Clinical Utility of Basophil CD203c as a Biomarker for Predicting the Timing of Hypersensitivity Reaction in Carboplatin Rechallenge: Three Case Reports

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ABSTRACT

Purpose: Drug desensitization has been found to be an effective option for carboplatin rechallenge in patients at risk for severe hypersensitivity reaction. However, identifying such patients requires precise clinical tests. This study was performed to evaluate the clinical utility of basophil CD203c to predict the timing of carboplatin-induced severe hypersensitivity reaction.

Methods: Here we report on 3 patients undergoing a carboplatin-desensitization protocol at Mie University Hospital. For all patients, ex vivo exposure to carboplatin resulted in increased levels of activated basophils in a previous occurrence of carboplatin-induced severe hypersensitivity reaction.

Findings: Basophil activation test using carboplatin was returned to negative just before the first course of carboplatin-desensitization protocol in all patients, and they successfully received their first course of the protocol with no signs of anaphylaxis. However, for all of the patients, increased basophil activation was once again detected after subsequent readministration of carboplatin and grade 3 or 4 anaphylaxis developed. Basophil activation test coincided precisely with the timing of carboplatin-induced anaphylaxis in all patients.

Implications: CD203c basophil activation testing might prove to be a reliable tool for risk stratification and clinical decision making for carboplatin desensitization in which severe hypersensitivity reaction is likely to occur. (*Clin Ther*. 2016;38:1537–1541)

Key words: allergy, basophil activation, biomarker, cancer chemotherapy, carboplatin, CD203c.

INTRODUCTION

Carboplatin (CBDCA)-induced severe hypersensitivity reaction (sHR) is a serious concern. The clinical manifestation of sHR includes systemic reactions, such as tachycardia, respiratory obstruction, and anaphylactic shock.[1,2] Several reports found that desensitization might be an effective option for patients at high risk for developing sHR and who require CBDCA treatment.[3–6] Just before submitting this case report, a literature search was performed on PubMed (date of implementation March 9, 2016) using the search terms *carboplatin*, *allergy*, and *risk stratification* and confirmed that skin testing is thought to be the only method used clinically to identify individuals sensitized to CBDCA. Risk stratification using skin testing has been proposed as a way to ensure tolerable CBDCA desensitization.[7,8] However, caution should be used when performing skin testing due to the occurrence of crucial allergic symptoms. In addition, CBDCA skin testing might not be ideal due to the risk of skin damage, environmental contamination, and exposure of health care workers to anticancer drugs.[9]

Findings from our previous study suggested that a specific IgE participates in CBDCA-induced sHR.[10] The study also found that an IgE-dependent mechanism incorporating FcεRI overexpression participates in CBDCA-induced basophil activation, one of the sites of action responsible for the development of sHR.[11] These findings strongly implied that a basophil activation test might be well-suited for the diagnosis and prediction of CBDCA-induced sHR.[12]

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This is particularly relevant, given that such a test can be performed without direct exposure of patients to anticancer drugs.

In the present report, we describe 3 ovarian cancer patients undergoing CBDCA desensitization and found that the clinical utility of basophil CD203c predicts the timing of CBDCA-induced sHR. All 3 patients were inpatients undergoing CBDCA-desensitization protocol at Mie University Hospital. The CBDCA-desensitization protocol was a modified version of the 4-step protocol reported by Nishio et al,[4] based on 4 different dilutions of CBDCA (Table I). The severity of anaphylaxis was evaluated using the scoring system presented by Sampson.[13]

A commercial kit (Allergenicity Kit; Beckman Coulter, Fullerton, CA) was used for the quantification of basophil CD203c expression.[14] CD203c-positive basophils were identified by the relatively higher fluorescence intensity (CD203c expression) compared with that of our negative control (basophils stimulated in 5% dextrose solution). Median fluorescence intensity (MFI) of total basophils, including both CD203c-positive and CD203c-negative basophils was also measured. ΔMFI was calculated as the difference between the MFI of the negative control for each subject. In accordance with our previous study, the approximate cutoff values for determining increased activated basophils and ΔMFI were 5.0% and 10.0, respectively.[12]

CASE REPORTS

Patient 1

A 61-year-old female was diagnosed with ovarian cancer 7 years earlier. Before her initial CBDCA-induced anaphylaxis, this patient had received the following regimens: 18 courses of TC (paclitaxel + CBDCA), 6 courses of DC (docetaxel + CBDCA), 4 courses of liposomal doxorubicin, and 7 courses of IP (irinotecan + cisplatin). She was readmitted due to recurrence and was started on a TC regimen (270 mg paclitaxel + 700 mg CBDCA). During her third course (total of 27 courses of CBDCA) of treatment, anaphylaxis with symptoms of generalized red flushing, tachycardia, hypotension, and vomiting (grade 4) occurred. An increase in the rate of activated basophils (20% and ΔMFI 17.4) after ex vivo exposure to CBDCA was observed on the day before the occurrence of grade 4 anaphylaxis (Figure 1**A**). A total of 27 courses of CBDCA had been administered up to that point. After the anaphylaxis, 2 courses of paclitaxel monotherapy and 3 courses of TP (paclitaxel + cisplatin) were given. Two months after the latest chemotherapy, a CBDCA-desensitization protocol was administered in combination chemotherapy with 60 mg irinotecan (day 1 and 2) and 600 mg CBDCA (day 1) every 3 weeks. Two courses (CBDCA 28 and 29 courses) of the desensitization protocol were successfully carried out, with no signs of anaphylaxis and no ex vivo basophil activation (Figures 1**B** and 1**C**). During the subsequent 3 courses (CBDCA 30–32 courses), grade 1 to 2 anaphylaxis developed and progressed to grade 3 anaphylaxis, with symptoms of generalized red flushing and tachycardia (CBDCA 33 courses). The grade 3 anaphylaxis occurred at the fourth-step CBDCA solution (1/1 dilution). The basophil activation test found a gradual increase in ΔMFI of anti-CD203c antibodies or cell activation before and with the onset of grade 3 anaphylaxis (23.8 and 12.5%, respectively) (Figures 1**C**–1**G**).

Table I. Desensitization protocol for carboplatin.

Step	Carboplatin Concentration	Volume (mL)	Infusion Time (min)
1	1/1000	250	60
2	1/100	250	60
3	1/10	250	60
4	1/1	250	120

Patient 2

A 65-year-old female was diagnosed with ovarian cancer 9 years ago. Before her initial CBDCA-induced anaphylaxis, she received the following regimens: 9 courses of TC and 6 courses of IP. After the recurrence of cancer, the TC regimen (240 mg paclitaxel + 600 mg CBDCA) was administered again; however, anaphylaxis with symptoms of generalized red flushing and tachycardia (grade 3) occurred during the second course. A total of 11 courses of CBDCA had been administered up to that point. An increase in the rate of activated basophils (7.7% and ΔMFI 35.4) after ex vivo exposure to CBDCA (Figure 1**H**) was observed on the day before onset of grade 3 anaphylaxis. After the anaphylaxis, 12 courses of paclitaxel monotherapy were given. Seven months from the latest chemotherapy, the patient was started on a CBDCA-desensitization protocol in combination with the TC (240 mg paclitaxel + 600 mg CBDCA)