

*Original article***Diagnostic and predictive value of skin testing in platinum salt hypersensitivity**

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Background: Hypersensitivity reactions to platinum salts are potentially lethal adverse events in chemotherapy, and often require its discontinuation. Several preventive procedures have been proposed: premedication, desensitization regimens, or replacement with a different platinum salt.

Objective: We therefore assessed the value of skin tests with platinum salts. A positive result would confirm their responsibility in hypersensitivity reaction, whereas a negative result would identify candidates for continuation of therapy using a different platinum salt.

Methods: Patch tests, prick tests, and intradermal tests with cisplatin, carboplatin, and oxaliplatin were performed in 21 patients.

Results: Skin tests were positive in 14 of 21 cases. Prick tests were positive in 5 cases with the suspected platinum salt. Intradermal tests were positive in 12 of 19 cases, always when the hypersensitivity occurred less than 2 hours after infusion. Cross-reactions were observed in 4 cases. Delayed readings of skin tests at 24 hours and 48 hours were positive in 3 patients. Patch tests were negative in all the 21 patients tested.

Replacement with another platinum salt was performed in 13 patients using one that gave a negative skin test. A relapse of symptoms occurred in 1 patient.

Conclusion: Intradermal tests are particularly indicated for the diagnosis of immediate hypersensitivity reaction. Their good negative predictive value allows safe retreatment by detecting a potential cross-reaction.

Clinical implications: The frequency of cross-reactions among cisplatin, carboplatin, and oxaliplatin has not been clearly established. Skin tests allow different platinum salts to be given and avoid discontinuation of chemotherapy. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Drug hypersensitivity, platinum salts, anaphylaxis, patch tests, prick tests, intradermal test

Abbreviations used

HR: Hypersensitivity reaction
IDT: Intradermal test
PS: Platinum salt

Hypersensitivity reactions (HRs) to platinum salts (PSs) are potentially lethal adverse events of cytotoxic drug treatments and often require their discontinuation. The extensive use of carboplatin and oxaliplatin over the period of the past decade has led to an increase in cases of PS HR.¹⁻⁶ Hypersensitivity to carboplatin (12% to 30%) seems to be more frequent than hypersensitivity to cisplatin (5% to 20%) or oxaliplatin (mild reactions, 10% to 12%; severe reactions, less than 1%). The clinical features of PS HR as well as their severity are variable and unpredictable. Symptoms can be mild or moderate, such as pruritus, urticaria, palmar erythema, facial flushing, erythematous rash, dizziness, diarrhea, facial or lingual swelling, tachycardia, hypotension, or hypertension, or severe, such as chest pain, angina pectoris, bronchospasm, anaphylaxis, respiratory arrest, and death. The exact mechanism responsible for PS HR is unknown, but several main mechanisms are suspected. Early-onset symptoms are thought to be a result of immediate IgE-mediated hypersensitivity (type I allergy) or alternatively of direct histamine release. The literature also mentions idiosyncratic reactions, more common with oxaliplatin, consisting of chills, fever, abdominal pain, and diarrhea, and occurring several hours after initiation of infusion. In such reactions, bronchospasm, cutaneous signs, and severe hypotension are absent, which stands against an anaphylactic mechanism.^{7,8} They are best explained by a massive release of TNF- α and IL-6, because elevated serum levels were found during clinical manifestations.⁷ These reactions do not require discontinuation of chemotherapy, because they can be prevented by premedication and slower infusion. In addition, a few cases of type II immunoallergic thrombopenia⁴ and type III delayed vasculitic urticaria⁹ have been described.

No common strategy for resuming treatment after discontinuation after an episode of hypersensitivity is agreed on. Because the resumption of treatment may be fatal, several preventive procedures have been proposed

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most often successfully: premedication, desensitization regimens, or replacement with a different PS. However, cross-reactivity may lead to the exclusion of all platinum salts. We therefore assessed the value of skin tests with platinum salts: a positive result would confirm the responsibility of the PS in HR, whereas a negative result would identify candidates for continuation of therapy using a different PS.

METHODS

Patients

A monocentric prospective study was performed between September 2002 and June 2005. Patients were referred by an oncology or drug monitoring department for any adverse event after PS infusion. Inclusion criteria were the existence of pruritus, rash, urticaria, angioedema, wheezing, bronchospasm, hypotension, or anaphylactic shock.

Experiments

Immunoallergologic investigations were performed after a minimal period of 6 weeks after resolution of the adverse reaction.

Patch tests were performed with Cisplatyl (cisplatin, injectable form, 10 mg/10 mL; Sanofi-Aventis France Laboratory, Paris, France), Carboplatine Teva (carboplatin, injectable form, 10 mg/mL; Teva Pharma, Paris, France), and Eloxatine (oxaliplatin, injectable form, 5 mg/mL; Sanofi-Aventis France Laboratory) diluted to 10% in water. The patch tests were applied on the back of patients under Finn Chambers on Scapon tape (Stallergenes SA, Antony, France) and were read 48 hours and 72 hours later in accordance with the European Society of Contact Dermatitis guidelines.¹⁰ Prick tests were performed on the forearm with a pure injectable form of each PS, using 0.9% saline and codeine phosphate 9% as negative and positive controls, respectively. Positive reactions were defined as a 3-mm or larger wheal at 20 minutes. In addition, the sites were examined at 6 hours, 24 hours, and 48 hours. Intradermal tests (IDTs) were performed by using a sterile solution of each PS, diluted sequentially (10^{-3} , 10^{-2} , 10^{-1}) in 0.9% saline. Dilutions were prepared under laminar flow within 2 hours before injection, and patients were monitored in the hospital for 24 hours. IDTs were performed on the back by injecting 0.04 mL sterile dilutions that produced a 4-mm to 6-mm wheal. Negative control was performed with saline sodium. For IDTs to be considered positive, a 2-fold increase in the diameter of the initial wheal after 20 minutes was required. The wheals were examined again at 6 hours, 24 hours, 48 hours, and 72 hours. When prick tests were strongly positive, IDTs were not performed.

After testing, chemotherapy was resumed with a different, negatively tested PS in surviving patients and according to the oncologist chemotherapy protocol's choice. Patients were informed of the potential hazards of this therapeutic option.

RESULTS

Twenty-one patients (11 females, 10 males; mean age, 62 years; range, 41-78 years) were enrolled. The causative PS was cisplatin in 2 cases, carboplatin in 8 cases, and oxaliplatin in 11 cases. The likelihood of the culprit identifying PS according to the French scoring system¹¹ was probable or very probable in all cases. The primary cancer type was digestive in 12 patients (9 colorectal, 3 pancreatic), gynecologic in 6 patients (5 ovary, 1 breast),

and pulmonary in 3 patients. All of them had distant metastases and were receiving combined cytotoxic treatment with a PS and fluorouracil (11 cases), paclitaxel (4 cases), docetaxel (2 cases), cyclophosphamide (2 cases), or gemcitabine (2 cases). A history of drug allergy was present in 2 patients only. Comedications were not tested.

Patients' characteristics, skin tests results, and resumption outcomes are shown in Table 1. Typical clinical features of immediate hypersensitivity associated with the initial treatment were observed in 18 of 21 patients (urticaria, hypotension, pruritus, palmo-plantar erythema, bronchospasm, angioedema, or anaphylactic shock in 2 cases). In the remaining 3 patients, symptoms were more suggestive of an idiosyncratic reaction. Two of them experienced chest pain, chills, hyperthermia, and hypotension without associated cutaneous signs, and 1 had eczematelike eruption with generalized pruritus.

The median number of courses administered until a reaction occurred was 9 (range, 1-22). In 14 cases, HR occurred within the first 2 hours after initiation of infusion. Among these, 2 cases of anaphylactic shock occurred within the first 5 minutes of infusion. In another 7 cases, HR occurred 3 hours or more after the end of infusion.

Skin tests with PS were positive in 14 of 21 cases. Prick tests were positive in 5 cases (carboplatin, 2 cases, and oxaliplatin, 3 cases; patients #2, 4, 5, 8, 14) in which HR had occurred within less than 2 hours. Anaphylactic shock had occurred in 2 of them (#4 and 14). In 1 case, the prick test was positive only at the delayed reading 24 hours later (patient #8).

Intradermal test were positive in 12 of 19 patients with the suspected PS (cisplatin in 1 case, carboplatin in 5 cases, and oxaliplatin in 6 cases). They were not performed in 2 patients because of a strongly positive prick test. IDTs were positive at dilution 10^{-3} in 2 of 12 cases, at dilution 10^{-2} in 4 of 12 cases, and at dilution 10^{-1} in 6 of 12 cases. In 8 cases, IDTs were positive for the suspected PS only. In 4 cases, tests were positive for 2 PSs (#1, 9, 12, 14), although 1 of the 2 had never been received by these patients. Most IDTs were positive on immediate readings at 20 minutes (9 cases), more rarely on delayed readings (3 cases, #8, 9, and 10). All patients with early symptoms (<2 hours) had at least 1 positive skin test (prick tests and/or IDT). In contrast, all patients who had experienced symptoms 3 hours or more after the end of infusion had negative skin tests. Patch tests were negative in all 21 patients tested.

Treatment with a different PS was performed in 13 patients. Eight of the 14 patients with a positive skin test received a negatively tested PS (cisplatin, 6 cases; carboplatin, 2 cases). No adverse drug reaction was observed, and cytotoxic treatment could be carried on for several courses (#1 = 4, #7 = 1, #8 = 6, #7 = 9, #8 = 3, #9 = 6, #10 = 1, #3 = unknown). PS therapy was also reintroduced in 5 of 7 patients with negative skin tests. A different PS was used in 3 cases (oncologist's choice), but the initially suspected PS was administered in 2 patients (#15 and 17). One of them (#15) experienced recurrence of a mild HR whose characteristics were similar to the first

TABLE I. Clinical features of reactions to PSs, results of skin tests, and readministration of PS

Patient no.	Age (y)	PS	Course at first occurrence of HR	Delay of onset/perfusion	Clinical features	Prick test	Patch test	IDT 0	IDT Ca	IDT Ci	PS readmin-istrated	Adverse effect
1	74	Ca	7	15 minutes after initiation	Urticaria	–	–	+1/10	+1/10	–	Ci	NR
2	72	O	15	45 minutes after initiation	Pruritus, urticaria	O+	–	NM	–	–	NM	
3	60	O	9	15 minutes after initiation	Dizziness, bronchospasm, palmar erythema, lingual edema	–	–	+1/10	–	–	Ci	NR
4	51	Ca	9	5 minutes after initiation	Anaphylactic shock	Ca+	–	–	NM	–	NM	
5	48	O	15	30 minutes after initiation	Urticaria	O+	–	+1/1000	–	–	NM	
6	57	Ci	7	30 minutes after initiation	Urticaria, nausea	–	–	–	–	+1/10	NM	
7	62	Ca	9	50 minutes after initiation	Urticaria	–	–	–	+1/10	–	Ci	NR
8	66	O	8	2 hours after initiation	Dizziness, chills, fever, urticaria, bronchospasm	O+ delayed	–	+1/100 at 24 hours	–	–	Ca	NR
9	55	O	22	30 minutes after initiation	Urticaria >48 hours, hypereosinophilia	–	–	+1/10 at 24 hours	+1/10 at 24 hours	–	Ci	NR
10	68	O	8	5 minutes after initiation	Urticaria, hypotension	–	–	+1/100 at 48 hours	–	–	Ca	NR
11	67	Ca	12	15 minutes after initiation	Angina, hypotension, angioedema, pruritus	–	–	–	+1/100	–	Ci	NR
12	60	O	12	15 minutes after initiation	Urticaria, vomiting, diarrhea	–	–	+1/100	+1/100	–	Ci	NR
13	72	Ca	14	30 minutes after initiation	Generalized eruption	–	–	–	+1/10	–	NM	
14	78	Ca	9	5 minutes after initiation	Anaphylactic shock	Ca+	–	–	+1/1000	+1/10	NM	
15	72	O	6	3 hours after the end	Dizziness, dyspnea, fever	–	–	–	–	–	O	Fever, dizziness, palmo-plantar erythema
16	67	Ca	10	>3 hours after the end	Urticaria	–	–	–	–	–	Ci	NR
17	41	O	3	24 hours after the end	Maculo-papular eruption	–	–	–	–	–	O	NR
18	55	Ca	2	72 hours after the end	Eczemalike eruption, pruritus	–	–	–	–	–	NM	

TABLE I. (Continued)

Patient no.	Age (y)	PS	Course at first occurrence of HR	Delay of onset/perfusion	Clinical features	Prick test	Patch test	IDT 0	IDT Ca	IDT Ci	PS readministered	Adverse effect
19	43	Ci	1	48 hours after the end	Urticaria	—	—	—	—	—	Ca	NR
20	73	O	5	3 hours after the end	Fever, pruritus	—	—	—	—	—	Ca	NR
21	67	O	23	3 hours after the end	Chills, fever, angina, tachycardia, hypertension then hypotension	—	—	—	—	—	NM	

Ca, Carboplatin; Ci, cisplatin; NM, not made; NR, no relapse; O, oxaliplatin.

reaction (same symptoms, delayed onset). Reintroduction of PS therapy was not made in 8 patients (death, different chemotherapy protocol for tumor escape). Thus, the outcome after reintroduction of a negatively tested PS allowed us to calculate a negative predictive value for skin tests of 0.92 (in 14 platinum salts tested negative, only 1 recurrence). In contrast, the positive predictive value could not be calculated, because the reintroduction of PS therapy in a patient with suspected cross-reactivity was deemed unethical.

DISCUSSION

The pathogeny of PS HR is not yet fully understood. The first reported reaction was described in refinery workers after prolonged exposure to inhaled platinum. Some of them became sensitized and experienced asthma, conjunctivitis, urticaria with positive skin prick tests, and platinum specific IgE. Khan et al¹² reported an HR to cisplatin where skin tests were positive for cisplatin, but also for other platinum complexes such as cis-diiododiammineplatinum, potassium chloroplatinate, and potassium chloroplatinite. Skin tests were negative when platinum was replaced with palladium, suggesting that platinum is essential for immediate induced HR. This could explain the cross-reactivity between platinum complexes. PS HR appears to be mediated by type I hypersensitivity reaction as well as by direct release of histamine from mast cells and basophils unrelated to IgE production. Unfortunately, no study has searched for platinum specific IgE in PS-treated patients, and there is not yet this type of test available in France. Other authors speculate that PSs could bind to major histocompatibility complex class 2 molecules and act as superantigens causing lymphocyte activation. Several predisposing factors are suspected. A past history of adverse drug reaction,¹³ geographic origin, HLA phenotype, or cigarette smoking¹⁴ could influence individual hypersensitivity to PS.

Hypersensitivity to PS occurs only after patients have undergone several courses of treatment. The median number of 9 courses before the first reaction that we found is similar to previous studies,¹⁻³ because long latency is a common feature in PS hypersensitivity.

Skin tests have already shown their predictive value in 2 previous studies by Zanotti et al² and Markman et al.¹⁵ They demonstrated that skin tests could be used prospectively to identify patients at risk for an allergic reaction to carboplatin before each chemotherapy course. Because 66% of our 21 patients had positive skin tests, our study confirms the value of prick tests and IDTs in investigating allergic reaction to PS as previously suggested by small studies.¹⁶⁻¹⁹ Finally, 2 groups appeared regarding to the onset of symptoms and skin tests positivity: in the first group (cases #1-14), all patients experiencing symptoms within 2 hours after initiation of infusion had positive prick tests and/or IDTs. In contrast, in the second group, all 7 patients (cases #15-21) experiencing symptoms 3 hours or longer after the end of infusion had negative skin tests. Thus, the earlier the reaction, the greater the value of predictive prick tests and IDTs. In 4 of these 7 negatively tested patients, the clinical features were more suggestive of an idiosyncratic reaction. Patch tests were negative in all cases, whether the reaction was early or delayed. Hence, in our opinion, they should not be performed. Skin tests seem safe because no serious induced systemic reaction has ever been reported. Positive IDTs observed with PS diluted at 10^{-3} support the hypothesis that IDTs should be performed at gradual dilutions beginning at 10^{-3} . We observed delayed reactions with prick tests (1 case) and IDTs (3 cases) in 3 patients with negative readings at 20 minutes. The physiopathology of such delayed positive skin tests remains unclear but confirms the need for delayed reading.

In our study, multiple positive tests suggesting cross-reactivity between 2 PSs were observed in 4 of 12 cases. No patient had positive skin tests with all 3 PSs. The incidence of cross-reactivity is not known but is thought

to be low. However, Zweizig et al²⁰ and Dizon et al²¹ reported 2 patients who died during retreatment with cisplatin after initial HR to carboplatin.

Eight of 14 patients with a positive skin test received further chemotherapy courses with a negatively tested PS. No relapse was observed. PS therapy was also re-introduced in 5 of 7 patients with negative skin tests. Only 1 false-negative test was observed in a patient who experienced relapse with delayed atypical symptoms, suggesting a non-IgE-dependent mechanism. These data suggest that negative results of prick tests and IDTs will identify suitable PSs for the continuation of therapy. Introduction of a different PS according to skin test results has only been done twice before. Porzio et al²² introduced cisplatin without adverse effect in 1 patient who experienced HR to carboplatin and had negative IDTs for cisplatin. Gottlieb et al²³ described the same protocol with no hypersensitivity reaction. Nevertheless, tumor chemosensitivity may limit PS replacement. The negative predictive value of our tests (0.92) is similar to those obtained by Zanotti et al² and Markman et al¹⁵ (0.99 and 0.985, respectively).

In conclusion, treatment strategies after a first PS HR episode should include a standardized protocol of skin testing. We propose that prick tests be routinely performed with pure injectable drugs and IDTs using sequentially diluted PS (from 10^{-3} to 10^{-1}). Patch tests have no value in these patients. Delayed readings of prick tests and IDTs are necessary. The frequency of cross-reactions among cisplatin, carboplatin, and oxaliplatin has not been clearly established, but they do exist and should not be overlooked. Cross-reactions can be detected by prick tests or IDTs, and because the negative predictive value is good, different PSs can be introduced with a low risk of relapse and may render interruption of treatment unnecessary. Moreover, they represent an alternative solution to desensitization protocols that have widely been used for the last 10 years, although without a real consensus.

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