

Unsuccessful Desensitization to Paclitaxel in a Patient with High Basophil Sensitivity

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Immediate hypersensitivity reactions (HSRs) occur during the administration of taxanes in 10%-30% of patients and are severe in up to 10% of patients(1). Desensitization has been shown to be safe and successful in the majority of patients with HSR, allowing most patients to be retreated with taxanes(2). However, even during desensitization, HSRs can occur in 15% of treated patients regardless of the severity of the initial reaction or skin test results. Reactions during desensitization are severe in 13% regardless of the initial reaction. Since the measurement of specific IgE to taxanes is not commercially available(3), the basophil activation test (BAT) could be a useful tool to detect IgE-mediated reactions. BAT was already shown as relevant biomarker of the outcome of rapid desensitization in platinum compounds-allergy(4). The results of diagnostic testing for taxanes allergy are scarce and often limited to case reports(1,3,5). To the best of our knowledge, the utility of BAT in taxanes allergy has not been fully evaluated yet. In food and insect venom, the allergy sensitivity of basophils can predict the severity and threshold of allergic reactions to allergens(6), but such experiences in drug allergies are limited (4,7). Herein, we report a case of highly positive BAT to paclitaxel in a patient with severe HSR at very low concentrations of paclitaxel during initial treatment and an attempt at desensitization.

A 50-year-old female with oestrogen receptor-positive and HER2-positive breast cancer was treated with adjuvant trastuzumab, pertuzumab and paclitaxel. The first two 3-weekly applications of both anti-HER-2 drugs were uneventful. During the first 5 minutes of the second infusion of weekly paclitaxel, the patient developed a grade 4 reaction with abdominal cramps, dyspnoea, generalized erythema, hypotension (RR 70/40 mmHg), tachycardia (110/min) and reduction of peripheral oxygenation to 80%. She was treated with methylprednisolone, clemastine, saline, and oxygen. The next day, chemotherapy with paclitaxel was restarted, again following premedication with clemastine and dexamethasone after 1 hour. After 15 ml of paclitaxel infusion, she presented with a grade 1 reaction with abdominal cramps, dyspnoea (RR 120/80 mmHg), heart rate 120 beats/min, and saturation 95%. The infusion was stopped, and she received methylprednisolone and clemastine. Tryptase was not measured during either reaction.

The skin prick test with paclitaxel was negative (1 mg/ml); however, the intradermal test was positive at 0.01 mg/ml (but negative at 0.001 mg/ml). Basal serum tryptase was normal (5.1 µg/l). To confirm the allergenic activity of paclitaxel sensitization, we performed BAT in which basophils were identified as CD123-positive and HLA-DR-negative cells, while CD63 was used as a marker of basophil activation. For the controls, the whole blood cells were exposed to stimulation buffer alone (negative control) or to 0.55 µg/mL of anti-FcεRI mAb and 50 µg/ml of fMLP (positive control)(8,9). An example of the gating strategy used for the flow cytometry basophil analysis is shown in Figure S1. The percentage of CD63+ basophils after stimulation with paclitaxel was 2, 67, 62, 69 and 80% for stimulation with paclitaxel from 0.005 to 50 µg/ml, respectively. Thus, BAT was highly positive even at low allergen

concentrations (Figure 1). The BAT response to paclitaxel in three healthy controls and in three paclitaxel exposed non-allergic controls was negative (all <5%CD63+ basophils; 0.005 to 50 µg/ml). After premedication with montelukast 10 mg, ranitidine 300 mg, clemastine 2 mg, methylprednisolone 100 mg, and a 12-step (3 bags) desensitization protocol were performed. At the cumulative dose of 0.022 mg paclitaxel, the patient already had a reaction with generalized erythema and pruritus. She was treated with adrenaline and clemastine, and desensitization was stopped. The next day, a 16-step protocol was started, and after 0.010 mg of paclitaxel was applied, generalized urticaria occurred. The infusion was stopped, and the patient was treated with adrenaline and clemastine. After 30 minutes, desensitization was continued, but the patient again had a reaction with generalized urticaria after a cumulative dose of 0.023 mg paclitaxel, and treatment was stopped. We did consider the use of omalizumab, as there are some favourable reports in drug hypersensitivity (10), however the patient declined this option as pretreatment with omalizumab would postpone chemotherapy treatment.

In our case, basophil activation provided important additional information on the mechanisms and severity of HSR to paclitaxel. As reaction occurred during the second application and BAT was positive, we believe that the reaction was IgE mediated, although mast cells could be activated through other mechanisms. High basophil sensitivity at low concentrations of paclitaxel may be associated with a lower threshold and a more severe allergic reaction. Our observations suggest BAT, if available, could be important in risk stratification procedures before desensitization, as it could help to identify patients at high risk for severe HSRs during desensitization and even failure to desensitize.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

1. Prieto García A, Pineda de la Losa F. Immunoglobulin E-mediated severe anaphylaxis to paclitaxel. *J Investig Allergol Clin Immunol*. 2010;**20**:170–1.
2. Solano-Solares E, Madrigal-Burgaleta R, Carpio-Escalona L, Bernal-Rubio L, Berges-Gimeno M, Alvarez-Cuesta E. Chemotherapy in Mastocytosis: Administration Issues, Hypersensitivity, and Rapid Drug Desensitization. *J Investig Allergol Clin Immunol*. 2017;**27**:315–7.

3. Kim SY, Kim J-H, Jang Y-S, Choi J-H, Park S, Hwang Y II, et al. The Basophil Activation Test Is Safe and Useful for Confirming Drug-Induced Anaphylaxis. *Allergy Asthma Immunol Res.* 2016;**8**:541.
4. Giavina-Bianchi P, Galvão VR, Picard M, Caiado J, Castells MC. Basophil Activation Test is a Relevant Biomarker of the Outcome of Rapid Desensitization in Platinum Compounds-Allergy. *J Allergy Clin Immunol Pract.* 2017;**5**:728–36.
5. Picard M, Pur L, Caiado J, Giavina-Bianchi P, Galvão VR, Berlin ST, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol.* 2016;**137**:1154-64.e12.
6. Korošec P, Žiberna K, Šilar M, Dežman M, Čelesnik Smodiš N, Rijavec M, et al. Immunological and clinical factors associated with adverse systemic reactions during the build-up phase of honeybee venom immunotherapy. *Clin Exp Allergy.* 2015;**45**:1579–89.
7. Rial M, Fernández-Nieto M, Rodrigo-Muñoz J, Sastre B, Sastre J, del Pozo V. Doxylamine Allergy in a Pregnant Woman: Suitability of the Basophil Activation Test. *J Investig Allergol Clin Immunol.* 2018;**28**:433–4.
8. Hoffmann HJ, Santos AF, Mayorga C, Nopp A, Eberlein B, Ferrer M, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy Eur J Allergy Clin Immunol.* 2015;**70**:1393–405.
9. Koren A, Lunder M, Molek P, Kopač P, Zahirović A, Gattinger P, et al. Fluorescent labeling of major honeybee allergens Api m 1 and Api m 2 with quantum dots and the development of a multiplex basophil activation test. *Allergy.* Published Online First: 17 January 2020. doi:10.1111/all.14185
10. Prieto-García A, Noguerado B, Rojas P, Torrado I, Rodríguez-Fernández A, Tornero P. Unexpected Anaphylaxis After Completing a Desensitization Protocol to Oxaliplatin: Successful Adjuvant Use of Omalizumab. *J Investig Allergol Clin Immunol.* 2019;**29**:53–5.

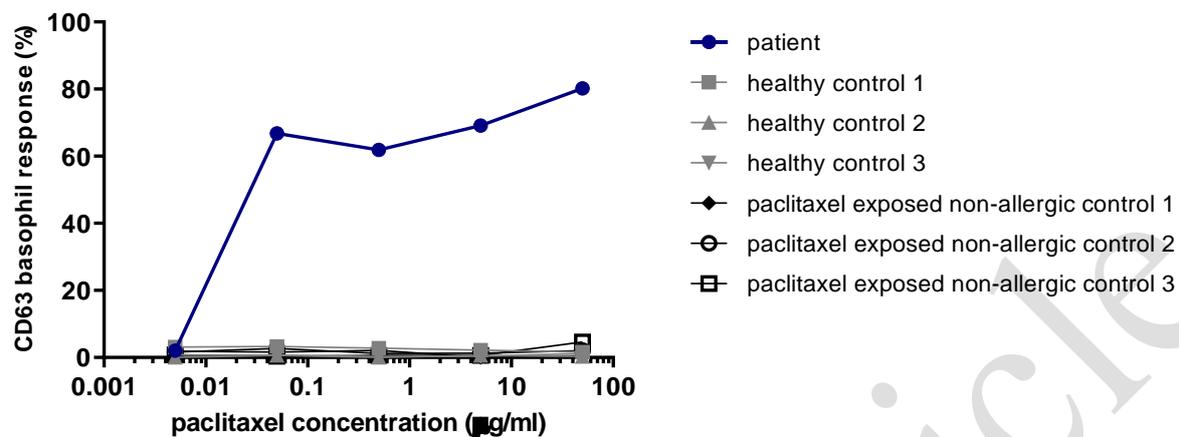


Figure 1: The results of the basophil activation test (BAT) in response to stimulation with various concentrations of paclitaxel (0.005-50 µg/ml) in a paclitaxel allergic patient, three healthy controls and in three paclitaxel exposed non-allergic controls.