



Value of skin tests for managing allergic hypersensitivity reactions to platinum compounds

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Abstract

Background Platinum-based therapy continues to be one of the pillars of the treatment of different types of cancer. However, many times the responsible clinician renounces its use after the appearance of a hypersensitivity reaction. **Objective** To assess the value of skin tests (ST) in clinical practice to address the treatment of patients with suspicion of immediate hypersensitivity reactions (HSRs) to platinum compounds. **Method** Single-center retrospective study of 3 years. Adult patients treated with any platinum compound who experienced HSR symptoms and for whom an oncologist requested ST, were included. ST with cisplatin, carboplatin and oxaliplatin were performed. **Results** Twenty-two patients were included. ST were positive in 12 patients (54.5%), of which 4 (33%) presented cross-reactivity to another platinum compound. Fifteen patients continued platinum-based chemotherapy: 9 patients with positive ST (4 continued by desensitization and 5 with another platinum compound) and 6 patients with negative ST, of which 1 repeated an HSR. A NPV of 0.91 was calculated. **Conclusion** ST helped physicians identify patients most susceptible to platinum derivative allergies and resume platinum-based therapy in many patients for whom no suitable therapeutic alternative was clinically acceptable.

Keywords Hypersensitivity reaction · Platinum · Skin test

Impacts on practice

- Platinum allergy testing should be an important tool in routine clinical practice, as it enables optimization of oncological treatment in patients who experience a reaction during infusion of platinum compounds.
- Clinical pharmacists should encourage the performance of these skin tests since it is a way to promote the best use of medications.

Introduction

Chemotherapy with platinum compounds continues to be one of the mainstays for treating several types of cancer. However, hypersensitivity reactions (HSR) have emerged as a frequent adverse event to these agents and may pose a limitation for their use, because HSR clinical symptoms are variable and unpredictable, and can even lead to life-threatening events [1, 2].

The incidence of platinum-induced HSR is variable and increases with the number of administrations, when are used as second-line or higher therapy, and with other risk factors (such as the platinum-free time interval, the cumulative dose in the case of carboplatin or concomitant radiation therapy, in the case of cisplatin) [1, 3]. The highest frequency has been reported for carboplatin, with percentages ranging from about 1%, when five or fewer cycles are administered, to 27% in patients receiving more than seven cycles, and up to 44% in second and third line therapies. Incidence is lower for oxaliplatin (10–25%) and cisplatin (5–20%). According to the mechanism of development, HSRs are classified into allergic reactions, which are caused by an immune mechanism and are mostly Ig-E-mediated reactions (type I or

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immediate allergic reactions), and non-allergic reactions, which are the result of a release of cytokines [2].

When a patient experiences an HSR, the clinician has to establish an accurate diagnosis of the HSR based on a careful analysis of the relationship with the platinum agent, the severity and clinical course of the reaction, and the type of HSR. This diagnosis allows for adequate management of the HSR and optimal therapeutic decisions, after prudently weighing the risk–benefit ratio.

Skin tests (ST) are effective in diagnosing type 1 immediate allergic reactions to platinum compounds and in determining cross-reactivity between the three platinum [4]. Thus, they comprise a helpful tool in addressing the treatment of patients with HSR, especially when no suitable alternative is available or acceptable, since management options will depend on whether or not the HSR is classified as allergic, and on the cross-reactivity among the platinum compounds. Approaches to overcoming allergic reactions on those occasions when platinum-based chemotherapy really needs to continue include controlled desensitization and switching to a different platinum compound with no cross-reactivity [2]. On the other hand, non-allergic reactions do not require discontinuation of chemotherapy and can generally be prevented with premedication and a slower infusion rate [5].

Aim of the study

The aim of this study was to assess the value of skin testing in clinical practice to address the treatment of patients with suspicion of immediate HSRs to platinum compounds.

Ethics approval

The study protocol was approved on October 28 2020, by the hospital's Clinical Research Ethics Committee (code: PI-2020-08-558).

Method

Single-center observational and retrospective study performed between February 2016 and February 2019. Patients eligible for this study were all oncological patients treated with any platinum compound who experienced HSR symptoms during the administration of the chemotherapy and were referred by an oncologist to undergo an allergic evaluation in the Allergy Service. No exclusion criteria were defined.

Allergy ST were conducted following the recommendations of the European Academy of Allergy and Clinical Immunology [6]. Patients underwent ST for all three

platinum compounds (carboplatin, cisplatin and oxaliplatin). Dilutions necessary to carry out both the prick-tests and the intradermal tests were prepared in the hospital pharmacy within 2 hours before injection, and the preparations were administered and monitored by the Allergy Service. The prick-test was performed on all patients and the intradermal test was performed only when the first one was negative.

Patients were considered to have suffered an allergic reaction to the platinum compound tested when either of the two techniques performed gave a positive result. Some patients did not show a positive ST for all three platinum compounds. The negative predictive value (NPV) of the ST was defined as the proportion of patients with a negative reading test for any of the platinum compounds who received some platinum again and did not experience an HSR. These included both patients who continued the same previous treatment and those who switched to a non-cross-reactive platinum after testing.

Data collected included demographic and clinical patient characteristics, results of ST, and oncological treatment before and after the ST. The median and range of the quantitative variables and the proportions of the categorical variables were calculated. Comparison of quantitative variables was performed using a non-parametric test (Mann–Whitney U test) and a p value < 0.05 was considered statistically significant.

Results

A total of 22 patients with immediate HSR symptoms were included of whom most were females (19; 86.4%). Baseline patient characteristics are summarized in Table 1. The main primary cancer type was gynecologic in 13 patients (ovarian and endometrial) and digestive in 5 cases (colorectal). The suspected platinum compound was carboplatin in 13 cases, oxaliplatin in 5 cases and cisplatin in 4 cases. ST were positive to these suspected platinum compounds in a total of 12 patients (54.5%).

Table 2 shows the characteristics of platinum-based chemotherapy that had been administered to patients and their ST results. The median platinum-free interval in patients who showed positive ST was 22 months, significantly longer than that of patients with negative ST (11 months) ($p < 0.05$). The total number of courses administered of the platinum compound and the number of courses received of the current treatment-line did not present statistical differences between patients with positive and negative ST.

ST results and therapy options carried out after skin testing are summarized in Table 3. As regards cross-reactivity, in 4 of the 12 patients (33%) with a positive ST to the suspected platinum, a positive ST to another platinum compound was identified. Specifically, 2 patients were positive

Table 1 Baseline patient characteristics and platinum compound suspected of HSR

Variable		Total	Skin test results	
			Positive	Negative
Patients, n (%)		22	12	10
Age (y), median (range)		57 (42–84)	62 (45–84)	52 (42–72)
Sex, n (%)	Male	3 (13.6)	1	2
	Female	19 (86.4)	11	8
Tumor type, n (%)	Ovarian	10 (45.6)	6	4
	Colorectal	5 (22.7)	2	3
	Endometrial	3 (13.6)	3	0
	Urotelial	2 (9.1)	1	1
	Head and neck	1 (4.5)	0	1
	Breast	1 (4.5)	0	1
	Cisplatin	4 (18.2)	1	3
Suspected platinum compound, n (%)	Carboplatin	13 (59.1)	9	4
	Oxaliplatin	5 (22.7)	2	3
	Cisplatin	4 (18.2)	1	3

Table 2 Platinum-based chemotherapy administered and skin test results

Variable	Total	Skin test results		
		Positive	Negative	<i>P</i> value
Patients, n (%)	22	12 (54.5%)	10 (45.5%)	–
Platinum free interval (months) ^a , median (range)	18 (1–35)	22 (8–35)	11 (1–17)	0.027
Total courses of platinum treatment, median [range]	9 (0–54)	9 (0–54)	8 (1–18)	0.716
Courses received at the current treatment-line, median (range)	2 (1–54)	3 (1–54)	2 (1–11)	0.864
Cumulative carboplatin dose (mg) ^b , median (range)	3,382 (0–7, 150)	4,420 (0–7, 150)	2,522 (535–6,570)	0.355

^aRefers to the period of time between the last platinum administration and the start of the current treatment line. For this data, only the 14 patients who had previously received a dose of platinum were taken into account

^bIn patients who reacted to carboplatin

Table 3 Therapeutic options carried out according to skin test results and outcomes

Platinum compound suspected (n)	Platinum compound with positive skin test	Tumor type	Patients (n)	Oncologist therapeutic decision	Repeat HSR
Patients with positive skin test results to some platinum compounds (n = 12)					
Carboplatin (9)	Carboplatin +, cisplatin + and oxaliplatin + Carboplatin + and oxaliplatin + Carboplatin +	Ovarian	2	Desensitization	No
		Ovarian	2	Switch to cisplatin	No
		Ovarian	2	Switch to cisplatin	No
		Endometrial	2	Desensitization	No
		Endometrial	1	Discontinue platinum	–
Oxaliplatin (2)	Oxaliplatin +	Colorectal	2	Discontinue platinum	–
Cisplatin (1)	Cisplatin +	Urotelial	1	Switch to carboplatin	No
Patients with negative skin test results to all platinum compounds (n = 10)					
Carboplatin (4)	–	Ovarian	2	Continue carboplatin	No
		Breast	1	Continue carboplatin	No
		Urotelial	1	Discontinue platinum	–
		Colorectal	3	Discontinue platinum	–
Oxaliplatin (3)	–	Ovarian	2	Continue cisplatin	No
Cisplatin (3)	–	Head and neck	1	Continue cisplatin	Yes

to the 3 platinum compounds and 2 were positive only to carboplatin and oxaliplatin.

Among the 12 patients with a positive ST to some platinum compound, the oncologists decided to resume with platinum in 9 patients (75%): 4 maintained the previous treatment administered through a controlled desensitization protocol and 5 were switched to a different platinum compound that had shown a negative ST. No HSR were notified in these patients following these platinum-based treatments. Of the 10 patients with negative ST to all platinum compounds, 6 restarted treatment with the same platinum. One experienced a recurrent HSR, with mild symptoms. Considering that in a total of 11 patients who showed a negative ST for some or all platinum compounds, treatment with platinum was reintroduced, and that 10 patients did not suffer another HST, a NPV for skin allergy tests of 0.91 was calculated.

Discussion

Understanding a patient's allergy status is important for ensuring safe, high-quality patient care. In cancer patients, in whom the ability to use first-line chemotherapeutic agents is critical, an accurate allergy diagnosis is also necessary for proper management of HSR and for providing optimal therapy.

In our study, ST in cancer patients with symptoms of a possible HSR during the administration of a platinum compound helped to identify patients with platinum allergy and to evaluate the cross-reactivity among these agents in order to safely reintroduce an alternative platinum. Altogether, ST allowed platinum-based treatment to continue in 15 patients, of whom 14 (64%) continued with good long-term tolerance. Only in 7 of the patients did the oncologist decide to discontinue treatment. These results are similar to those observed in other published studies that analyzed the treatment options followed in patients and their outcomes after performing ST. Pradelli et al. [4] in a recent publication reported that 65% of patients with suspected HSRs who were referred for the study of hypersensitivity continued with the platinum-based therapy, while Leguy et al. [5] in a previous study reported a somewhat lower percentage, 57%, probably because they did not perform controlled desensitization in patients with positive ST.

The high NPV found in our study (0.91) is consistent with that described in the literature, the latter being between 0.92–0.99, even reaching 100% true negatives in some cases [5, 7]. These data indicate that ST may predict with reasonable reliability the absence of a future HRS. Published data also indicate that in patients with false negative results

subsequent reactions are usually mild, as we saw with our patient [8, 9].

Regarding the risk factors for HSR to platinum compounds, these reactions occur after patients have undergone several courses of treatment [3]. We found that the median number of courses before the suspected HSR was 9, consistent with those collected in previous studies, but we did not find statistical significance between the patients with positive and negative ST, probably due to the small sample size. However, we obtained statistically significant differences in the platinum-free interval between patients with positive and negative results, with the median of positives at 22 months, which is another widely described risk factor [10].

This study has some limitations that we must acknowledge, principally the small patient population and the retrospective and observational nature. However, the study suggests the need and opportunity to evaluate ST as a possible diagnostic test serving to minimize adverse drug reactions or the necessity of interrupting individual chemotherapy protocols and anticancer therapy. Broad series prospective studies are needed to more precisely determine the usefulness of these tests.

Conclusion

ST helped physicians identify patients most susceptible to platinum allergy and resume platinum-based therapy in many patients for whom no suitable therapeutic alternative was clinically acceptable.

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Conflicts of interests The authors declared that they have no conflict of interest.

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