Original Article

Basophil Activation Test Is a Relevant Biomarker of the Outcome of Rapid Desensitization in Platinum Compounds-Allergy

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What is already known about this topic? Rapid drug desensitization has become a cornerstone in the management of immediate drug hypersensitivity reactions to chemotherapeutic agents. Because of the inherent risk of anaphylaxis during the procedure, biomarkers to predict patients at risk of developing such severe reactions are needed.

What does this article add to our knowledge? Basophil activation test (BAT) is positive in carboplatin and oxaliplatin IgE-sensitized patients, and identified patients more likely to have a reaction during rapid drug desensitization (RDD). Higher CD63 expression is observed in patients with severe RDD reactions. BAT remains positive in multiple RDDs.

How does this study impact current management guidelines? BAT identifies platinum compounds IgE-sensitized patients and predicts outcomes of RDD, being a potential biomarker for this procedure.

BACKGROUND: Rapid drug desensitization (RDD) has become a cornerstone in the management of immediate drug hypersensitivity reactions (DHRs) to chemotherapeutic agents. Because of the inherent risk of anaphylaxis during RDD, biomarkers to predict patients at risk of developing such severe reactions are needed. The basophil activation test (BAT) has been used in DHRs as a diagnostic tool.

OBJECTIVE: We evaluated basophil CD63 and CD203c expression (BAT) as a biomarker to assess the safety and effectiveness of RDD in platinum compounds-allergic patients.

METHODS: Patients allergic to platinum compounds (n = 15) undergoing RDD were assessed through clinical history, skin testing, serum tryptase levels, and BAT. BAT was performed immediately before RDD, assessing CD203c and CD63 expression on basophils. BAT was also performed in 6 patients tolerant to platinum compounds and in 6 healthy volunteers.

RESULTS: BAT was positive to CD203c or CD63 in 11 out of 15 patients allergic to platinum compounds (73%), with increased expression of CD203c and CD63 in 11 (73%) and 6 (40%) patients, respectively. Increased CD63 expression tended to be associated with more severe initial reactions. All controls had negative test results. Reactions during RDD were associated with BAT positivity and increased tryptase levels. Only 1 of 4 patients with negative BAT had a mild reaction during RDD. BAT remained positive in multiple sequential RDD.

CONCLUSIONS: BAT identified patients allergic to platinum compounds with an increased risk of reactions during desensitization and higher CD63 expression was observed in severe reactions. Multiple RDDs to platinum compounds did not induce persistent hyporesponsiveness on basophils. BAT is a potential biomarker for RDD. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

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Adverse reactions to chemotherapy have increased dramatically worldwide, and oncologic patients presenting with drug hypersensitivity reactions (DHRs) are often and irreversibly labeled as allergic, preventing the use of first-line therapies in the treatment of primary or relapsing tumors. An alternative approach is the use of rapid drug desensitization (RDD), a groundbreaking procedure that allows patients to transiently tolerate the medication that triggered the original reaction.[1-5]

RDD is a procedure that induces temporary unresponsiveness in a short period of time to a medication that had previously induced a DHR, thereby allowing patients to be safely reexposed,

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Abbreviations used
BAT- Basophil activation test
BTR- Breakthrough reaction
DHR- Drug hypersensitivity reaction
gMFI- Geometric mean fluorescence intensity
RDD- Rapid drug desensitization
SI- Stimulation index

protecting them against anaphylaxis. Such temporary unresponsiveness can be achieved by gradual reintroduction of doubling doses of the drug up to the full therapeutic dose, through powerful inhibitory mechanisms activated on mast cells and basophils.[6-9] Many clinical RDD protocols are available, but there are no biomarkers to identify patients at risk of severe reactions and to monitor RDD procedures.[1-3,5,10-12]

Platinum compounds are mainly used in chemotherapy of ovarian, colorectal, endometrial, and pancreatic cancer, and DHR to carboplatin ranges from 9% to 27%.[13-15] Typically, patients with ovarian cancer may become sensitized during the first course of chemotherapy (6 carboplatin treatments). Upon reexposure when the cancer recurs, patients can present IgE-mediated hypersensitivity and anaphylaxis after 1, 2, or more carboplatin exposures.[13]

The basophil activation test (BAT) has been useful in the investigation of hypersensitivity reactions to allergens, especially when skin tests and specific IgE are inconclusive.[16-21] Studies in food allergy have shown that basophil reactivity assessed through BAT correlates with clinical severity and acquisition of tolerance.[16,22,23] BAT assesses the expression of basophil activation-related proteins (CD63 and CD203c) by flow cytometry after stimulation with the allergen of interest.[24] The glycoprotein CD63 is not specific for basophils, being found in platelets, eosinophils, and monocytes, whereas CD203c is specific for basophils and mast cells.[24] CD63 is expressed on the surface of basophils when activation occurs because of the fusion between granules and cell membranes.[18] In contrast to CD63, CD203c presents a constitutive expression on resting basophils, which is markedly enhanced during activation.[25]

BAT has been used as a diagnostic tool to identify patients who have presented DHR,[20,26] including chemotherapy. Two preliminary reports indicated that carboplatin induced the expression of CD203c on basophils of carboplatin-allergic patients and could be used as a potential predictor of DHR.[27,28] A case report of a cisplatin-allergic patient showed increased basophil CD63 expression after cisplatin exposure.[29] No data are available regarding the combined expression of both markers, CD63 and CD203c, in carboplatin and oxaliplatin-allergic patients, and its application in patients undergoing RDD.

We present here the largest series of platinum-allergic patients undergoing RDD in whom CD63 and CD203c (BAT) were assessed as a biomarker of their initial DHR and the safety and efficacy of RDD. Our data suggest that BAT identifies platinum compounds-allergic patients more prone to have severe reaction during RDD.

METHODS

Study design

This was a prospective cohort study assessing BAT in cancer patients undergoing RDD because of platinum compounds DHR (anaphylaxis). Patients were recruited from the Dana Farber Cancer Institute (DFCI) and Brigham and Women's Hospital, Harvard Medical School—affiliated Hospitals, Boston, and from Hospital das Clínicas, University of São Paulo, Brazil. The study protocol was approved by the institutional review boards at Brigham and Women's Hospital (2012P002275), DFCI (13-288), and Hospital das Clínicas (22701913.6.0000.0068). The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All the participants provided written informed consent to be included in the study.

Oncologic patients aged 18 to 80 years, allergic to a platinum compound (carboplatin or oxaliplatin), and undergoing RDD to the culprit drug were enrolled from October 2013 to March 2015. All included patients had a documented history of anaphylaxis and a positive immediate skin test (skin prick or intradermal test) to a platinum compound, and were considered allergic. For skin prick testing, a drop of carboplatin (10 mg/mL) or oxaliplatin (5 mg/mL) was applied to the volar surface of the forearm. For intradermal injection, 0.03 mL of carboplatin (1 and 10 mg/mL) or oxaliplatin (0.5 and 5 mg/mL) was injected.[2] Skin prick or intradermal test showing a wheal with the largest diameter 3 mm longer than that of the negative control was considered positive.

Exclusion criteria consisted of uncontrolled and/or other severe chronic diseases, severe anemia, chronic use of corticosteroids, and history of anaphylaxis triggered by other etiologies. Control groups included oncologic patients treated at the DFCI who had received more than 8 infusions of platinum-based agents (carboplatin or oxaliplatin) and were tolerant to these drugs (control group 1) and healthy volunteers who had never been exposed to platinum-based agents (control group 2).

BAT for platinum compounds was standardized by assessing the expression of CD63 and CD203c on basophils of allergic patients. BAT was the study's primary outcome, and it was correlated with clinical features and RDD outcomes, as well as with serum tryptase levels. The test results from allergic patients to platinum compounds and control groups were compared. Several patients were evaluated in multiple RDD procedures.

The initial DHRs, as well as the breakthrough reactions (BTRs) during RDD, were defined as immediate hypersensitivity reaction according to the World Allergy Organization.[30,31] The severity of these reactions was graded according to Brown's classification as mild (skin and subcutaneous tissues only), moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement), or severe (hypoxia, hypotension, or neurologic compromise).[32] Atopic participants were those with a diagnosis of rhinitis and/or asthma and/or atopic dermatitis associated with positive skin prick test to common aeroallergens. Tryptase measurement and BRCA 1/2 mutation were not primary outcomes and were not available for all patients.

Basophil activation test

Blood was collected immediately before RDD, just before premedications to avoid interference with the BAT. After blood collection, patients were premedicated according to National Cancer Institute guidelines with antihistamines and corticosteroids, and underwent RDD. The control group of oncologic patients tolerant to platinum compounds had 1 blood collection before regular chemotherapy infusion, and healthy volunteers had 2 blood collections for BAT on 2 different days.

For the BAT, whole blood aliquots (200 μL) were incubated at 37°C for 45 minutes with 100 μL of the chemotherapeutic agent. Four different concentrations were tested: 500, 50, 5, and