: writing – original draft; JG, LC, EP, JC: writing – review & editing.

Declaration of interest:

The authors declare that they have no relevant conflicts of interest.

REFERENCES:

1. Otani IM WJ, Banerji A. Platinum Chemotherapy Hypersensitivity: Prevalence and Management. Immunol Allergy Clin North Am. 2017;37(4):663-77; doi: 10.1016/j.iac.2017.06.003.

2. De las Vecillas Sánchez L, Alenazy LA, Garcia-Neuer M, Castells MC. Drug Hupersensitivity and Desensitizations: Mechanisms and New Approaches. Int. J. Mol. Sci. 2017, 18, 1316; doi: 10.3390/ijms18061316.

3. Caiado J, Castells MC. Presentation and Diagnosis of Hypersensitivity to Platinum Drugs. Curr Allergy Asthma Rep. 2015;15(4):9; doi: 10.1007/s11882-015-0515-3.

4. Kim EH, Yang L, Ye P, Guo R, Li Q, Kulis MD, et al. Long-term sublingual immunotherapy for peanut allergy in children: Clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2019;144(5):1320-6.e1; doi: 10.1016/j.jaci.2019.07.030.

5. Krishna MT, Huissoon AP. Clinical immunology review series: an approach to desensitization. Clin Exp Immunol. 2011 Feb;163(2):131-46. doi: 10.1111/j.1365-2249.2010.04296.x.

6. Caiado J*, Brás R*, Paulino M, Costa L, Castells M. Rapid Desensitization to antineoplastic drugs in an outpatient Immunoallergology Clinic: outcomes and risk factors. Ann Allergy Asthma Immunol, 2020; 125: 325-333; doi: 10.1016/j.anai.2020.04.017.

7. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004;114(2):371e376. doi: 10.1016/j.jaci.2004.04.029.

8. Tüzer C, Sari M, Çetin EA, Ak N, Büyüköztürk S, Çolakoğlu B, et al. Rapid drug desensitization for platinum-based chemotherapy drugs significantly increases peripheral blood IL-10 levels. Allergy. 2020 Nov; 75(11):2942-2945. doi: 10.1111/all.14311

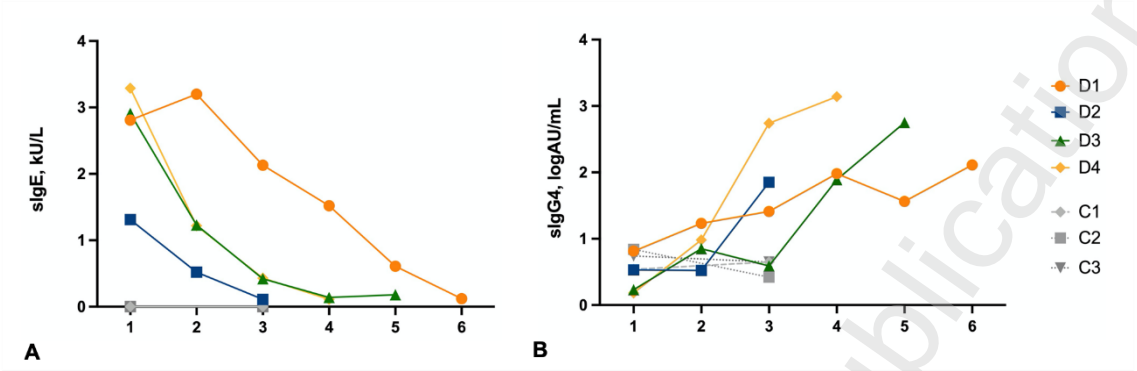
9. Caiado, J.; Venemalm, L.; Pereira-Santos, M.C.; Costa, L.; Barbosa, M.P.; Castells, M. Carboplatin-, Oxaliplatin-, and Cisplatin-specific IgE: Cross-reactivity and Value in the Diagnosis of Carboplatin and Oxaliplatin Allergy. J. Allergy Clin. Immunol. Pract. 2013, 1, 494–500: doi: 10.1016/j.jaip.2013.06.002.

Table I. Characterization of the study population

Patient	Gender	Age	Atopy	Drug allergy	Neoplasia	Drug	Previous infusions	Hypersensitivity reaction	Grade of severity	Total IgE (kU/L)	Skin tests
1	F	45	Yes	No	Colorectal	Oxaliplatin	15	*Flushing*, generalized pruritus, cough, dyspnea, abdominal pain, sudoresis, hypotension	III	296	-
2	F	61	No	No	Ovarian	Carboplatin	9	*Flushing*, palmoplantar pruritus	I	57.8	-
3	F	76	No	No	Colorectal	Oxaliplatin	10	Generalized pruritus, chest tightness, general malaise	II	40.9	Positive (ID 0,5mg/mL)
4	M	78	No	No	Colorectal	Oxaliplatin	14	Nausea, general malaise, heat feeling, paresthesia and palmar pruritus.	II	72.6	Positive (ID 0,05mg/mL)

F: Female, M: Male, ID: Intradermal skin tests.

Figure 1. Specific IgE (**A**) and IgG4 (**B**) along consecutive desensitizations of the study population. C: control, D: patient, sIgG4: Specific IgG4, sIgE: Specific IgE.



Supplementary Table I. sIgE and sIgG4 values in patients vs controls.

Patient	sIgE, kUA/L						sIgG4, log AU/ml					
	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6
1	2.81	3.20	2.13	1.52	0.61	0.12	0.81	1.23	1.41	1.98	1.56	2.11
2	1.31	0.52	0.11	NP	NP	NP	0.53	0.52	1.85	NP	NP	NP
3	2.91	1.23	0.42	0.14	0.18	NP	0.23	0.85	0.59	1.89	2.75	NP
4	3.29	1.22	0.43	0.11	NP	NP	0.18	0.98	2.74	3.14	NP	NP
Control 1	< 0.1	<0.1	NP	NP	NP	NP	0.54	0.65	NP	NP	NP	NP
Control 2	< 0.1	<0.1	NP	NP	NP	NP	0.84	0.42	NP	NP	NP	NP
Control 3	< 0.1	<0.1	NP	NP	NP	NP	0.74	0.65	NP	NP	NP	NP

NP: Not Performed.