Low Cross-Reactivity Between Cisplatin and Other Platinum Salts

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Abstract

Background: Hypersensitivity reactions to platinum salts (PS) (cisplatin (CI), carboplatin (CA) and oxaliplatin (OX)) can be severe and their incidence is increasing due to their widespread use in cancer treatment.

Objective: To determine the rate of cross-reactivity between platinum salts and whether CI can be administered without prior allergy testing in patients with a history of CA or OX hypersensitivity.

Methods: From September 2002 to April 2016, patients with suspected immediate PS hypersensitivity were tested and cross-reactivity between the three PS was evaluated. We then studied patients who were given cisplatin without desensitization after immediate hypersensitivity to other PS.

Results: A total of 155 patients were included. Skin tests were positive in 97 patients (OX: 51, CA: 43 and CI: 3). Cross-reactivity to CA in OX-allergic patients was 45% (23/51) (95%CI: 36% to 66%) and cross-reactivity to OX in CA-allergic patients was 37% (16/43) (95%CI: 23% to 53%). In contrast, cross-reactivity to CI was 0% (0/51) (95%CI: 0% to 7%) in OX-allergic patients and 7% (3/43) (95%CI: 2% to 17%) in CA-allergic patients. All these 3 patients had previously been exposed to CI in previous courses of chemotherapy. CI was initiated in 24 patients with proven hypersensitivity to CA or OX and had no hypersensitivity reactions.

Conclusion: Initiating CI in patients with proven immediate hypersensitivity to CA or OX appeared to be safe in our study.

Highlights Box: □

1. What is already known about this topic? The management of immediate hypersensitivity to platinum salts consists in carrying out skin testing and setting up a desensitization protocol. Moreover, cross-reactivity between the three platinum salts is a matter of debate.

2. What does this article add to our knowledge? This study demonstrates that cross-reactivity between carboplatin and oxaliplatin □is very frequent whereas cross-reactivity between cisplatin and the other platinum □salts is rare. The use of cisplatin after hypersensitivity to carboplatin or oxaliplatin appears □safe. □

3. How does this study impact current management guidelines? If desensitization can not be proposed and in the accordance with oncologist, cisplatin can be administered safely in patients with a history of carboplatin or oxaliplatin hypersensitivity provided it has never been used before.

Keywords: Allergy, Immediate hypersensitivity, Platinum salt, Cross-reaction, Skin testing, Chemotherapy, Intradermal test, Anaphylaxis.

Abbreviations

CA Carboplatin
CI Cisplatin
IDTs Intradermal Tests
LDH Lactate dehydrogenase
OX Oxaliplatin
PS Platinum salt

INTRODUCTION

Platinum salts (PS) (cisplatin (CI), carboplatin (CA) and oxaliplatin (OX)) are commonly used for the treatment of various cancers such as colorectal, pancreatic and ovarian cancer[1-7]. Immediate hypersensitivity reactions to PS are frequent and estimated at 15 to 20% in different studies, and can be severe[8-14]. Hypersensitivity reactions to PS are generally observed after a mean of eight infusions[13,15], although recent studies have shown that they can appear earlier [1,2,16]. Different studies have identified various potential risk factors linked to hypersensitivity: the interval between the end and the resumption of treatment if more than two years[17], total dose received [9,18], age[19], history of drug allergy[17], HLA DR3[20], and high serum lactate dehydrogenase (LDH) level at the beginning of chemotherapy[21].

For diagnosis, skin testing especially intradermal tests (IDTs) are commonly used [22-24]. Many authors [1,22,25] demonstrated that IDTs are reliable and have a good negative predictive value.

Currently, the incidence of cross-reactivity between the three PS is unclear, although some studies in a small number of cases have shown that switching to CI in patients with CA or OX hypersensitivity was safe in a majority of patients[26-28].

When an allergic reaction occurs during an infusion of PS, treatment is immediately stopped and all three PS are contraindicated until consultation with a specialist and skin allergy testing. Desensitization is considered safe and supported by many publications.

If desensitization is not an option, could cisplatin be safely used in patients reactive to oxaliplatin or carboplatin in accordance with oncologist?

The aim of this study was to determine the rate of cross-reactivity in patients receiving PS in a teaching hospital in France and whether CI can be administered without prior allergy testing in patients with a history of CA or OX hypersensitivity.

METHODS

We conducted a retrospective, descriptive, single-center study from September 2002 to April 2016 at the Dermatology Department of Dijon University Hospital, France. Patients coming for a dermato-allergology consultation for immediate hypersensitivity reactions to PS were included. An immediate reaction to PS was defined as a reaction that occurs during the infusion or within 1 hour after the infusion of one of the three PS (CA, OX or CI). Skin tests were performed after a minimum of 4-6 weeks after resolution of the hypersensitivity reaction. Indeed, false negative skin testing is possible if it is too early after the hypersensitivity reaction probably due to a period of "anergy" after a systemic reaction.[25,29]

Intradermal tests (IDTs) were performed by using a sterile solution of each PS (active product and excipients): Cisplatine Accord® (cisplatin, injectable form, 100mg/100ml; Accord Healthcare France), Carboplatine Hospira® (carboplatin, injectable form, 450mg/45ml; Hospira, France) and Oxaliplatine Hospira® (oxaliplatin, injectable form, 100mg/20ml; Hospira, France) diluted in 0.9% saline successively according to the following sequence (1/1000, 1/100 and 1/10). Dilutions were prepared following a standardized procedure at the Dijon University Hospital Pharmacy Department under laminar flow 2 hours before injection. IDTs were performed on the patients' upper back by injecting 0.02 mL of sterile dilutions, which produced a 4 mm to 6 mm wheal. IDTs were considered positive if the diameter of the wheal measured 3 mm more than the diameter of the initial one after 20 minutes.

All concomitant treatments and/or premedications (corticosteroids, antiemetic agents, other chemotherapy agents) were also tested if suspected, according to the European Society of Contact Dermatitis guidelines for drug skin testing[30].

After the dermatology consultation and IDTs, the oncologist was consulted to choose the most appropriate PS that was negative during the test to be used for the patient. The drug was then initiated at the therapeutic dose and regimen, without desensitization. Any hypersensitivity reactions were assessed.

In addition, clinical data were collected: age of the patient, sex, cancer type, number of courses administered until a reaction occurred and symptoms of the hypersensitivity reaction. Symptoms were graded according to Brown's classification[31].

RESULTS

Patients

During the 14-year study period, 184 patients had investigations for hypersensitivity reactions to PS. Among these patients, 29 were not analysed because they had a delayed rather than immediate reaction. Finally, 155 remaining patients with immediate hypersensitivity were included (see figure 1). Patients' clinical data are summarized in Table I.

Treatments and hypersensitivity reactions

The suspected PS was CA in 64 cases, OX in 87 cases and CI in 4 cases. The median number of courses administered until the reaction occurred was nine (range: 1-37). Eleven patients had already received another treatment with a different PS in the past (CA: 5, OX: 2 and CI: 4). Clinical signs of immediate hypersensitivity to the PS were grade 1 (mild) in 30% (47/155), grade 2 (moderate) in 62% (96/155) and grade 3 (severe) in 8% (12/155) according to Brown's classification[31]. The most common symptoms were cutaneous manifestations in 107 patients (107/155: 69.0%). These cutaneous signs were urticaria, pruritus, erythema and angioedema. Other manifestations are detailed in Table II. There were six cases of anaphylactic shock, which occurred during the drug infusion.

Skin tests

Skin tests were positive to the suspected PS in 97 of the 155 patients (62.6%) (CI: 3 cases, CA: 43 cases, OX: 51 cases). Tests were thus negative for 58 patients (58/155: 37.4%) and two hypersensitivities to concomitant treatment were seen: one positive test for epirubicin (Farmorubicine®, Pfizer) anthracycline chemotherapy and another for raniditine (Azantac®, GlaxoSmithKline) an antagonist of histamine receptor type 2 (Figure 1). No incidents occurred during the test procedures.

Among patients with positive skin tests, 41 patients were positive to more than one PS. Thirty-eight patients had positive IDTs to CA and OX, two patients had positive IDTs to CA and CI and only one had positive IDTs to all three PS. Cross-reactivity to CA in OX-allergic patients was 45% (23/51) (95%CI: 36% to 66%) and cross-reactivity to OX in CA-allergic patients was 37% (16/43) (95%CI: 23% to 53%). In contrast, cross-reactivity to CI was 0% (0/51) (95%CI: 0% to 7%) in OX-allergic patients and 7% (3/43) (95%CI: 2% to 17%) in CA-allergic patients but those 3 patients had been previously exposed. In

the 38 cases of cross-reactivity between CA and OX, only two patients had received the two PS successively. The results about the different positive skin tests are resumed in Table III.

Drug re-exposure

After skin testing, the oncologists decided to reinfuse PS in 58 patients (30 patients with positive tests and 28 patients with negative tests). The choice of PS was made by the oncologists and the PS was reinfused without any particular precautions and at the recommended dose.

Among the 28 with negative tests: 16 patients were re-exposed to the same PS (CA: 6 and OX: 10), and 12 patients to another PS (CA: 1, OX: 2 and CI: 9). No hypersensitivity reactions were notified.

Among the 97 patients to which skin tests were positive, 30 patients were re-exposed with another PS: 24 with CI, two with CA and four with OX; and one patient was desensitized with OX. There were no reactions during the administration (Table IV).

Al together, 33 patients were given cisplatin. These patients were given between one and 24 cycles of cisplatin (mean 9 cycles). No patients experienced hypersensitivity reactions. The treatment was stopped for three reasons: renal failure, deterioration of the patient's general health status, or lack of efficacy.

DISCUSSION

Hypersensitivity to PS was first described by Hunter et al. in 1945 among employees working in a refinery[32]. Since then, the incidence of hypersensitivity has risen due to the widespread use of PS in many cancers treatments. Skin testing has proven to be helpful in the diagnosis of IgE-mediated hypersensitivity to a platinum salt. [22,25,29]

We present here, a study with a large number of patients tested after immediate hypersensitivity to PS. Our study included 155 patients with the same baseline epidemiological profile as other published studies on hypersensitivity to PS[10,26,33,34].

To date, the incidence of cross-reactivity between the three most widely used PS is not well-established. Some rare previous studies have demonstrated cross-reactivity between PS based on skin tests [35,36]. In a majority of studies about hypersensitivity to PS, skin tests have been performed just with the suspected PS, and cross-reactivity has been not investigated [1]. Brault et al. have found only one case of cross-reactivity between CA and OX in 14 patients with positive IDTs to PS[37]. All IDTs to CI were negative. In our study, we showed for the first time that cross-reactivity between CA and OX was very frequent: cross-reactivity to CA was 45% in OX-allergic patients and cross-reactivity to OX was 37% in CA-allergic patients with only two patients who had received both PS in the past. This finding therefore probably reflects a true cross-reactivity. In contrast, cross-reactivity between CI and OX or CA was rare: 0% in OX-allergic patients and 7% in CA-allergic patients. In our study, there were no cases of cross-reactivity between CI and other PS when CI had never been used in previous courses of chemotherapy. To our knowledge, this observation has never been described in the literature.

The different chemical structures of the PS could explain this phenomenon (Figure 2). The three molecules are different and have various pharmacological properties: CI is a diaminodichloroplatin, CA is cyclobutane-dicarboxyloplatin, and OX is a diaminohexane-platin derivative. The first hypothesis suggested by Caiado et al. [38] was that the central platinum atom was an epitope. They supported ~~her~~ their theory by showing the presence of platinum specific IgE. Our testing results, however, did not confirm this hypothesis. Indeed, the active metabolites do not seem to be involved in cross-reactivity because CI and CA are transformed into the same diaquaplatin after hydrolysis and these two PS were less involved in cross-reactivity in our study. We therefore propose a new hypothesis,

namely that the nitrogen-platinum-oxygen-carbon-oxygen-carbon chain (N-Pt-O-CO-C), which is present only in CA and OX and not in CI, could be the common epitope explaining cross-reactivity.

Moreover, our study showed that there were no hypersensitivity reactions when CI was initiated in patients with hypersensitivity to CA and OX, when CI had never been used before. In the same way, several studies have shown that re-exposure with CI after OX or CA hypersensitivity is safe [3,8,28,36,39-46]. To date, only Zweizig et al. [47], Shelbak et al. [48] and Dizon et al. [26] have reported hypersensitivity reactions following a switch to CI. There were four cases of patients who received CI after a hypersensitivity reaction to CA and subsequently developed a severe reaction to CI. Analysis of these four cases showed that all of these patients had received CI several years previously for the first treatment of the cancers. Callahan et al. [27] and Bergamini et al. [45] also reported eleven cases of hypersensitivity to CI at re-exposure after a hypersensitivity reaction to CA. In ten cases, the reaction developed after a median of 3 courses of CI. In our opinion, these cases cannot be regarded as a failure of the re-exposure, but as a new hypersensitivity to CI. In our study, no patient re-exposed to CI experienced hypersensitivity reaction. In two cases of the Callahan et al.[27] and the Ottaiano et al. [49] studies, patients experienced a reaction to CI during the first infusion of the re-exposure. Unfortunately, we do not have enough information to analyze these hypersensitivity reactions as we do not know if the patient had previously been treated with CI.

In 2015, Kolomeyevskaya et al. [39] proposed the reintroduction of OX in patients with an allergy to CA, without a skin test. Our results go against this strategy because our tests showed a high frequency of cross-reactivity between CA and OX.

The results of all these different studies are summarized in Table V.

When patients experience a hypersensitivity reaction during PS infusion, treatment should be stopped immediately. The collaboration between allergist and oncologist is essential. After patient's risk stratification, as proposed by Giavina-Bianchi et al. [50] based on the severity of the initial reaction, the patient's comorbidities and the drug given to the patients, several possibilities can be proposed to the oncologist. If the oncologist wants to continue the same PS, skin testing should be done as soon as possible. If these tests are positive, desensitization is the best option. Indeed several studies have reported that desensitization is a safe and effective method. [29,25,37,50] However, this approach needs to be used repeatedly before each infusion. If the oncologist wants to change for any reason, the best approach is skin testing with the three PS: OX, CA and CI. If the oncologist chooses

CI, the risk of immediate hypersensitivity reaction seems very low as shown in this study. In our experience, this option can be useful in gynecologic cancer but less so in digestive cancer as the three PS are not equivalent in terms of efficacy and tolerance. If skin testing is negative, a drug provocation test or regular infusion can be proposed based on the risk stratification[50]. As the administration of chemotherapy is far from risk-free, the benefit-risk ratio must always be evaluated. Moreover, patients should be advised about the risk and closely monitored by experienced medical staff.

Figure legends

Figure 1. Flowchart of the study. 155 patients had immediate hypersensitivity to PS and were included in the retrospective study.

Figure 2. Chemical structure of cisplatin (a), carboplatin (b) and oxaliplatin (c) molecules are presented in this figure. The N-Pt-O-CO-C chain present in both carboplatin and oxaliplatin is highlighted in the blue diagram.

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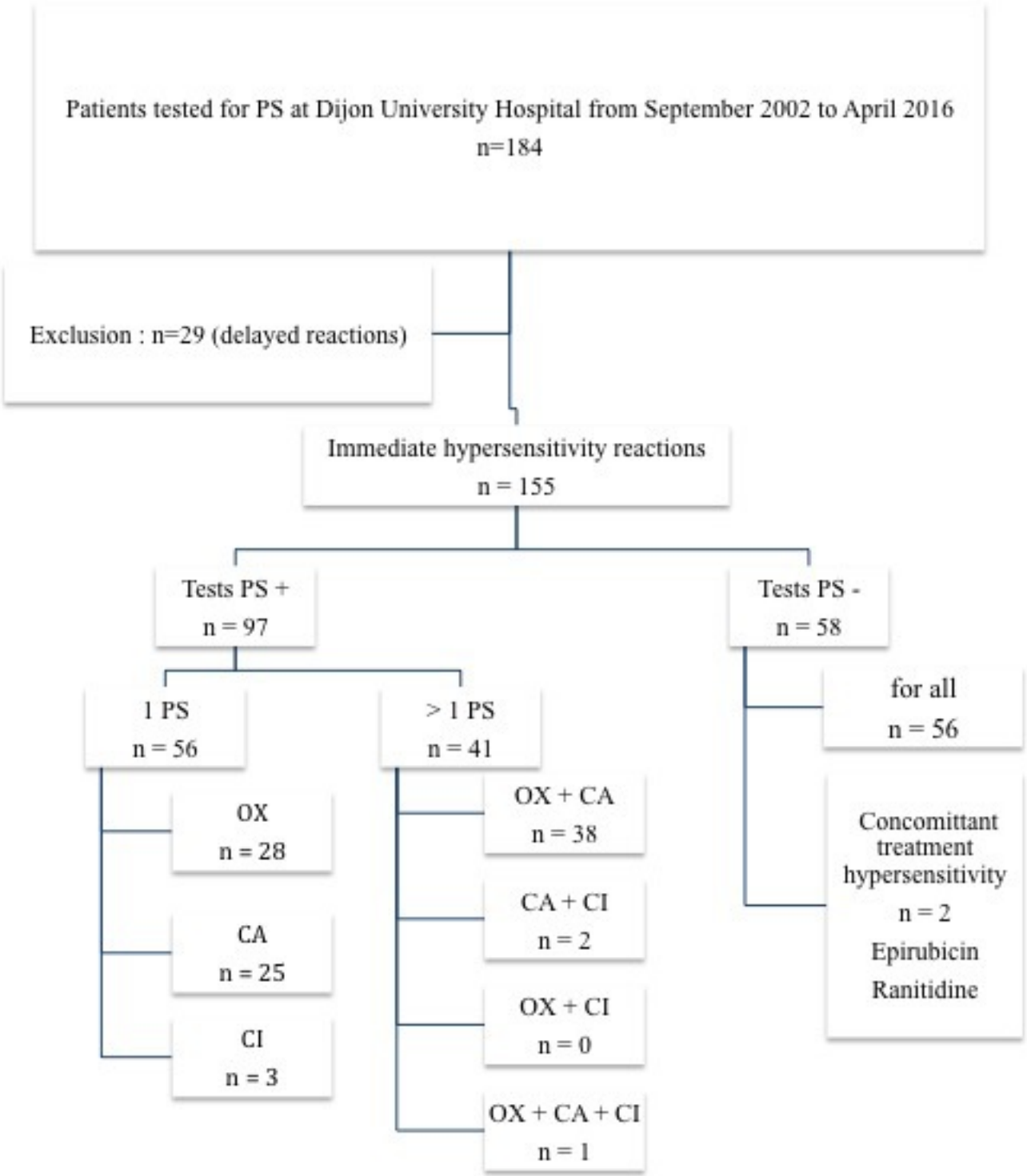
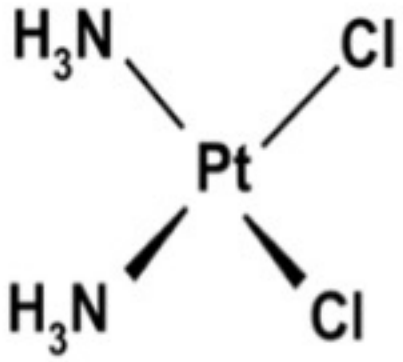
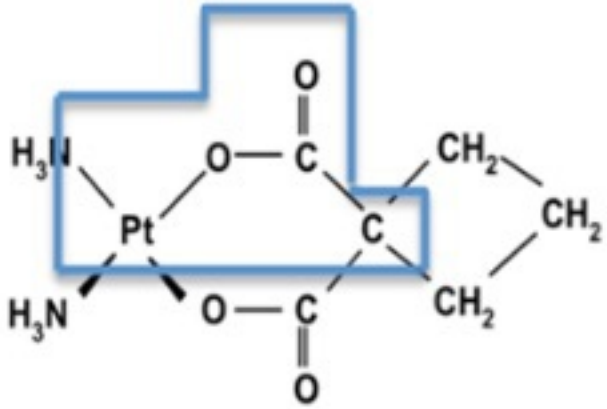
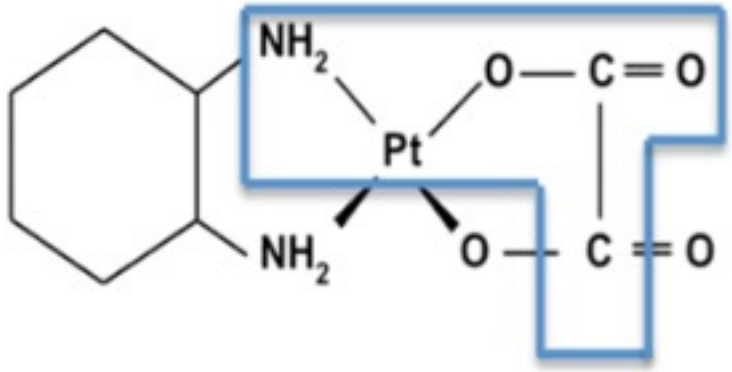

Patients tested for PS at Dijon University Hospital from September 2002 to April 2016
n=184
Exclusion : n=29 (delayed reactions)
Immediate hypersensitivity reactions
n = 155
Tests PS +
n = 97
Tests PS -
n = 58
1 PS
n = 56
> 1 PS
n = 41
for all
n = 56
OX
n = 28
CA
n = 25
CI
n = 3
OX + CA
n = 38
CA + CI
n = 2
OX + CI
n = 0
OX + CA + CI
n = 1
Concomittant treatment hypersensitivity
n = 2
Epirubicin
Ranitidine



a. cisplatin



b. carboplatin



c. oxaliplatin

N-Pt-O-CO-C chain

Table I. Baseline demographic characteristics of patients (n = 155)

Age, years	
Range	27-82
Mean	60.8
Median	60
Gender, no (%)	
Female	103 (66.4)
Male	52 (33.6)
Sex ratio	1.9
Tumor type, no (%)	
Colorectal	55 (35.5)
Ovarian	52 (33.6)
Pancreatic	14 (9)
Cholangiocarcinoma	6 (3.8)
Gastric	6 (3.8)
Pulmonary	6 (3.8)
Breast	4 (2.6)
Endometrial	4 (2.6)
Esophageal	3 (1.8)
Cervix	1 (0.7)
Fallopian tube	1 (0.7)
Peritoneal	1 (0.7)
Pharynx	1 (0.7)
Prostate	1 (0.7)

Table II. Clinical signs experimented during hypersensitivity reaction with platinum salts in the 155 patients.

Clinical signs	**Patients, no (%)**
Cutaneous (erythema, pruritus, urticaria, angioedema)	107 (69)
Cardiovascular (chest tightness, Tachycardia, blood pressure alterations)	47 (30)
Pulmonary (dyspnea, bronchospasm, desaturation)	18 (12)
Gastro-intestinal (nausea, vomiting, diarrhea)	13 (8)
Neurological (paresthesia, malaise, vertigo)	45 (29)

Table III. Results of positive IDTs: risk of cross-reactivity between the platinum salts (n=97)

Suspected PS with positive IDTs	IDTs results	Patients, no. (%)
Oxaliplatin n=51	OX alone	28 (55)
	OX + CA	23 (45)
	OX + CI	0 (0)
	OX + CA + CI	0 (0)
Carboplatin n=43	CA	25 (58)
	CA + OX	15 (35)
	CA + CI	2 (5)
	CA + CI +OX	1 (2)
Cisplatin n=3	CI alone	3 (100)
	CI + CA	0 (0)
	CI + OX	0 (0)
	CI + OX +CA	0 (0)

IDTs, Intradermal tests
OX, Oxaliplatin
CA, Carboplatin
CI, Cisplatin

Table IV. Re-administration of PS in patients with POSITIVE allergy testing (n=30)

Suspected PS		Results of skin tests	PS administered		Hypersensitivity reaction
Cisplatin	n = 1	CI +	Carboplatin	n = 1	NO
Carboplatin	n = 9	CA +	Cisplatin	n = 6	NO
			Oxaliplatin	n = 3	NO
	n = 8	CA +, OX +	Cisplatin	n = 8	NO
Oxaliplatin	n = 7	OX +	Cisplatin	n = 6	NO
			Carboplatin	n = 1	NO
	n = 5	OX +, CA +	Cisplatin	n = 4	NO
			Oxaliplatin (desensitization)	n = 1	

PS, platinum salts; CA, carboplatin; OX, oxaliplatin; CI, cisplatin; + means positive skin test

Table V. Cisplatin rechallenge studies.

Study		Type of cancer	n	PS suspected	Successful, no (%)	Allergy, no (%)	Skin testing
Our study	2016	all types	33	Carboplatin Oxaliplatin	33 (100)	0	Yes
Bergamini et al.	2016	gynecological	38	Carboplatin	33 (86.8)	5 (13.2)	No
Kolomeyevskaya et al.	2015	gynecological	19	Carboplatin	19 (100)	0	No
Syrigou et al.	2010	ovarian, pulmonary	3	Carboplatin	3 (100)	0	Yes
Greene et al.	2009	gynecological	1	Carboplatin	1 (100)	0	No
Enrique et al.	2008	ovarian	2	Carboplatin	2 (100)	0	Yes
Elligers et al.	2008	pancreatic	1	Oxaliplatin	1 (100)	0	Yes
Callahan et al.	2007	gynecological	24	Carboplatin	18 (75)	6 (25)	No
Kandel et al.	2005	gynecological	5	Carboplatin	5 (100)	0	No
Libra et al.	2003	ovarian	3	Carboplatin	3 (100)	0	NA
Ottaiano et al.	2003	ovarian	10	Carboplatin	9 (90)	1 (10)	NA
Dizon et al.	2002	ovarian	7	Carboplatin	5 (71.4)	1 (14.3)	No
Porzio et al.	2002	ovarian	1	Carboplatin	1 (100)	0	Yes
Polygos et al.	2001	ovarian	4	Carboplatin	4 (100)	0	No
Shukunami et al.	1999	ovarian	1	Carboplatin	1 (100)	0	NA
Shelbak et al.	1995	ovarian	1	Carboplatin	0	1 (100)	No
Weidmann et al.	1994	ovarian, pancreatic	2	Carboplatin	2 (100)	0	No
Zweizig et al.	1994	ovarian	1	Carboplatin	0	0	No

NA, Not available; PS, Platinum Salt