

Short Communication

An Experimental Biological Test to Diagnose Hypersensitivity Reactions to Carboplatin: New Horizons for an Old Problem

Mauro Pagani^{1,*}, Lennart Venemalm², Patrizia Bonnadona³, Pier Paolo Vescovi¹, Carmen Botelho⁴ and Josefina R. Cernadas⁴

¹Department of Internal Medicine, Allergology and Oncology Service Asola Hospital, Mantova, Italy, ²Phadia Diagnostics, Uppsala, Sweden, ³Allergology Service, Azienda Ospedaliera Verona, Verona, Italy and

⁴Immunoallergology Department, H. S. João EPE, Porto, Portugal

*For reprints and all correspondence: Mauro Pagani, Ospedale Civile di Asola Piazza 80° Fanteria, 1, 46041 Asola (Mantova) Italy. E-mail: mauro.pagani@aopoma.it

Received May 29, 2011; accepted January 15, 2012

Carboplatin, a second-generation platinum compound, is a chemotherapeutic drug effective in many types of cancers. Its use is limited by the development of systemic allergic reactions in up to 30% of the cancer patients. Therefore, it is very important to make a correct diagnosis of true carboplatin allergy, for the crucial clinical implications. In this regard, no biological test is actually available to detect specific immunoglobulin E in the sera of patients allergic to carboplatin. We evaluated a new experimental biological test in patients with suspected immunoglobulin E-mediated reactions to carboplatin. Three patients with suspected hypersensitivity reactions to carboplatin underwent skin tests with an undiluted aliquot (10 mg/ml) of carboplatin preparation planned for infusion. Total serum immunoglobulin E and specific immunoglobulin E to the two platinum salts carboplatin and cisplatin were determined with the ImmunoCAP system (Phadia AB, Uppsala, Sweden). We detected specific immunoglobulin E to carboplatin in all three patients, whereas specific immunoglobulin E to cisplatin was observed in one patient. The positivity of specific immunoglobulin E against carboplatin in these three patients is a new and encouraging observation for the development of a new important instrument that can help clinicians in their therapeutic decisions, after a hypersensitivity reaction to a platinum salt.

Key words: carboplatin hypersensitivity – biological test – skin tests – chemotherapy

INTRODUCTION

Carboplatin is a second-generation platinum compound derived from the first synthesized drug of this class, cisplatin.

The drug can be administered in monotherapy or, as it is done more frequently, in combination with other cytostatics, especially taxanes, but also gemcitabine, epipodophyllotoxins, cyclophosphamide and anthracyclines.

The use of carboplatin is limited by the development of systemic allergic reactions in up to 30% of cancer patients (1). The current data suggest that this drug has increasingly been reported to cause hypersensitivity reactions, mainly in

adults. The onset of carboplatin-induced hypersensitivity typically occurs after multiple cycles, most commonly during the eighth cycle, which corresponds to the second dose of re-induction therapy following tumor relapse. These reactions can include flushing, nausea, diarrhea, abdominal pain, bronchospasm, urticaria, hypotension and death. Symptoms usually develop within the first 30 min of an infusion and occur despite premedication with dexamethasone and antihistamines, which are usually given routinely (2,3). No obvious risk factors are apparent that might allow the identification of those patients who might experience severe reactions as opposed to mild symptoms. Literature data

suggest that most of these reactions are immunologically mediated. In fact, clinical features are typical of type I immunoglobulin E (IgE)-mediated reactions, and several patients have also positive skin tests (4,5).

Affected patients must either avoid the drug completely, with suboptimal therapeutic alternatives, or undergo desensitization, a difficult procedure, indicated only for selected cases. Therefore, it is very important to make a correct diagnosis of true carboplatin allergy for crucial clinical implications. In this regard, no biological test is actually available to detect specific IgE in the sera of patients allergic to carboplatin. The aim of our study was to evaluate a new experimental biological test in patients with suspected IgE-mediated reactions to carboplatin. The authors present the preliminary results.

METHODS

Three patients with a high suspicion of type I reactions to carboplatin underwent skin tests with an undiluted aliquot (10 mg/ml) of carboplatin preparation planned for infusion. The first step was to perform a prick test with the undiluted drug on the forearm.

When the prick tests were found to be negative, the skin tests were repeated with the intradermal injection of 0.02 ml of carboplatin solutions, at a concentration of 0.01–0.1 and 1 mg/ml, respectively. These concentrations were obtained with the dilution of the commercial drug in physiological saline solution. Each test was read and evaluated after 15, 20 and 30 min from administration. In conformity with EAACI recommendations, the prick test was considered positive when the cutaneous response was a wheal of at least 3 mm with a surrounding flare, while the intradermal test was considered positive with a wheal of at least 5 mm with a surrounding flare (6). The subjects were then observed again during the days (24, 48 and 72 h after the test) to find out if there were any possible delayed reactions. A blood sample of each patient was collected and stored at -20°C . Carboplatin and cisplatin were conjugated to human serum albumin (HSA) by mixing an excess of the drugs (3 M equivalents of cisplatin and 18 M equivalents of carboplatin) to HSA (1 M equivalent) in phosphate buffer at pH 7.4 and incubated for 24 h. Excess drug was separated by dialysis and the drug conjugates were immobilized to the activated cellulose sponge (ImmunoCAP). The limit of quantitation for the specific IgE test is 0.1 kUA/l and levels above this indicate sensitization to the specific allergen.

CASE REPORTS AND RESULTS

The first patient, a 65-year-old woman with metastatic ovarian cancer, developed diffuse erythroderma and dyspnoea 20 min after the beginning of the seventh carboplatin administration. The infusion was immediately stopped and she received 10 mg of chlorphenamine and 1000 mg of

hydrocortisone intravenously (i.v.). The dyspnoea disappeared within 2 h, whereas the erythroderma completely resolved in 6 h. To assess whether the patient was allergic to carboplatin, we performed skin testing 20 days after the reaction that showed positive results for the intradermal test (IDT) at a concentration of 0.01 mg (wheal of 9 mm). Total serum IgE was 191 kUA/l and specific IgE antibodies against carboplatin were positive at 0.35 kUA/L, while specific IgE against cisplatin was not detected. On the basis of these data, we decided to start desensitization procedures on the patient as per the 12-step Castells protocol (7). During the first desensitization procedure, the woman developed a generalized and very itchy rash at the ninth step, but after a temporary stop of the carboplatin infusion and administration of hydrocortisone 1000 mg i.v., the procedure was completed. The same was observed during the second and third procedures, whereas the other three carboplatin infusions were conducted without problems and the patient completed the planned cycles of chemotherapy.

The second case regards a 61-year-old woman with metastatic ovarian cancer, who had had anaphylactic shock during the eighth administration of carboplatin. Therefore, carboplatin was replaced with liposomal doxorubicin and was administered for a total of six cycles. The abdominal computed tomographic scan performed a month later the end of this chemotherapy demonstrated progression of the disease; thus, we planned to begin a chemotherapy with carboplatin once more. We performed skin testing for carboplatin that was slightly positive for IDT at the concentration of 0.1 mg/ml (wheal of 6 mm). Total IgE in the serum of the patient was 200 kUA/l, specific IgE antibodies against carboplatin were positive at 0.40 kUA/L and we did not observe specific IgE for cisplatin. Then, the patient underwent the desensitization procedure. The first desensitization caused dyspnoea, hypotension and generalized rash during the 12 step; however, even in this case, the temporary stopping of therapy and the administration of 10 mg of chlorphenamine and 1000 mg of hydrocortisone i.v. permitted us to complete the procedure. The other five desensitization cycles were administered without problems and the patient could complete the chemotherapy as planned.

The third patient was a 3-year-old girl with a diagnosis of optochiasmatic low-grade glioma, with severe eye proptosis and significant visual impairment.

She had been on treatment with carboplatin and vincristine using a scheme based on SIOP protocol. After a 10-week induction phase with vincristine and carboplatin and a pause of 3–4 weeks, both drugs were administered every 4 weeks for 1 year.

The child had severe anaphylaxis, with multisystemic involvement, in the sixth cycle, independently of pre-treatment.

Although hypersensitivity reactions were severe, carboplatin remained the best choice for treatment; therefore, the desensitization procedure to carboplatin according to the Castells protocol (7) was selected.

Table 1. Characteristics of reactions, results of skin test and biological test

Patient no.	Age	Course at occurrence of hypersensitivity reaction	Symptoms	Prick test	Intradermal test	Total IgE (kUA/l)	IgE for carboplatin (kUA/l)	IgE for cisplatin (kUA/l)
1	65	7	Erythroderma, dyspnoea	Neg	Pos 0.01 mg/ml	191	0.35	Neg
2	61	8	Anaphylactic shock	Neg	Pos 0.1 mg/ml	200	0.4	Neg
3	3	6	Anaphylactic shock	Neg	Not done	400	1.6	4.2

IgE, immunoglobulin E.

The skin prick test to carboplatin was performed with a 0.02 mg/ml solution before the desensitization procedure, with negative results. Because the child was very young and severely ill, we did not perform intradermal tests. The child had a new severe reaction at the beginning of Step 12, after a cumulative dose of 59 mg of carboplatin was infused.

At this stage, specific IgE for carboplatin and cisplatin was determined by Phadia[®]. Total serum IgE was 400 kUA/l and specific IgE antibodies against carboplatin were 1.6 kUA/L. Moreover, specific IgE to cisplatin was determined, which also had positive values of 4.2 kUA/l. Based on these results, we decided to stop subsequent administration of platinum salts. Table 1 summarizes the test results.

DISCUSSION

Correct identification and diagnosis of hypersensitivity reactions to cytostatics play a crucial role in the treatment of neoplastic patients because unlike other drugs (e.g. antibiotics) that may be easily replaced in cases of adverse reactions, chemotherapeutic drugs are often 'unique' and essential for the treatment of the disease. Hence, the correct diagnosis of an allergic side effect to a cytostatic drug is crucial and cannot be postponed. Carboplatin is a second-generation platinum compound derived by the first synthesized drug of this class, cisplatin. It is effective with many types of cancers and plays a major role in ovarian and non-small lung cancer. As with all platinum compounds, carboplatin can cause hypersensitivity reactions with prolonged use. The habitual schedules of chemotherapy plan six administrations of carboplatin; hence, most allergic reactions occur when the patient undergoes a retreatment for a relapse of the neoplasm (8). Mild reactions have an incidence of ~60–70%, which appear during chemotherapy, up to 3 days after the end of treatment and involve the skin. Most severe reactions are less frequent (30–40%), developing about 30 min after the beginning of chemotherapy and involve the skin, abdominal tract, respiratory and cardiovascular system (9). The reactions are probably IgE-mediated; in fact, they develop after several administrations, during the infusion of carboplatin, and skin tests result positive, especially in more severe

cases. The role of skin tests was evaluated either for the diagnosis or for the prevention of hypersensitivity reactions and apropos of this, Markman et al. (10) demonstrated on a wide group of patients that the intradermal skin test with undiluted 0.02 m/l of carboplatin performed 30 min before chemotherapy was able to identify patients who could receive carboplatin safely with a negative predictive value of 98.5%. Nowadays, no biological tests are available for the assay of specific IgE against carboplatin; therefore, the diagnosis is based not only on clinical history, but also on skin test results. Unfortunately, it is not always possible to perform skin tests on these kinds of patients, either due to the age of the patient, as in our third case, or underlying diseases, or, as often occurs, due to concomitant intake of drugs, namely steroids, which impede a correct interpretation of the results. Therefore, the detection of serological IgE against carboplatin in these three patients is an encouraging observation for the development of a new important instrument that could very much help clinicians in their therapeutic decisions, after a hypersensitivity reaction to a platinum salt. In addition, detection of specific IgE for cisplatin in the serum of the third patient is a demonstration that has never been observed before of cross-reactivity of the platinum-specific IgE, which limits the possibility of substituting carboplatin with other platinum compounds. These preliminary results, with an experimental biological test to diagnose hypersensitivity reactions to carboplatin, demonstrate the relevance of this test in confirming the IgE mechanism when studying patients with suspected type I reactions to these compounds. Moreover, the possibility of studying cross-reactivity among these agents is of outmost importance in helping oncologists to take the most appropriate clinical decisions. More cases have to be studied to determine sensibility and specificity of this biological test.

Conflict of interest statement

None declared.

References

1. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999;17:1141–5.

2. Sliesoraitis S, Chikhale PJ. Carboplatin hypersensitivity. *Int J Gynecol Cancer* 2005;15:13–8.
3. Lee C, Gianos M, Klausermeyer WB. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. *Ann Allergy Asthma Immunol* 2009;102:179–87.
4. Menczer J, Barda G, Glezerman M, Hyat H, Brenner Y, Brickman CM, et al. Hypersensitivity reactions to carboplatin. Results of skin tests. *Eur J Gynaecol Oncol* 1999;3:214–6.
5. Leguy-Seguin V, Jolimoy G, Coudert B, Pernot C, Dalac S, Vabres P, et al. Diagnosis and predictive value of skin testing in platinum salts hypersensitivity. *J Allergy Clin Immunol* 2007;119:726–30.
6. Brockow K, Romano A, Blanca M, Ring J, Pichler WJ, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57:45–51.
7. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barret NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574–80.
8. Gadducci A, Tana R, Teti G, Zanca A, Fanucchi A, Genazzani AR. Analysis of the pattern of hypersensitivity reactions in patients receiving carboplatin retreatment for recurrent ovarian cancer. *Int J Gynecol Cancer* 2008;18:615–20.
9. Pagani M. The complex clinical picture of presumably allergic side effects to cytostatic drugs: symptoms, pathomechanism, reexposure and desensitization. *Med Clin N Am* 2010;94:835–52.
10. Markman M, Zanotti K, Peterson G, Kulp B, Webster K, Belinson J. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003;21:4611–4.