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ORIGINAL PAPER

Evaluation of the basophil activation in immediate type hypersensitivity reactions to chemotherapeutic agents

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ABSTRACT

Introduction: Revealing the responsible mechanisms of hypersensitivity reactions (HSRs) to chemotherapeutics may guide the prevention of these reactions and provide re-use of the responsible drug.

Aim: To evaluate the role of basophils during the immediate-type HSRs and desensitization to culprit chemotherapeutics.

Material and methods: Twenty patients were included in the study. Peripheral whole blood samples were obtained from patients immediately after the reaction and pre- and post- desensitization procedures in the next cycle. Basophil activation was assessed by flow cytometry. A stimulation index (SI) was calculated by proportioning the values at the time of reaction and post-desensitization to the pre-desensitization values.

Results: Desensitization with the culprit chemotherapeutic was performed in 14 of 20 patients. The culprit drug was cisplatin in 4 patients, taxanes in 5 and etoposide in 5 patients. In patients who had HSRs to cisplatin and etoposide (except one with etoposide hypersensitivity), reaction time SI was greater than 2, indicating basophil activation. In a patient who had a breakthrough reaction to cisplatin during desensitization, basophil activation was also detected at the time of this reaction. None of the patients with taxane hypersensitivity reaction showed basophil activation at the time of the reaction. Post-desensitization basophil activation was not detected in any patient. There was a significant tryptase increment during the index reaction in all cisplatin patients, only one taxane patient, and during the breakthrough reaction to cisplatin.

Conclusions: Basophil activation has been shown to play a role in the mechanism of immediate-type HSRs to cisplatin and etoposide. Desensitization procedures in this group of patients prevent basophil activation and ensure the safe use of the drug.

KEY WORDS

basophil activation, chemotherapeutic hypersensitivity, cisplatin hypersensitivity, taxane hypersensitivity, etoposide hypersensitivity.

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INTRODUCTION

Although not fully known different immunologic and non-immunologic mechanisms are responsible for developing hypersensitivity reactions (HSRs) to different chemotherapeutic agents. Revealing the responsible mechanisms of HSRs may guide the prevention of these reactions and provide re-use of the responsible drug [1].

Basophils and mast cells are key effector cells in immediate-type HSRs, they can be activated by either IgE-mediated or non-IgE-mediated immediate-type HSRs. IgE-mediated HSRs involve cross-linking of specific IgEs bound to their membrane-bound high-affinity IgE receptor (FcεRI) on blood basophils and mast cells, resulting in activation of these cells and release of several mediators, resulting in the symptoms [2, 3].

IgE-mediated basophil activation is associated with increased levels of specific basophil cell membrane surface markers, such as cluster of differentiation (CD) 203c or CD63. These surface markers can be quantified by flow cytometry and form the basis of the basophil activation test (BAT). CD203c is expressed on resting cells at low levels, and its expression is rapidly upregulated following activation. CD63 is normally expressed on the inner side of the granule membrane, and can be detectable after fusion of the intracellular granules with the cytoplasmic cell membrane during basophil degranulation [3–7].

Desensitization is an important treatment option to ensure re-use of the drug in patients and is useful in both IgE-mediated and non-IgE mediated reactions. Although the exact mechanism is not yet fully known, *in vitro* and *in vivo* studies show that rapid drug desensitization induces a temporary tolerance in mast cells and basophils [8, 9].

AIM

This study aims to evaluate the role of basophils during the immediate-type HSRs and desensitization to culprit chemotherapeutics.

MATERIAL AND METHODS

PATIENT GROUP

This is a prospective case-control study assessing the role of basophil activation during immediate-type drug HSR to chemotherapeutics and after desensitization to the culprit chemotherapeutic. Patients who had immediate-type HSRs during chemotherapy infusion and underwent desensitization to the culprit drug were included in the study. The study was approved by the local ethics committee (approval number 2012-KAEK-491).

STUDY DESIGN

Baseline data, including patients' characteristics (age, gender, previous drug allergy history, diagnosis), drug hypersensitivity reaction (DHR) characteristics (culprit chemotherapeutic, cycle number, the symptoms, and severity of DHR), skin test results, if performed, were recorded.

Peripheral whole blood samples were obtained from patients immediately after the reaction and before and after the (pre- and post-) desensitization procedure in the next cycle. The flow cytometric analysis was carried out within 24 h of the sampling, and basophil surface markers CD63 and CD203c were evaluated. CD63 and CD203 positive basophils were defined as activated basophils. The percentage of pre-desensitization activated basophils was accepted as the basal value. The ratio between the percentage of activated basophils at the reaction time and the basal value was defined as reaction time stimulation index (SI). The ratio between the percentage of post-desensitization activated basophils and the basal value was defined as post-desensitization SI. The basophil activation test result was considered positive when SI was ≥ 2.

Tryptase activity was measured in some patients after the index reaction and before and after the (pre- and post-) desensitization procedure in the next cycle. Pre-desensitization tryptase was accepted as the basal value. A significant tryptase increment was defined as proposed by the consensus group; the acute serum total tryptase level should be at least 20% plus 2 ng/ml over the baseline tryptase level to indicate mast cell activation [10]. Also, tryptase increment ratios were defined by proportioning the reaction time and post-desensitization tryptase levels with the basal levels.

FLOW CYTOMETRIC ANALYSIS

BAT was performed using Flow CAST® Highsens (Bühlmann Laboratories, BAT, Switzerland) flow cytometry kits containing lysing reagent, stimulation buffer containing calcium and heparin; stimulation control containing anti-FcεRI monoclonal antibody (mAb) for the non-IgE-mediated pathway; stimulation control containing N-formyl-methionyl-leucyl-phenylalanine (fMLP) for

the IgE-mediated pathway; and staining reagent consisting of anti-CD63-PE-DY647/anti-CD203c-PE-DY647/anti-CCR3-PE mAb mixture.

Whole blood samples were taken into an anticoagulated with K_3-ethylenediaminetetraacetic acid (EDTA) tube. Basophil activation tests were performed within 24 h of sample collection. Four flow tubes were prepared before testing. At first, 50 µl of the corresponding stimulus to each tube was pipetted for each sample. Accordingly, stimulation buffer was added into PB (Patient Background) tube; anti-FcεRI mAB was added into PC 1 (patient control) tube; and fMLP was added into PC 2 tube. Thereafter, 100 µl of stimulation buffer and 50 µl of sample's whole blood were added to each tube, respectively. After mixing gently, 20 µl of the staining reagent containing anti-CD63-PE-DY647/anti-CD203c-PE- DY647/anti-CCR3-PE was dispensed to each tube and incubated for 15 min at 37°C in a water bath. At the end of this period, 2 ml of pre-warmed (18–28°C) lysing reagent was delivered to each tube, mixed gently, and incubated for 5–10 min at 18–28°C. After centrifuging the tubes for 5 min at 500 x g, the supernatants were decanted by using blotting paper, and the cell pellets were resuspended with 300 µl of wash buffer. After slightly mixing, all prepared tubes were analyzed within 1 h using a FACS Canto II flow cytometry device (BD, San Jose, USA) and FACS Diva software.

For analyses, leukocytes were identified according to their size and granular structure by passing them in front of the laser light of the flow cytometry device, and basophilic cells were identified using CD63+CD203c+ antibodies. For each sample, at least 300 basophilic cells (on average 800-1000 basophilic cells) were counted in the basophil gate. Basophil activation was considered positive when SI was ≥ 2.

DEFINITION AND GRADING OF REACTIONS

Immediate-type HSR to a chemotherapeutic agent was defined as a reaction during chemotherapy infusion with signs and symptoms such as cutaneous symptoms (pruritus, flushing, urticaria, angioedema), rhinitis, conjunctivitis, respiratory symptoms (dyspnea, bronchospasm), gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea), changes in blood pressure or anaphylaxis. The severity of drug HSRs and breakthrough reactions (BTRs) during desensitization were graded according to the Ring-Messmer classification [11].

SKIN TESTING

Skin tests were performed with the culprit chemotherapeutic in patients who agreed to skin testing. Skin tests were conducted as follows: for the positive control, a prick test with a solution of histamine hydrochloride (10 mg/ml), whereas for the negative control, a physiological saline (0.9% saline) solution was used. A skin prick test (SPT) was performed with a concentration of 6 mg/ml for paclitaxel, 1 mg/ml for cisplatin, and 20 mg/ml for etoposide. After a negative skin prick result, an intradermal test (IDT) was performed with a concentration of 0.06 mg/ml for paclitaxel, 0.01 mg/ml and 0.1 mg/ml for cisplatin, 0.2 mg/ml and 2 mg/ml for etoposide. The prick test result was considered positive when the cutaneous response was a wheal of at least 3 mm with a surrounding flare, whereas the intradermal test result was considered positive with a wheal of at least 5 mm with a surrounding flare [12].

DESENSITIZATION PROTOCOLS

A 3-bag 12-step desensitization protocol described by Brigham and Women's Hospital was implemented [13]. Written informed consent was obtained before each desensitization procedure. Thirty minutes before starting the desensitization, premedication with methylprednisolone 40 mg, H_1- antihistamine (pheniramine 45.5 mg), and H_2-antihistamine (famotidine 20 mg or ranitidine 50 mg) was administered as a routine practice of the oncology team before each chemotherapy cycle. All desensitizations were carried out under close observation with one-on-one nurse-to-patient care in the allergy unit. If any BTR occurred during the protocol, the infusion was suspended, and the reaction was treated. After the reaction was resolved, the protocol was continued starting from the previous step, in which BTR occurred.

STATISTICAL ANALYSIS

All statistical analyses were performed using the SPSS (Statistical Package of Social Sciences) for Windows 18.0 software package. In evaluating the data, mean and standard deviation for normally distributed data, the median and interquartile range for data that did not show normal distribution, values, and percentages for ratios were determined by the descriptive statistical method. In univariate analyses, χ^2, Fisher, Student's *t*-test, and Mann-Whitney *U* tests were used, as appropriate. All *p*-values lower than 0.05 were considered to be statistically significant.

RESULTS

During the study period, a total of 20 patients with a female/male ratio of 1/19 had immediate-type HSRs during chemotherapy infusions. The culprit chemotherapeutic was cisplatin in 5, etoposide in 9, and taxanes in 6 patients. Four of the taxane reactions were with docetaxel,

and two were with paclitaxel. Characteristics of patients, disease, therapy, and index reaction are shown in Table 1.

The mean age of the patients was 59.75 ±5.79 years. There was no significant difference related to the ages of the patients between platin, taxane, and etoposide groups ($p = 0.897$). However, some significant clinical differences were observed according to the culprit chemotherapeutic. Platin reactions were observed at more advanced cycles than etoposide and taxane reactions with a median of 7 (5–10) vs. 2 (1–2) and 2 (1–2) cycles, respectively ($p = 0.002$). Taxane reactions were more severe than platinum and etoposide reactions, with a median grade of 3 (2–3) vs. 1 (1–3) and 1 (1–3), respectively ($p = 0.039$).

After an HSR, the culprit chemotherapeutic was discontinued in 6 of 20 patients in whom the culprit drug was replaced with an alternative therapy or stopped by primary physicians. The remaining 14 patients underwent desensitization to the culprit chemotherapeutic. Desensitizations were performed with cisplatin in 4 patients, etoposide in 5 patients, and taxanes in 5 patients.

Skin tests (SPT and IDT) with the culprit chemotherapeutic were performed in 8 patients. Cisplatin skin tests

TABLE 1. Demographics, disease, therapy and index reaction characteristics of patients

Patient number	Age	Gender	Malignancy	Culprit chemotherapeutic	Cycle number	Grade	Symptoms
1	60	Male	NSCLC, Adeno CA	Cisplatin	5	1	Generalized pruritus and erythema
2	59	Male	MPM	Cisplatin	7	1	Palmar itch, generalized erythema
3	67	Male	NSCLC, Adeno CA	Cisplatin	10	1	Generalized erythema
4	57	Male	NSCLC, Squamous CA	Cisplatin	10	3	Generalized erythema, dyspnea, bronchospasm, cyanosis, desaturation
5	56	Male	NSCLC, Squamous CA	Cisplatin	5	1	Palmar itch, generalized erythema
6	56	Male	SCLC	Etoposide	2	2	Generalized erythema, dyspnea, hypertension
7	60	Male	SCLC	Etoposide	2	3	Flushing, dyspnea, bronchospasm, cyanosis, desaturation, hypertension
8	59	Male	NSCLC, Squamous CA	Etoposide	1	1	Facial erythema, flushing
9	61	Male	NSCLC, Adeno CA	Etoposide	1	1	Facial erythema, flushing
10	66	Male	SCLC	Etoposide	2	1	Generalized erythema
11	66	Male	SCLC	Etoposide	1	1	Generalized erythema
12	47	Male	SCLC	Etoposide	2	3	Dyspnea, bronchospasm, cyanosis, desaturation, hypertension
13	61	Male	SCLC	Etoposide	2	2	Generalized erythema, dyspnea
14	67	Male		Etoposide	1	1	Generalized erythema
15	71	Male	NSCLC, Squamous CA	Paclitaxel	2	3	Generalized erythema, dyspnea, bronchospasm, cyanosis, desaturation, dizziness, confusion
16	58	Male	MPM	Paclitaxel	2	2	Generalized erythema, pruritus, dyspnea, hypertension
17	51	Male	NSCLC, Adeno CA	Docetaxel	2	3	Facial erythema, dyspnea, bronchospasm, cyanosis
18	60	Female	NSCLC, Adeno CA	Docetaxel	2	3	Dyspnea, bronchospasm, cyanosis, hypertension, drowsiness
19	60	Male	NSCLC, Adeno CA	Docetaxel	1	2	Flushing, dyspnea, hypertension
20	532	Male	NSCLC, Adeno CA	Docetaxel	2	3	Dyspnea, bronchospasm, cyanosis, desaturation, back pain, hypertension

CA – carcinoma, SCLC – small cell lung carcinoma, NSCLC – non-small cell lung carcinoma, MPM – malignant pleural mesothelioma.

were positive in 2 of 4 patients, negative in 1, and could not be evaluated in 1 patient due to histamine deficiency. The etoposide skin test was positive in 2 of 3 patients and negative in 1. The paclitaxel skin test result was negative in 1 patient.

In 13 patients, the desensitization procedure was completed uneventfully in the next cycle after the index reaction. One patient (no. 1) had a grade 1 BTR during cisplatin desensitization. After appropriate management, the procedure was successfully completed. Blood samples were obtained from this patient to evaluate the CD63+ CD203c expression and tryptase activity during the BTR.

No significant difference was detected between basal activated basophil percentages in the platinum, etoposide and taxane groups with median (min.–max.) values of 5.5 (3.4–6.9), 2.4 (1.4–19.5) and 6.6 (3.8–13.3), respectively ($p = 0.438$).

In all patients with cisplatin and etoposide hypersensitivity, the reaction time SI was > 2 except 1 patient with etoposide hypersensitivity. Reaction time SI was not > 2 in patients with taxane hypersensitivity. Post-desensitization SI was < 2 in all 14 patients with cisplatin, etoposide, and taxane hypersensitivity (Table 2).

Tryptase activities were measured in 3 cisplatin and 4 taxane patients immediately after the reaction and also before and after desensitization. There was a significant tryptase increment during the index reaction in all cisplatin patients and only 1 taxane patient (Table 3). At the time of the index reaction, tryptase increment ratios were > 2 in cisplatin patients. Although tryptase increment ratios were higher in cisplatin patients than taxane patients, it was not found to be statistically significant ($p = 0.057$)

During desensitization procedures, 1 patient with cisplatin hypersensitivity had a BTR. BTR time SI, which is defined as "the ratio of the activated basophil percentages during BTR and pre-desensitization", was 2.64. Also, a significant tryptase increment was detected during BTR (Tables 2 and 3).

DISCUSSION

In this prospective case-control study, we reported the role of basophil activation and tryptase release as a mast cell mediator during immediate-type HSRs and desensitizations to chemotherapeutic agents. Different basophil activation test results were observed with different chemotherapeutics. Results were positive with cisplatin and negative with taxanes, however different results were observed with etoposide. Additionally an important result

TABLE 2. Basophil activation test and skin test results of patients

Patient number	Culprit chemotherapeutic	Skin test result	Reaction time activated basophil %	Pre-desensitization activated basophil % (baseline)	Post-desensitization activated basophil %	Reaction time SI	Post-desensitization SI	Breakthrough reaction time activated basophil%	Breakthrough reaction time SI
1	Cisplatin	Positive	22.4	5.4	7.1	4.15	1.31	14.3	2.64
2	Cisplatin	Negative	14.3	3.4	5.1	4.21	1.5		
3	Cisplatin	Histamine deficiency	17.2	5.7	6.1	3.02	1.07		
4	Cisplatin	Positive	14.4	6.9	8.5	2.09	1.23		
6	Etoposide	Positive	9.6	2.4	3.1	4.0	1.29		
7	Etoposide	ND	10.0	1.4	1.9	7.14	1.36		
8	Etoposide	Negative	20.9	19.5	18.3	1.07	0.93		
9	Etoposide	Positive	15.2	5.9	8.4	2.58	1.42		
10	Etoposide	ND	9.5	1.7	2.0	5.59	1.18		
15	Paclitaxel	Negative	10.0	6.6	7.6	1.52	1.15		
16	Paclitaxel	ND	10.1	8.5	6.5	1.19	0.76		
17	Docetaxel	ND	7.5	3.8	4.0	1.97	1.05		
18	Docetaxel	ND	24.6	13.3	15.9	1.85	1.2		
19	Docetaxel	ND	7.5	4.0	5.2	1.88	1.3		

ND – not done, SI – Stimulation index.

TABLE 3. Tryptase levels of platin and taxane patients

Patient number	Culprit chemo-therapeu-tic	Index reaction tryptase	Pre-desensi-tization tryptase (baseline)	Post-desensi-tization tryptase	Significant tryptase increment during the index reaction	Index reaction tryptase increment ratio	Post-desensi-tization tryptase increment ratio	Break-through reaction tryptase	Significant tryptase increment during break-through reaction
1	Cisplatin	7.22	1.44	7.56	Yes	5.01	5.25	4.89	Yes
3	Cisplatin	12.6	4.49	4.86	Yes	2.81	1.08		
4	Cisplatin	64	11	13	Yes	5.82	1.18		
15	Paclitaxel	5.93	4.97	3.93	No	1.19	0.79		
16	Paclitaxel	12.5	14.4	11.3	No	0.87	0.78		
17	Docetaxel	4.33	5.28	4.95	No	0.82	0.94		
19	Docetaxel	11.8	7.82	9.74	Yes	1.51	1.25		

in this study was that the desensitization procedure prevented basophil activation.

We detected BAT positivity during cisplatin HSRs in all patients and at the time of the BTR in 1 patient who had a BTR during desensitization. Previous studies reported similar results to our study showing basophil activation in platin HSRs [14–18].

Viardot-Helmer *et al.* first reported increased CD63 expression on basophils after cisplatin exposure in a patient with cisplatin allergy [14]. Iwamoto *et al.* detected increased expression of CD203c+ basophils (%) and mean fluorescence intensity of CD203c+ basophils in patients with carboplatin-related HSR, especially in patients with grade 4 anaphylaxis [15]. CD203c expression was reported to be a more sensitive marker than CD63 expression in the diagnosis of platin hypersensitivity, and CD63 was suggested as a marker of reaction severity [17, 18]. Giavina-Bianchi *et al.* reported BAT positivity with a sensitivity of 73% and specificity of 100% in diagnosing patients with platin allergy [17].

Iwamoto *et al.* also reported that BAT test positivity with platins could predict platin hypersensitivity and BTRs during desensitization. They detected BAT positivity after *ex vivo* exposure to carboplatin on the day before the occurrence of carboplatin hypersensitivity and also on the day before and the onset of BTR during desensitization [15, 16].

Although BAT results in our study were similar to previous studies, the BAT methodology used in our study was different. The BAT methodology used in the literature was based on *in vitro* stimulation of patients' blood basophils with different concentrations of the culprit drug. Unlike these studies, we evaluated the *in vivo*-activated basophils during HSR and before and after the desensitization procedure. Percentages of pre-desensitization activated basophils were accepted as basal values and no significant difference was observed between the basal values of patients who had HSRs to different chemotherapeutic agents.

The fact that platin HSRs in our study occurred after multiple exposures and the skin test positivity in 2 patients suggest that these reactions are IgE-mediated [13, 19, 20]. Iwamoto *et al.* confirmed that an IgE-dependent mechanism incorporating FcεRI overexpression participates in carboplatin-induced basophil activation [21].

In our study, although the severity of taxane reactions was higher than for other chemotherapeutics, no basophil activation test positivity was detected in taxane reactions. All of these reactions occurred on the first or second cycle of chemotherapy and also the skin test result was negative in 1 patient who had skin testing performed. The reason why basophil activation with taxanes was not shown in our study may be that the reactions are most likely not IgE-mediated.

The mechanism(s) of HSRs to taxanes remain to be established. Since a significant number of taxane reactions occur in the first cycle and skin test positivity could not be shown in earlier studies, most of the authors hypothesized that immediate HSRs to these molecules were non-IgE-mediated and solvents Cremophor EL and polysorbate 80 capable of causing direct complement activation were responsible for HSRs [22–25]. Recent findings have raised the possibility that some of taxane HSRs are IgE-mediated based on the findings that a positive skin test result to paclitaxel and/or docetaxel could be elicited in a subset of patients who had experienced an immediate HSR to these molecules and that the development of severe HSRs were caused by nab-paclitaxel which does not contain Cremophor EL [22–24, 26].

There are few studies evaluating the basophil activation test in taxane reactions. Compatible with our results,

there are case series in which BAT was negative in taxane reactions [27]. However in different studies BAT positivity has also been reported in skin test positive cases.

Kopac *et al.* reported BAT positivity in a patient with positive skin tests and severe HSRs to paclitaxel. They used CD63 as a marker of basophil activation [28]. De Campos *et al.* reported BAT positivity for CD203c in eight of 15 patients and for CD63 in 5 of 15 patients with anaphylaxis to taxanes. They stated that all reactions occurred in the first or second exposure, and reactions were at the first exposure in 12 of 15 patients. They also stated that skin tests were positive in 11 patients and two individuals from the control group. The fact that most patients with BAT positivity had a positive skin test suggests that these reactions are IgE-mediated. However, the fact that 12 of the reactions occurred in the first exposure and two individuals in the control group had a positive skin test suggests that these patients may have a cross-reactive sensitivity [29].

Taxanes are isolated from different species of yew trees and different parts of the plant, including its pollen. Skin test positivity with taxanes may partly be explained by sensitization to yew tree pollen [22, 26, 29]. In our geographic region, yew HSRs seem to have different mechanisms and a different basophil activation test.

To the best of our knowledge, our study is the first report of BAT analysis of patients with etoposide hypersensitivity and showed a positivity in 4 of 5 (80%) etoposide patients. In this study we obtained different results in patients who underwent skin testing with etoposide, including two positive and one negative test result. Our data suggest that IgE-mediated allergic reactions may be responsible in some etoposide reactions. Although they are not standardized there are reports of skin test positivity in patients with etoposide hypersensitivity. Skin testing protocols with etoposide should be standardized in further studies [30, 31]. Our results suggest that BAT can help to identify patients with hypersensitivity to etoposide and may therefore be a promising *in vitro* diagnostic method.

The fact that basophil activation was not demonstrated in any of the patients after the desensitization procedure proves that desensitization is a successful procedure to prevent basophil activation and ensure safe use of the drug.

Tryptase is the major protease released during mast cell activation. In this study, we also evaluated the role of tryptase release in some patients with platin and taxane hypersensitivity. We detected significant tryptase increases in all 3 patients during index platin reactions and in a patient during the breakthrough reaction indicating mast cell activation. Our results suggest that basophils and mast cells play an active role together in platin HSRs. Giavina-Bianchi *et al.* reported that 2 of 3 patients had elevated tryptase levels during initial platin hypersensitivity and tryptase levels were significantly higher in patients allergic to platinum compounds who had desensitizations with BTRs as compared to patients without BTRs [17]. We detected a significant tryptase increment during taxane reactions only in 1 of 4 patients. De Campos *et al.* measured tryptase in 3 patients after HSRs to taxanes and all results were within normal limits. However no comparison was made with the basal value [29]. When all the results were evaluated together, it is thought that different mechanisms that do not involve mast cells or basophils may be responsible in taxane reactions and further studies are needed to elucidate these mechanisms.

CONCLUSIONS

In our study, basophil activation has been shown to play a role in the mechanism of immediate-type HSRs to cisplatin and etoposide. Desensitization procedures in this group of patients prevent basophil activation and ensure safe use of the drug. Failure to demonstrate basophil activation during taxane reactions suggests that there may be different factors in the mechanism of these reactions. The use of the basophil activation test remains a research test and the predictivity of BAT with chemotherapeutics is still unclear. The number of patients included in the studies is low, more studies with a larger patient population are needed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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