

A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions

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Background: Management of patients with carboplatin-induced hypersensitivity reactions (HSR) has been complicated by high false-negative rates of carboplatin skin test (ST) results. These patients might be at risk for future carboplatin-induced HSRs. In this article we identify a strategy to improve risk stratification of patients with a history of carboplatin-induced HSRs by using a protocol that includes repeat skin testing and drug desensitization.

Objective: We sought to identify a management strategy for patients with a history of carboplatin-induced HSRs with negative carboplatin ST results.

Methods: From 2008-2010, patients with carboplatin-induced HSR underwent risk stratification per a protocol using 3 repeat STs with intervening drug desensitizations.

Results: Of the 44 patients with carboplatin-induced HSRs, 39 completed the protocol. Patients were classified as having positive ST results ($n = 16$), having negative ST results ($n = 11$), or ST converters when the ST result converted to positive after an initial negative result ($n = 12$). ST converters are more likely to have HSRs during subsequent desensitizations than patients with negative ST results (56.1% vs 4.5%, $P < .001$). ST converters had a significantly longer time interval between their initial HSR and initial ST evaluation compared with either patients with true-negative ST results (22.1 vs 6.0 months, $P = .03$) or patients with positive ST results (22.1 vs 1.8 months, $P = .001$).

Conclusion: Our experience suggests that repeat STs are necessary for risk stratification in patients with a remote clinical history of HSR and an initial negative ST result because there is a significant rate of conversion to a positive ST result. ST converters have an increased risk of HSRs during subsequent carboplatin treatment. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: Carboplatin, hypersensitivity, skin testing, drug allergy, desensitization

Abbreviations used

HSR: Hypersensitivity reaction

ST: Skin test

Platinum-based chemotherapeutic agents are commonly used in the treatment of many types of cancers, including ovarian cancer. Repeated administration of these agents, as required in most chemotherapy regimens, results in an increased likelihood of having hypersensitivity reactions (HSRs).¹⁻³ The incidence of such reactions increases from 1% after the first dose of carboplatin to 27% after 7 doses.² The clinical manifestations of HSRs to these agents range from cutaneous symptoms, such as pruritus or urticaria, to more severe systemic reactions, including anaphylactic shock.^{4,5} Drug desensitization has been found to be an effective treatment for patients with hypersensitivity who require platinum-based agents.^{6,7}

Skin testing with the drug has been demonstrated to be helpful in confirming the diagnosis of hypersensitivity to platinum-based chemotherapeutic agents, including carboplatin, cisplatin, and oxaliplatin.^{2,8,9} However, the false-negative rate of carboplatin skin test (ST) results (ie, the development of HSRs with next exposure after a negative ST result) is reported to be as high as 8% to 8.5% in the literature.^{10,11} We have observed that some patients with a clinical history suggestive of a platinum agent-induced HSR but with negative initial ST results experienced HSRs with subsequent drug exposure, even when that exposure occurred during attempted drug desensitization.¹² Additionally, we have observed that in some of these patients, ST results converted from initially negative to positive.

Because of concerns for patient safety, rather than relying on one round of STs alone, we have used a protocol with a modified desensitization approach followed by repeat STs in an attempt to differentiate patients with true-negative ST results from those with false-negative ST results. The goal of this study was to define a strategy to safely manage patients with a history of HSRs who had initial negative carboplatin ST results.

METHODS

Patient recruitment

We prospectively studied all patients referred to Massachusetts General Hospital's Allergy and Immunology service from January 2008 to December 2010 with possible HSRs to carboplatin for evaluation of hypersensitivity and consideration for desensitization. Approval was obtained from the Massachusetts General Hospital Institutional Review Board.

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Evaluation of HSRs

The following components of clinical history were considered suggestive of an HSR to carboplatin: cutaneous symptoms (flushing, pruritus, urticaria, or angioedema), respiratory symptoms (dyspnea or wheezing), abdominal symptoms (nausea, emesis, or abdominal pain), laryngeal angioedema, or cardiovascular symptoms (hypotension, hypertension,¹ or tachycardia).² HSR severity was graded according to a previously reported 4-point scale¹³: grade 0 (absent) if there was no reaction; grade 1 (mild) if there was less than 50% of the skin involved in a cutaneous reaction (flushing, urticaria, or pruritus); grade 2 (moderate) if there was generalized cutaneous involvement or angioedema, excluding laryngeal angioedema; and grade 3 (severe) if there was laryngeal angioedema or when respiratory, gastrointestinal, or cardiovascular symptoms were associated with cutaneous symptoms.

Carboplatin STs

Informed consent was obtained from each patient before skin testing and desensitization procedures. Carboplatin skin prick testing (10 mg/mL) and 3-step intradermal testing (0.1, 1, and either 3 or 5 mg/mL) with 0.02 mL were performed as previously described.¹² Histamine (Histatrol; 0.1 mg/mL histamine base; Alk-Abelló, Hørsholm, Denmark) was used as a positive control, and saline was used as a negative control (Allergen Laboratories, Inc, Oklahoma City, Okla). A positive ST result to carboplatin was defined as a wheal with a greatest diameter of 3 mm greater than that seen with saline. The lowest concentration of carboplatin that met the criteria for a positive ST result was selected, and the maximal recorded wheal-and-flare result at this concentration was used in our analysis.

The time interval in weeks between the ST and carboplatin-induced HSR was derived from chart review.

Protocol

Patients with a clinical history suggestive of a carboplatin-induced HSR underwent an initial carboplatin ST. Patients who had positive ST results at this stage of the protocol were deemed to have confirmed carboplatin allergy and were managed by using a 12-step desensitization procedure for each subsequent carboplatin exposure.¹⁴ Patients with negative ST results were managed by using a modified 8-step desensitization for their next carboplatin treatment,¹² followed by repeat STs. Repeat STs were performed at least 2 weeks after the previous desensitization. If the ST results remained negative, the 8-step desensitization was used again for the subsequent carboplatin treatment. If ST results remained negative 3 times, with intervening uneventful treatment using the 8-step desensitization, these patients were deemed to be not allergic to carboplatin and received all subsequent carboplatin infusions without further desensitization. In patients whose ST results converted from negative to positive during the protocol, a 12-step desensitization was used for all subsequent carboplatin treatments (Fig 1).

Patients were categorized as "ST positive" if their initial ST result was positive, "ST converters" if their initial ST result was negative but converted to a positive ST result subsequently, or "ST negative" if the ST result remained negative on the 3 repeat STs in the protocol.

Carboplatin desensitizations

A standard pretreatment medication regimen was used with 10 mg of oral loratadine and 10 mg of oral cetirizine on the evening before desensitization, the morning of desensitization, and immediately before initiation of desensitization. Previously published 8-step and 12-step desensitization procedures were used.^{6,12} All desensitization procedures were prescribed and supervised by the allergy and immunology service and were conducted in inpatient beds of the oncology service.

If symptoms of an HSR developed during the desensitization procedure, the infusion was immediately stopped, and 50 mg of parenteral diphenhydramine was administered. For severe or recurrent reactions, 60 mg of parenteral methylprednisolone was also added. Intramuscular epinephrine was used for grade 4 reactions, including hypotension. Once HSR symptoms resolved, the desensitization was resumed at a prior step and completed.

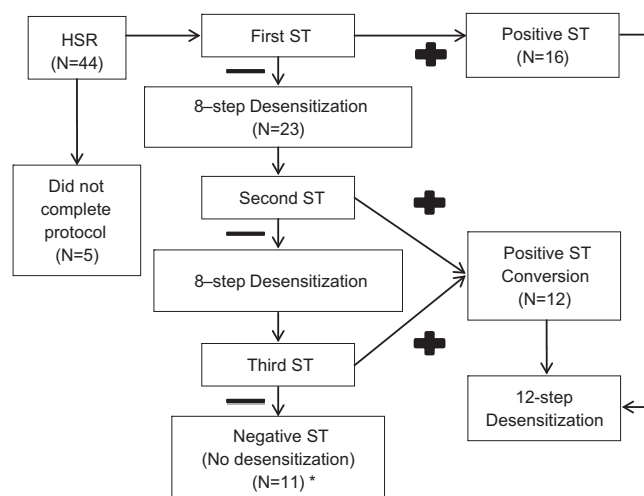


FIG 1. Protocol for risk stratification and carboplatin desensitization: protocol used for STs in patients with a clinical history concerning an HSR to carboplatin. *Six of the 11 patients required further carboplatin therapy, which was tolerated without desensitization in all of these patients.

Statistical analysis

A 1-way ANOVA with the Bonferroni correction was used in comparisons of ST results. The Student *t* test was used in comparisons of ST characteristics, time intervals between HSRs and STs, grading of HSR severity, and demographics. The Fisher exact test was used to compare categorical measures between ST groups. Comparisons were considered statistically significant at a *P* value of .05 or less. Statistical analysis was performed with Stata software (Stata Corp, College Station, Tex).

RESULTS

There were 44 patients who underwent 148 carboplatin desensitizations. Five of these patients who were deemed by their oncology physicians to not require further platinum therapy did not complete the study protocol. These 5 patients were excluded from subsequent analysis.

Clinical characteristics of the patient study population are summarized in Table I. Of the 39 patients, there were 38 female patients and 1 male patient, with an average age of 58.1 years. Thirty-seven of the 39 patients had gynecologic malignancies, 1 patient had squamous cell carcinoma, and 1 patient had non-small cell lung carcinoma.

Skin testing

Sixteen patients had positive ST results at their initial evaluation. Twenty-three patients initially had negative ST results. Eleven patients who had negative ST results at initial evaluation continued to have negative ST results throughout the study protocol (ie, after 2 subsequent carboplatin treatments received through modified [8-step] desensitization). Twelve patients were ST converters during this protocol; 6 patients converted after their first modified (8-step) desensitization, and 6 patients converted after their second modified (8-step) desensitization. Overall, during this study, 52% of patients who had negative ST results at initial evaluation converted to having positive STs results and were considered carboplatin ST converters.

Among all the patients with positive ST results, including the ST converters, 14% were identified on epicutaneous skin prick

TABLE I. Baseline clinical characteristics of the study population

Characteristic	All patients (n = 39)	Positive ST result (n = 16)	ST converter (n = 12)	Negative ST result (n = 11)
Mean age (y)	58.1	56.5	61.8	56.3
Female sex	38 (97%)	16 (100%)	12 (100%)	10 (91%)
No. of carboplatin doses at the time of HSR	9.3	9.0	9.1	9.8

testing and 86% on intradermal testing (29% at 0.1 mg/mL, 18% at 1 mg/mL, 18% at 3 mg/mL, and 21% at 5 mg/mL). The distribution of the ST step at which ST results were positive was similar in patients with positive ST results and ST converters ($P = .23$).

The size of the positive carboplatin ST results after conversion was not different from the size recorded in patients with initially positive ST results (mean wheal size, 7.3 vs 7.0 mm [$P = .81$]; mean flare size, 25.7 vs 18.6 mm [$P = .17$]).

HSRs during desensitization

In the study period 23 (59%) patients experienced at least 1 HSR during desensitization procedures. The percentage of patients who experienced at least 1 HSR during their desensitizations varied by ST category ($P < .001$, 75% in patients with positive ST results, 83.3% in ST converters, and 9.1% in patients with negative ST results). Of the 11 patients with negative ST results, only 1 had a reaction during the 8-step desensitization. This single reaction was comprised of cutaneous pruritus only and completely resolved with parenteral diphenhydramine. The patient's next 8-step desensitization was completed without any HSR symptoms.

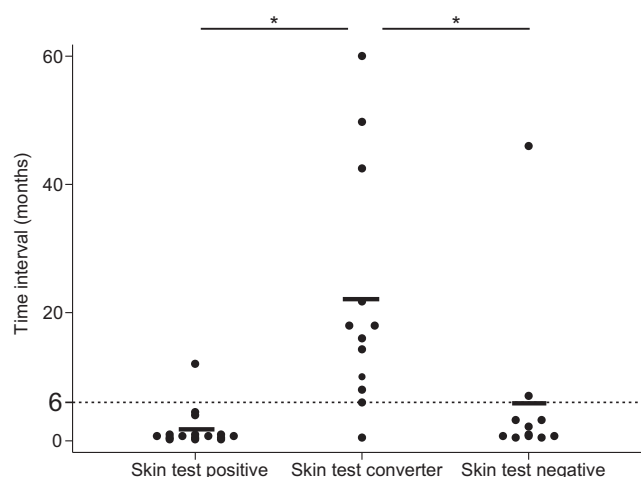
The percentage of desensitizations complicated by HSRs was similar in patients with positive ST results and ST converters (58.5% vs 56.1%, $P = .87$), but patients who undergo ST conversion were significantly more likely to have desensitizations complicated by HSRs than patients with negative STs (56.1% vs 4.5%, $P < .001$).

The large majority of patients with a negative initial ST result, irrespective of their final ST classification, tolerated their following 8-step desensitization without HSRs (90.9% of patients with negative ST results vs 83.3% of ST converters, $P = .59$).

Six of the 11 patients who continued to have negative ST results required further carboplatin treatments after completion of the study protocol. An average of 2.5 subsequent doses per patient were administered. Precautions were used, including a similar antihistamine premedication regimen used in our protocol and a slowed infusion rate at 50% of the standard infusion rate. All of these patients tolerated their subsequent carboplatin infusions without any HSRs or further requirement for desensitization.

Time interval between HSR and initial ST

The average time interval between the original HSR and the first ST among all patients was 9.2 months (range, 0.3–60 months). ST converters were found to have had a significantly longer time interval between their HSRs and the first ST evaluation than either patients with negative ST results (22.1 vs 6.0 months, $P = .001$) or patients with positive ST results (22.1 vs 1.8 months, $P = .03$), as

**FIG 2.** Time interval between HSRs and STs. The interval between patients' HSRs and STs was significantly different in patients who were ST converters. * $P < .05$.

seen in Fig 2. Indeed, 92% of the ST converters had a time interval of greater than 6 months between the original HSR and ST compared with 27% of the patients with negative ST results ($P < .05$).

Severity of initial HSR

Patients who had positive ST results had a more severe original carboplatin-induced HSR than patients who continued to have negative ST results (severity grade, 2.4 vs 1.6; $P = .04$). Similarly, ST converters also had a more severe original HSR compared with patients with negative ST results (severity grade, 2.3 vs 1.6; $P = .02$). In ST converters those who converted after their first or second 8-step desensitization had similar severity of initial HSR (severity grade, 2 vs 2.7; $P = .2$).

The mean number of previous carboplatin treatments at the time of the original HSR was 9.3 (range, 4–17 treatments) in the 39 patients. There was no significant difference in the number of previous doses of carboplatin administered among the 3 ST categories of patients (9.0 doses in patients with positive ST results, 9.1 doses in ST converters, and 9.8 doses in patients with negative ST results; $P = .75$).

DISCUSSION

A significant proportion of patients who receive multiple doses of carboplatin for the treatment of cancer have carboplatin-induced HSRs, which limits their ability to further receive this potentially life-saving therapy. Skin testing has been used in the diagnosis and management of patients with HSRs to carboplatin. However, in studies using a single carboplatin ST for diagnosis of carboplatin hypersensitivity, false-negative ST results have been previously reported, making decisions about subsequent management of these patients problematic.^{9,10,12}

This study focused on the evaluation and management of patients with a history of a carboplatin-induced HSR who were referred to the allergy and immunology service for evaluation. We found that 52% of patients with negative initial ST results subsequently converted to positive results (ie, had a false-negative result on the first test), and 83% of those patients had additional HSRs to carboplatin, even when administered using

desensitization procedures. In contrast, only a minority (9%) of patients who continued to have negative ST results (ie, had truly negative results) had an HSR during subsequent carboplatin desensitization. Informatively, the vast majority of patients who demonstrated ST conversion had a time interval of greater than 6 months between the original HSR and the first ST. Our protocol identifies a strategy to safely manage patients with a clinical history of carboplatin-induced HSRs and whose initial ST result is negative.

We believe that the patients who had false-negative ST results would have been at risk for worse HSRs if chemotherapy had not been administered by using desensitization. The frequency of HSRs in ST converters was similar to that of patients with positive ST results, despite the use of desensitization. Thus reliance on a single negative ST result to determine which patients require desensitization places the patient with false-negative ST results at significant risk for a HSR. Although Hesterberg et al¹² suggested that patients who undergo ST conversion were at risk for a more severe grade of HSR, our findings did not demonstrate a higher severity of HSRs during desensitization in ST converters. This difference in findings might be reflective of the larger patient population of ST converters seen in this study.

We analyzed several potential risk factors for ST conversion, including lifetime number of doses of carboplatin at the time of the original HSR and the severity of the original HSR. We found that the most significant risk factor for ST conversion was the time interval between the patient's original HSR and the first ST. This interval is significantly greater in patients with false-negative ST results than in those with true-negative ST results. Further empiric stratification of patients using a cutoff of 6 months revealed that patients with false-negative ST results were significantly more likely to have a time interval greater than 6 months between their HSR and ST. This result is consistent with previous work on a nonoverlapping cohort of patients at our institution.¹²

In the ST converters, the negative initial ST result might represent a hypersensitivity state that has waned to a level less than the threshold detectable by means of STs, which is related to the prolonged time interval between the original HSR and the first ST. Re-exposure to carboplatin might lead to activation of memory responses and a more clinically evident immediate hypersensitivity state. Interestingly, we have also observed the phenomenon of ST conversion with other platinum-based chemotherapeutic agents, such as oxaliplatin. Although *de novo* sensitization during the ST protocol in this article cannot be excluded as a cause of ST conversion, it does not explain the previous history of HSRs that is shared by these patients.

Also important is the accurate identification of patients with truly negative ST results, who we observed were able to tolerate carboplatin without desensitization after completion of the protocol. For increased caution, these patients were administered carboplatin with antihistamine premedication and at a lower rate of infusion than normal. Categorization of these nonallergic patients might lead to an improvement in health care use and resource allocation, as well as improvement in the patient's quality of life. Larger studies of this population with truly negative ST results are needed to clarify their long-term tolerance of carboplatin therapy.

One possible explanation for the high rate of false-negative ST results in this study might relate to the concentration of carboplatin used in the ST procedure. Although others have

used a concentration of up to 10 mg/mL,^{6,8,9,11} we did not use a concentration greater than 5 mg/mL for intradermal testing. We believe that testing at this concentration is adequate for identification of patients with carboplatin allergy. In a study by Castells et al,⁶ in which intradermal skin testing at concentrations of 0.1, 1, and 10 mg/mL was performed, 88% of patients with carboplatin allergy were identified by means of skin prick testing or with an intradermal test concentration of less than or equal to 1 mg/mL, suggesting that only 12% of patients required a higher concentration for identification. In our study 39% of patients with positive ST results were identified at concentrations of greater than 1 mg/mL, making it very unlikely that we missed patients with potentially positive results by omitting the 10 mg/mL concentration. The accuracy of our classification after the initial ST is underscored by the very low rate of HSRs in the next carboplatin exposure immediately after a negative ST result. Furthermore, in our experience use of intradermal testing with a 10 mg/mL concentration of carboplatin can result in significant local skin necrosis and subsequent scarring. None of our patients experienced skin necrosis after testing at our top concentration of 5 mg/mL.

In conclusion, we urge caution in the management of patients with a clinical history of hypersensitivity to carboplatin who are found to have a negative ST result and highlight the concern that it might represent a false-negative result. Importantly, almost one third of patients who require more than 6 cycles of carboplatin chemotherapy have HSRs. Our study shows that more than half of the patients with negative initial ST results will convert to positive results after further carboplatin exposure and have an increase in the risk of HSRs. Repeat STs improve patient safety by distinguishing patients who have truly negative results for carboplatin allergy and might tolerate further treatment without desensitization from those who are truly allergic and require repeated desensitization for each future treatment.

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Clinical implications: One negative ST result in a patient with carboplatin hypersensitivity should not be considered predictive of future tolerance, especially in patients whose interval between the HSR and ST is greater than 6 months.

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