Original Article

Carboplatin-, Oxaliplatin-, and Cisplatin–specific IgE: Cross-reactivity and Value in the Diagnosis of Carboplatin and Oxaliplatin Allergy

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What is already known about this topic? Cross-reactivity among platins has been documented through skin testing, but platin intradermal injection may induce cutaneous toxicity. Patients with anaphylactic reactions are at risk for a reaction due to skin testing.

What does this article add to our knowledge? Specific IgE to carboplatin and oxaliplatin can be detected in patients who are sensitized to platin. Cross-reactivity among platins may also be assessed by platin specific IgE measurement. Oxaliplatin appears to be the most immunogenic platin.

How does this study impact current management guidelines? Platin specific IgE seems to be a valuable diagnostic aid. Patients who are sensitized to oxaliplatin seem to be at a higher risk of developing a reaction to carboplatin and cisplatin, whereas patients reactive to carboplatin may be able to tolerate oxaliplatin.

BACKGROUND: The diagnosis of hypersensitivity reactions (HSR) to platins is based on the characterization of the reaction and the results of skin testing. Platins can be irritants when used in skin testing; therefore, in vitro testing may offer an alternative diagnostic tool.

OBJECTIVE: To evaluate sensitivity and specificity of platin specific IgE (sIgE) in patients with HSRs and in controls.

METHODS: Twenty-four patients with immediate HSR to platins were included (carboplatin, 12; oxaliplatin, 12): 19 women and 5 men (mean age, 61 years). The control group included 17 patients exposed to platin and with no HSR. Skin testing was performed on 22 patients. Carboplatin sIgE and oxaliplatin sIgE were measured in 24 patients and 17 controls; carboplatin sIgE was measured in 21 patients.

RESULTS: Skin test results were positive in 22 patients (carboplatin, 12/12; oxaliplatin, 10/12). Seven of 12 patients sensitive to carboplatin (59%) had positive carboplatin sIgE, 2 also had positive cisplatin sIgE, and all had negative oxaliplatin sIgE; 9 of 12 patients sensitive to oxaliplatin (75%) had positive sIgE to oxaliplatin, 8 of 12 (67%) also had positive carboplatin and cisplatin sIgE, to which they had not been exposed. All 5 carboplatin controls had negative sIgE; 3 oxaliplatin controls (25%) had positive carboplatin sIgE, and 2 had positive oxaliplatin sIgE.

CONCLUSION: Carboplatin sIgE is very specific but less sensitive. In contrast, oxaliplatin sIgE had higher sensitivity but lower specificity. Analysis of our data suggests that oxaliplatin exposure was more immunogenic. This could be clinically relevant because patients sensitized to carboplatin may be able to tolerate oxaliplatin, but patients sensitized to oxaliplatin may be at risk when exposed to carboplatin and cisplatin. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:494-500)

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Hypersensitivity reactions (HSR) have been reported for all chemotherapeutic agents, and, due to their wide use in ovarian and colorectal cancers, carboplatin and oxaliplatin, respectively, are among the most frequent agents that elicit HSRs.[1] HSRs to platins, such as carboplatin and oxaliplatin, are usually IgE mediated[2] as opposed to taxanes, which are considered non-IgE mediated. Until now, the diagnosis of HSRs to platins was based on the characterization of the reaction and the results of skin testing after the reaction.

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Abbreviations used
−- *Negative*
+- *Positive*
Cis- *Cisplatin*
Crb- *Carboplatin*
HSR- *Hypersensitivity reaction*
ID- *Intradermal*
Ig- *immunoglobulin*
ND- *Not done*
NPV- *Negative predictive value*
Ox- *Oxaliplatin*
PPV- *Positive predictive value*
Sens- *Sensitivity*
sIgE- *Specific IgE*
Spec- *Specificity*
SPT- *Skin prick test*

At the present time, patients are identified at the time of reaction, and there are no prospective studies that evaluated predictors that could protect patients from an HSR. Some researchers advocate that skin testing before the sixth[3] or eighth[4] carboplatin infusion can identify patients at risk who may develop HSR. There are no prospective studies that have evaluated if patients with a positive skin test develop HSRs on regular infusions, but Markman et al[5] described, in a small study, that 6 of 7 patients exposed to carboplatin (86%) and with no HSR who had positive carboplatin skin testing experienced an HSR when the subsequent regular carboplatin infusion was initiated.

Thus, patients undergoing a second carboplatin course, ie, more than 6 infusions, should be skin tested before the seventh or eighth infusion to evaluate sensitization.[5] If skin testing is positive, even if no reaction occurs, then patients should undergo a standard desensitization protocol[3-8] or an empiric modified 8-step desensitization as proposed by Patil et al[9] because of the potential risk of a reaction during subsequent infusions. Adverse reactions, however, can occur during intradermal skin testing when chemotherapy agents are used due to their local cytostatic activity, such as cutaneous toxicity. Hesterberg et al[10] has already suggested that, for carboplatin, 10 mg/mL for intradermal testing can be too high and induce local necrosis. As reported for batalactam[11-13] and other drugs,[5,14-16] systemic reactions could also be triggered by skin testing. In addition, some patients may have negative skin test results even after an HSR,[6] and, currently, there is no available alternative test that could help us to identify these patients.

Concerning in vitro evaluation, fluorescent enzyme immunoassays are available, which quantifies specific antibodies (IgE and IgG). Specific IgE (sIgE) has been used for several years in the diagnosis of allergy to foods, inhalants, latex, and venoms. An in vitro diagnosis of drug allergy, including betalactams is recommended for patients with severe reactions and anaphylaxis.[17-19] The role of sIgE in the diagnosis of platin allergy is yet to be determined. Pagani et al[20] recently published the value of carboplatin sIgE in the diagnosis of moderate-to-severe hypersensitivity to carboplatin in 3 patients. Carboplatin sIgE was positive in all the patients (2 of them with positive skin test results) with cisplatin also only positive in one. One of the patients, a 3-year-old girl with optochiasmatic low-grade glioma was not able to have skin testing. We also had preliminary data that indicated that carboplatin sIgE and oxaliplatin sIgE can be detected in patients sensitized to platin and might be a valuable diagnostic aid.[21]

In this study, our objective was to evaluate sensitivity and specificity of platin sIgE (carboplatin and oxaliplatin) in patients with previous HSR compared with patients exposed to similar amounts of platins without an HSR. Cross-reactivity among carboplatin, oxaliplatin, and cisplatin was also assessed by adding cisplatin sIgE to the in vitro evaluation panel.

METHODS

The present study was retrospective. Oncologic patients with ovarian, endometrial, colon, and pancreatic cancers who had HSR to carboplatin or to oxaliplatin were referred to the allergy department. To confirm platin sensitization, skin testing was performed (prick and intradermal) with the culprit drug 2 to 4 weeks after the reaction, and a blood sample was also collected and frozen for subsequent analysis. If the drug was considered as first-line therapy, then patients were enrolled in the desensitization program.

After informed consent was obtained, 24 patients with immediate HSRs during platin infusion were enrolled. Eight patients were from Boston's Brigham and Women's Hospital, and 16 were from Lisbon's Santa Maria Hospital allergy departments. Twelve patients had reacted to carboplatin and 12 to oxaliplatin. Nineteen patients were women and 5 were men, with a mean age of 61 years old (Tables I and II). In the carboplatin-sensitive group, the patients were exposed to a mean of 7 carboplatin infusions (4-9) and, in the oxaliplatin group, to a mean of 10 (6-14). Immediate HSRs were classified according to Brown's classification[22] as mild when there was only cutaneous and/or subcutaneous involvement; moderate when features that suggested respiratory, cardiovascular, or gastrointestinal involvement were present; and severe when hypoxia, hypotension, or neurologic compromise were observed.

Skin testing with carboplatin and oxaliplatin was performed as previously reported.[6,16,23-25] A carboplatin skin prick test (10 mg/mL) was performed, and, when results were negative, we proceeded to intradermal testing with a 0.02-0.05−mL injection of 0.1, 1, and 10 mg/mL; for oxaliplatin, a similar protocol was applied by using the full-strength concentration of 5 mg/mL for a skin prick test and 0.5 and 5 mg/mL for intradermal testing. Histamine (0.1 mg/mL) was used as a positive control, and saline solution was used as a negative control. A positive skin test result was defined as a mean wheal diameter at least 3 mm greater than the negative control.[6] Skin testing was performed with the culprit drug only.

SIgE was determined for carboplatin and oxaliplatin in all 24 patients with prior HSR; cisplatin sIgE was also measured in 21 patients; it was not performed in 3 patients because their serum was no longer available. All frozen blood samples were sent to Phadia AB (Uppsala, Sweden). The platinum salts were conjugated to human serum albumin by mixing an excess of the drugs in phosphate buffer at pH 7.4 and then by incubating for 24 hours. Excess drug was separated by dialysis, and the drug conjugates were immobilized to the activated cellulose sponge (ImmunoCAP; Phadia AB).[20] A cutoff of 0.10 kU_A/L was used for negative in vitro testing.

Seventeen patients exposed to platin and who did not experience any HSR were used as controls: 5 were exposed to carboplatin (received 3-9 infusions; mean, 6.6 infusions), and