

# Value of Skin Tests for Managing Hypersensitivity Reactions to Platinum Salts

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## Research Article

**Keywords:** Platinum, hypersensitivity reaction, skin test

**Posted Date:** February 10th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-185052/v1>

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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 salts.

**Methods:** Single-center retrospective study performed for 3 years. Adult patients treated with any platinum salt 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 salt. Fifteen patients continued platinum-based chemotherapy: 9 patients with positive ST (4 continued by desensitization and 5 with another platinum) and 6 patients with negative ST, of which 1 repeated an HSR. A NPV of 0.91 was calculated.

**Conclusion:** ST allowed accurate identification of platinum allergy patients and the resumption of platinum-based therapy in many patients for whom no suitable therapeutic alternative was clinically acceptable.

## Highlights

- 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 salts.
- 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 salts 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 [1, 2]. 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 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 [2].

Skin tests are effective in diagnosing type 1 immediate allergic reactions to platinum salts and in determining cross-reactivity between the three platinum salts [2, 3]. 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 between the platinum salts. Approaches to overcoming allergic reactions when platinum-based chemotherapy needs to continue include controlled desensitization and switching to a different platinum salt 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 [4].

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 salts.

## Methods

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 salt 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. The study protocol was approved by the hospital's Clinical Research Ethics Committee.

Allergy skin tests were conducted following the recommendations of the European Academy of Allergy and Clinical Immunology [5]. Patients underwent skin tests for all three platinum salts (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 it was negative.

Patients were considered to have suffered an allergic reaction to the platinum salt tested when either of the two techniques performed gave a positive result. The negative predictive value (NPV) of the skin tests was defined as the proportion of non-allergic patients (i.e. patients who tolerated reintroduction of platinum) among the patients with a negative reading test for some platinum salt who received platinum

again. This included both patients who continued the same previous treatment and those who switched to non-cross-reactive platinum after testing.

Data collected included demographic and clinical patient characteristics, results of skin tests, and oncological treatment before and after the skin tests. 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 salt was carboplatin in 13 cases, oxaliplatin in 5 cases and cisplatin in 4 cases. Skin tests were positive to the suspected platinum salt in 12 patients (54.5%) with 9 reactions to carboplatin, 2 to oxaliplatin, and 1 to cisplatin.

Table 1  
Baseline patient characteristics and platinum salt 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          |
| Suspected platinum salt, n (%) | Carboplatin   | 13 (59.1)  | 9                 | 4          |
|                                | Oxaliplatin   | 5 (22.7)   | 2                 | 3          |
|                                | Cisplatin     | 4 (18.2)   | 1                 | 3          |

Table 2 shows the characteristics of platinum-based chemotherapy administered according to skin test results. Patients with a positive skin test had a median of platinum-free interval (22 months) significantly higher than patients with negative results (11 months) ( $p < 0.05$ ). The total number of courses administered of the platinum salt and the number of courses received of the current treatment-line did not present statistical differences in patients with positive and negative skin tests.

Table 2  
Platinum-based chemotherapy administered and skin test results.

| Variable   | Total           | Skin test results |                   |         |
|--|-----------------|-------------------|-------------------|---------|
|  |                 | Positive          | Negative          | P value |
| Patients, n (%)  | 22              | 12 (54.5 %)       | 10 (45.5 %)       | -       |
| Platinum free interval (months) <sup>a</sup> , 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) <sup>b</sup> , median [range]   | 3,382 [0–7,150] | 4,420 [0–7,150]   | 2,522 [535–6,570] | 0.355   |
| <sup>a</sup> Refers 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. <sup>b</sup> In patients who reacted to carboplatin. |                 |                   |                   |         |

Skin test results and therapy options carried out after skin testing are summarized in Table 3. In 4 of the 12 patients (33%) with a positive skin test to the suspected platinum a positive skin test to another platinum salt was identified. Two patients were positive to the 3 platinum salts and 2 were positive to carboplatin and oxaliplatin.

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

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

Among the 12 patients with positive skin tests, the oncologists decided to resume with platinum salts in 9 patients (75%): 4 maintained the previous treatment administered through a controlled desensitization protocol and 5 were switched to a different platinum salt with a negative skin test. No HSR were notified. Of the 10 patients with negative skin tests, 6 restarted treatment with the same platinum salt. One experienced a recurrent HSR, with mild symptoms. Considering the patients who showed no allergies to

any platinum salt and who did not suffer another HSR when this platinum salt was reintroduced, 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, skin tests in cancer patients with symptoms of a possible HSR during the administration of a platinum salt helped to identify patients with platinum allergy and to evaluate the cross-reactivity between these agents in order to safely reintroduce an alternative platinum. Altogether, skin tests 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 series that analyzed the treatment options followed in patients and their outcomes after performing skin tests. Pradelli et al. [3] 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. [4] in a previous study reported a somewhat lower percentage, 57%, probably because they did not perform controlled desensitization in patients with positive skin tests.

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 [4, 6, 7]. Published data also indicate that in patients with false negative results subsequent reactions are usually mild, as happened with our patient [7, 8]. These data indicate that skin tests may predict with reasonable reliability the absence of a future HRS in case of further chemotherapy with a negatively tested platinum salt.

Regarding the risk factors for HSR to platinum salts, these reactions occur after patients have undergone several courses of treatment [6, 7, 9]. Although we found that the median number of courses before the suspected HSR was 9, consistent with those collected in the bibliography, we did not find statistical significance between the patients with positive and negative skin tests, probably due to the small sample size. It should be noted that with respect to another widely described risk factor, which is having a platinum-free interval greater than 12 or 24 months [9, 10], in our study, statistically significant differences were obtained in the platinum-free interval between patients with positive and negative results, with the median of positives at 22 months.

This study provides initial evidence of the value of skin testing as a diagnostic aid. Nevertheless, we must acknowledge some limitations, principally the small patient population and the retrospective and observational nature of the study. Prospective studies in wide series are needed to more precisely determine the usefulness of these tests.

In conclusion, skin testing allowed accurate identification of patients with platinum allergy and the resumption of platinum-based therapy in many patients for whom no suitable therapeutic alternative was clinically acceptable.

## Declarations

## Funding:

None

## Conflict of interest:

None

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