ORIGINAL ARTICLE

Allergy evaluation in hypersensitivity to platinum compounds and taxanes: a 5-year experience

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Summary

Background. Platinum compounds (PC) and taxanes (TX) are drugs frequently administered for the treatment of several cancers. In recent years, their increased use has been accompanied by a relatively high prevalence of hypersensitivity reactions (HSRs). In this study, we report our comprehensive experience of allergy skin test (ST) evaluation in 276 patients who experienced HSRs to PC and/or TX. Primary objectives were to determine the clinical characteristics of HSRs, and to assess the role of STs in the diagnosis and prevention of HSRs in order to address the subsequent treatments. Secondary objective was to evaluate any cross-reactivity between PC (cisplatin, oxaliplatin and carboplatin) and among TX (paclitaxel and docetaxel). **Methods.** A monocentric, retrospective, observational, cohort study including patients who experienced one or more HSR during PC and/or TX chemotherapy was conducted from May 2018 to July 2023 in the Allergy and Clinical Immunology Unit at the "Fondazione Policlinico Universitario A. Gemelli" IRCCS, Rome. **Results.** A total of 114 patients with positive ST were identified: 102 for PC, 11 for TX and one for both. 162 patients were tested negative. Patients with HSR to PC were found to be allergic in 64%, compared to 9,9% of patients with HSR to TX ($p < 0.0001$). Patients who experience more serious reactions have a higher chance to have a positive result on STs ($p < .01$). **Conclusions.** STs to investigate sensitization to TX or PC is a highly valuable diagnostic tool in selecting the appropriate therapy when a hypersensitivity reaction occurs.

Key words:

Hypersensitivity; platinum compounds; taxanes; skintest; cross-reactivity.

Impact statement

In this paper, we report our comprehensive experience of allergological evaluation by skin tests in 276 patients who experienced a hypersensitivity reaction to platinum compounds and/or taxanes.

INTRODUCTION

Platinum compounds (PC) and taxanes (TX) are drugs frequently administered for the treatment of several cancers. In recent years, their increased use has been accompanied by a relatively high prevalence of hypersensitivity reactions (HSRs). When such an event occurs, the clinician is faced with the dilemma of choosing whether to continue the treatment, exposing the patient to the risk of further reactions, or whether to interrupt it and replace it with alternative drugs. Three PC are most frequently used in oncological patients: carboplatin, cisplatin and oxaliplatin. They can cause heterogeneous reactions (from mild skin reactions to severe cardiovascular anaphylaxis) and are usually observed after multiple administrations. Pathogenesis can result from type I (IgE- and non IgE-mediated mechanisms), cytokine release and mixed reactions. The incidence of PC-HSRs ranges from 12% to 17%: carboplatin is the main culprit with an incidence up to 46% in patients who received seven administrations, while oxaliplatin can induce HSRs in about 10-19%, and cisplatin in about 5-20% (1,2).

TX are antineoplastic agents used for the treatment of several cancers; they include paclitaxel, docetaxel, nab-paclitaxel, and cabazitaxel. In most patients, cutaneous signs (most commonly flushing) and back pain occur. Cardiovascular, respiratory and gastrointestinal symptoms may also happen. Pathogenesis of these reactions can result from type I IgE-mediated mechanism, direct activation of basophils, and IgG-mediated complement activation. Solvents for TX, Cremophor EL for paclitaxel and polysorbate 80 for docetaxel, can activate mast-cells by an IgE-mediated mechanism or through direct complement activation. The

reported incidence of immediate TX-HSRs is between 10% to 70%, typically at the first or second exposure (3,4,5).

Skin prick tests (SPT) and intradermal tests (IDT) are the main diagnostic tools for the identification of PC- and TX-HSRs. Skin tests (STs) concentrations and procedures are standardized and defined in accordance with the ENDA/EAACI recommendations (6).

According to guidelines (7,8), allergy testing should be performed between 6 weeks and 6 months following the reaction. STs reported sensitivity is 66% for cisplatin and 100% for carboplatin and oxaliplatin, with a negative predictive value of 92% for PC and 100% for TX (2). Several cases of cross-reactivity between molecules of the same family were also highlighted, especially to cisplatin and oxaliplatin in patients who reacted to carboplatin, while less cross-reactivity has been highlighted between cisplatin and other PC (9,10).

Regarding the diagnostic role of patch testing, it is not recommended; the study of delayed reactions can be carried out through delayed reading (24 hours, 48, up to 7 days) of intradermal reactions (11).

In this study, we report our comprehensive experience of allergy STs evaluation in 276 patients who experienced HSRs to PC and/or TX.

MATERIALS AND METHODS

Study design and objectives

A monocentric, retrospective, observational, cohort study including patients who experienced one or more HSR during PC and/or TX chemotherapy was conducted from May 2018 to July 2023 and was approved by the local ethical committee ("Comitato Etico Territoriale Lazio Area 3 - approval number: 3883). STs were conducted in the Allergy and Clinical Immunology Unit at the "Fondazione Policlinico Universitario A. Gemelli" IRCCS, Rome.

Primary objectives were:

a) to determine the clinical characteristics of HSRs, and

b) to assess the role of STs in the diagnosis and prevention of HSRs in order to address the subsequent treatments.

Secondary objective was to evaluate any cross-reactivity between PC (cisplatin, oxaliplatin and carboplatin) and among TX (paclitaxel and docetaxel).

Materials and allergy evaluation

The patients were identified based on clinical symptoms that were compatible with immediate HSRs according to the criteria set by the ENDA/EAACI Interest Group on Drug Hypersensitivity (6). Clinical data were collected, and the HSRs were reviewed and classified by an Allergy specialist according to Brown's classification (12).

Inclusion criteria were: age ≥ 18 years and a clinical history of immediate HSR after the administration of PC (carboplatin, oxaliplatin or cisplatin) or TX (paclitaxel or docetaxel).

Exclusion criteria were instead a clinical history of delayed HSR and a diagnosis of previous Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

An allergist gathered a detailed history of the patients' HSR and STs were performed at least 3 weeks after the reaction. Histamine and saline solution were used as positive and negative controls, respectively. Both procedures were performed on the volar surface of the forearm. Firstly, SPTs were performed and, if negative, IDTs were carried out till the maximum non-irritant concentration (see table I). STs were read according to EAACI guidelines.

Sample size

For calculation of the sample size, we considered: 1) a population of 276 patients with a HSR to PS and/or TX, 2) a margin error of 10% and 3) a chosen sampling confidence level of 90%.

Statistical analysis

The sample was described in its clinical and demographic characteristics through descriptive statistics techniques. The qualitative variables are represented by tables of absolute frequencies and percentages. Qualitative variables have been summarized with mean and standard deviations. The normality of data has

been verified with the Kolmogorov-Smirnov test and the proportions were compared applying the Chi-square test. A P value of less than 0.05 was considered statistically significant. All the statistical analyses have been performed with Statistical Package for the Social Sciences (SPSS) statistical software (Released 2017, IBM SPSS Statistics for Windows, Version 25.0; IBM Corp., Armonk, NY).

RESULTS

Patient characteristics

Over 5 years, 276 female patients with a clinical history of at least one HSR to PC and/or TX were enrolled. 155 patients presented a reaction with PC, 115 with TX, 6 patients with both drugs. Patients' ages ranged from 27 to 87 years (mean, 59 years). The most common malignancies were ovarian (69,6%), endometrial (10,5%) and cervical (9%), follow by mammal and rectum. 105 patients were treated for primary cancers, 166 were treated for recurrent cancers, and for 5 patients no data were available. The most common agent responsible for hypersensitivity was carboplatin in 146 (51,8%) patients, followed by paclitaxel in 121 (42,9%), cisplatin 11 (3,9%), and oxaliplatin 4 (1,4%).

HSRs characteristics

224 patients had only one reaction (81.1%), 43 patients had two (15.6%), 8 patients had three (2.9%) and only one patient had four.

A mild reaction was experienced by 32.6% of patients, 43.8% of patients presented a moderate reaction and the 23.6% experienced a severe reaction.

The most common symptoms were cutaneous, respiratory, gastrointestinal, neurological, and cardiovascular.

Platinum compounds HSRs

A total of 161 patients had reactions with at least one platinum compound: 146 with carboplatin, 11 with cisplatin and 4 with oxaliplatin.

The HSRs to PC were recorded mainly during the II-III cycle of therapy, but it is important to underline that most of the reactions occurred during the second therapeutic line, therefore identifying the eighth or

ninth administration of the drug. The main symptoms were cutaneous (erythema) and respiratory (dyspnoea). Of all the reactions, 29.8% were mild, 42.3% moderate and 27.9% were severe.

Taxanes HSRs

All 121 patients reacted after the exposure to paclitaxel, and the majority (92.5%) reacted on the first or second exposure despite the use of premedication. 80% of the patients were at their first therapy line. The main symptoms were cutaneous (erythema), respiratory (dyspnoea) and neuromuscular (back pain). Of all the reactions, 36.4% were mild, 45.5% moderate and 18.1% were severe.

Taxanes and platinum compounds HSRs

Six patients had reactions with both types of chemotherapy. In all these patients carboplatin and paclitaxel were involved, and the reactions occurred during separate infusion sessions.

Skin test results

All patients with HSRs to PC and TX underwent ST (SPT and IDT) with the culprit drug and with cross-reacting drugs. The time interval between the reaction and the allergological evaluation was conducted between 3 weeks following the reaction (in 94 patients) up to over a year (38 patients), as summarized in Table II.

A total of 114 patients with positive ST were identified: 102 for PC, 11 for TX and one for both. 162 patients were tested negative. Patients with HSR to PC were found to be allergic in 64%, compared to 9,9% of patients with HSR to TX ($p < 0.0001$) (see Table III).

Skin test to platinum agents

Skin reactions were positive for at least one platinum salt in 103/161 patients (64%) while 58/161 patients (36%) had negative skin tests. 76 patients tested positive for only 1 agent, 22 patients tested positive for 2 platinum agents, while 5 patients tested positive for all 3 molecules.

In total, 22 patients had positive ST for cisplatin, 100 for carboplatin and 13 for oxaliplatin. Of the 22 cisplatin-positive patients, only 6 had a history of HSR with this drug: of the remaining, 15 had reacted to carboplatin and 1 to oxaliplatin. Of the 100 patients who presented a positive allergy test for carboplatin, this was implicated in 99 reactions, while in only one patient the culprit drug was oxaliplatin. 13 patients

had positive skin tests for oxaliplatin, but only in 2 occasions this drug was responsible for the HSR. Over 48 patients with grade 1 reaction, 23 had positive ST (47,9%), while over the 68 patients with moderate (grade 2) reaction we found 44 positivity (64,7%), and among 45 patients with grade 3 reactions, 37 were positive (82,2%), meaning that patients with more severe reactions have a higher possibility of being positive compared to patients with minor reactions ($p < .01$) (see table IV).

Skin test to taxanes

STs were positive for at least one taxane agent in 12 patients over 121 (9,9%), while were negative in 109 patients. All patients reacted to paclitaxel and all of them presented a positive ST to this agent. In 9/12 patients (75%), the allergological exam tested positive also for docetaxel. Over 44 patients with grade 1 reaction, only 1 had positive ST (2,3%), while over the 55 patients with moderate (grade 2) reaction we found 2 positivity (3,6%). Indeed among 22 patients with severe HSRs, ST were positive in 9 (40,9%), meaning that patients who experience more serious reactions have a higher chance to have a positive result on skin test (p value < .01) (see table V).

DISCUSSION AND CONCLUSIONS

HSRs to PC occurred mainly in patients already chemo-treated (91% of patients) during the II-III cycle of therapy, which in the re-treated patients corresponds to the VIII-IX cycle. These data are in agreement with studies in the literature which highlight how the risk of developing an adverse reaction to PC increases with the progressive number of exposures; in detail, for cisplatin and carboplatin a significant increase in the risk of reaction is described after a median of 8 cycles, particularly during re-treatment for relapse, with a risk of HSR up to 100% at the third treatment (1). Furthermore, in accordance with literature data (13), reactions of moderate severity (grade 2 according to Brown's classification) mainly occurred (approximately 42,2%) and the most common manifestations were skin symptoms and dyspnoea. Although the severity of the reaction is statistically correlated with the ST result, 47.9% of patients who had a grade I reaction to a PC were found to be allergic; this high percentage indicates that an allergological evaluation would also be indicated in these patients in order to avoid more severe reactions in subsequent infusions.

HSRs to TX occurred in almost all cases (92.5%) during administration of the first infusions (I-II) with moderate severity (45.5% grade 2 reactions); this timing of onset can be explained by the fact that the underlying pathogenetic mechanism is rarely immune-mediated, but often induced by complement activation or direct degranulation of mast cells and/or basophils.

In contrast, the high number of ST positivity in the PC-treated patients is indicative of a frequent underlying IgE-mediated mechanism; in fact, of 161 patients with HSRs to PC, 103 tested positive (64%), while of the 121 patients with HSRs to TX, only 12 (9.9%) tested positive (p value < .0001). This result is comparable to those reported in the literature, in which a greater frequency of IgE-mediated reactions due to PC is found (14).

STs were performed within an average of five weeks from the time of the adverse reaction. Moreover, we found that 71 patients who tested positive underwent the allergological work-up before the 6 weeks defined by the guidelines and 40/71 already presented positive tests 3 weeks after the reaction. This could certainly accelerate the resumption of chemotherapy, but could also lead to false negative tests (8). Therefore these patients, after receiving a new infusion of the same drug via a desensitization protocol, could be retested; in fact, some patients tend to become positive after re-exposure to the drug (15). Patients who remain negative may undergo a challenge, if they are low grade in the risk stratification estimated by the allergist. This procedure could also be used in patients who are tested 6 months after the reaction, as it has now been demonstrated that skin tests tend to become negative over time with a significant decrease in sensitivity (16).

There is no unanimous consensus in the literature on the concentrations to be used for skin tests; in our Centre, we use the same concentrations as those proposed by Alvarez-Cuesta E et al (17). Pradelli et al. found an excellent negative predictive value of ST (92% for PC and 100% for TX) using, for PC, the same concentrations as ours (for both SPT and IDT) while, for TX, a more concentrated dilution for IDT (the same as the highest concentration used for SPT) (2).

Pagani et al. suggested instead a more diluted maximum concentration for IDT with carboplatin, more concentrated for SPT with cisplatin, the same concentration for oxaliplatin, more diluted for IDT with

paclitaxel and more diluted for both IDT and SPT with docetaxel (14). We could not follow those concentrations because our study started before its publication, however our concentrations did not deviate too much from those utilized in the literature and, in our experience, minimize the risk of false positives and false negatives.

In this work, possible cross-reactivity between drugs belonging to the same family was also evaluated: a cross-reactivity between all three platinum compounds was highlighted, since a positive allergy test was recorded for oxaliplatin in 10 patients and for cisplatin in 15 patients with IgE-mediated allergy to carboplatin and negative history for the other two molecules. Furthermore, in a patient with a positive history of reaction to oxaliplatin, the skin reactions were also positive for cisplatin. 5 patients tested positive for all 3 molecules, 4 of them had experienced an HSR to carboplatin and one to oxaliplatin. As regards taxanes, the cross reactivity recorded was 75% as out of 12 patients with IgE- mediated hypersensitivity to paclitaxel, 9 had positive skin tests also for docetaxel in the absence of adverse reactions to this molecule (see table VI).

Finally, when an IgE-mediated reaction occurs, a rapid drug desensitization (RDD) protocol is indicated to allow patients who have no other treatment option to continue their therapy. Numerous cases of patients successfully treated with a 12-RDD protocol are described in the literature, but this is beyond the scope of this article and certainly deserves to be analyzed in future works (18).

HSRs to chemotherapy are an increasingly widespread problem that requires correct management. STs to investigate sensitization to TX or PC in patients undergoing these therapies is a highly valuable diagnostic tool in selecting the appropriate therapy when a hypersensitivity reaction occurs, particularly for PC. With regard to TX, however, since STs were positive in only 9.9% of patients who experienced an HSR, it would be more appropriate to assess the severity of the reaction presented, despite the negativity of the STs, before selecting the subsequent therapy.

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AUTHOR CONTRIBUTIONS

DL: Data curation, Formal Analysis, Project administration, Software, Writing – review & editing. **CS**: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft. **GA**: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft. **AA**: Supervision, Validation, Visualization, Writing – review & editing. **AR**: Supervision, Validation, Visualization, Writing – review & editing. **EN**: Supervision, Validation,

CONFLICTS OF INTEREST STATEMENT

The authors declare not having any conflict of interests.

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	SPT concentration	IDT concentration
Carboplatin	10 mg/ml	1 mg/ml
		5 mg/ml
		10 mg/ml
Cisplatin	1 mg/ml	0.01 mg/ml
		0.1 mg/ml
		1 mg/ml
Oxaliplatin	5 mg/ml	0.05 mg/ml
		0.5 mg/ml
		5 mg/ml
Paclitaxel	6 mg/ml	0.1 mg/ml
		1 mg/ml
Docetaxel	10 mg/ml	0.1 mg/ml
		1 mg/ml

Table I. STs Concentration for PC and TX.

Time interval between ST and reaction	**N° patients (%)**
3 weeks	94 (34,05%)
4 weeks	60 (21,8)
5 weeks	25 (9,05%)
6 weeks	11 (3,98%)
6 weeks - 6 months	38 (13,76%)
6 months - 1 year	10 (3,62%)
>1 year	38 (13,76%)

Table II. Weeks between the HSR and the allergological exam.

		PC HSRs	TX HSRs	PC + TX HRSs	p-value
STs	**Positive**	102	11	1	
	Negative	53	104	5	
TOT		155	115	6	<.0001

Table III. Comparison between HSRs.

Grade of reaction according to Brown's classification (n° patients)	STs positivity, n° (%)
I (48)	23 (47.9%)
II (68)	44 (64.7%)
III (45)	37 (82.2%)

Table IV. ST positivity according to the type of reaction in patients treated with PC.

Grade of reaction according to Brown's classification (n° patients)	STs positivity, n° (%)
I (44)	1 (2.3%)
II (55)	2 (3.6%)
III (22)	9 (40.9%)

Table V. ST positivity according to the type of reaction in patients treated with TX.

Drug reaction (ST positivity with the culprit drug, n)	**Crossreactivity in STs** (ST positivity with other drugs, n)		
	Carboplatin	Oxaliplatin	Cisplatin
Carboplatin (99)	/	1	0
Oxaliplatin (2)	10	/	1
Cisplatin (6)	15	1	/
	Crossreactivity in STs (ST positivity with other drug, n)		
	Paclitaxel	Docetaxel	
Paclitaxel (12)	/	9	
Docetaxel (0)	/	/	

Table V. Cross-reactivity between PC and TX. On regard of PC, 76 patients tested positive for only 1 agent, 22 patients tested positive for 2, while 5 patients tested positive for all 3 molecules.