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Risk-stratification protocol for carboplatin and oxaliplatin hypersensitivity: repeat skin testing to identify drug allergy

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ABSTRACT

Background: Hypersensitivity reactions (HSRs) to platinum-based chemotherapies are increasingly being recognized. The authors developed a novel risk-stratification protocol that was used successfully in a small number of patients with carboplatin-induced HSRs.

Objective: To describe the utility of this protocol in a large number of patients with carboplatin- or oxaliplatin-induced HSRs.

Methods: A 5-year retrospective review of patients referred to Massachusetts General Hospital with carboplatin- or oxaliplatin-induced HSR was performed. Patients were managed using a risk-stratification protocol using 3 repeat skin tests (STs) with intervening desensitizations. If the repeat ST result remained negative 3 times, patients received subsequent infusions without desensitization.

Results: From 2008 to 2012, 142 patients (92 treated with carboplatin, 50 treated with oxaliplatin) completed 574 desensitizations. Most patients were women (84.5%, mean $\pm$ SD 58.1 $\pm$ 9.3 years). Patients with carboplatin-induced HSRs were classified as having positive ($n = 32$, 34.8%), negative ($n = 38$, 41.3%), or converted ($n = 22$, 23.9%) ST reactions when the initial negative ST reaction converted to positive at repeat ST. Of those with oxaliplatin-induced HSRs, 22 (44%) had positive, 25 (50%) had negative, and 3 (6%) had converted ST reactions. Of the patients with negative ST reactions, 17 with carboplatin-induced HSRs and 16 with oxaliplatin-induced HSRs safely completed 59 and 95 outpatient infusions, respectively, without desensitizations. For carboplatin and oxaliplatin, ST conversion was associated with an interval of at least 6 months from the HSR to the initial ST (carboplatin, $P = .002$; oxaliplatin, $P = .045$).

Conclusion: This risk-stratification protocol for presumed carboplatin- and oxaliplatin-induced HSRs safely identifies false-negative ST reactions and nonallergic patients who can receive infusions without desensitizations. This leads to fewer unnecessary desensitizations and improved patient care.

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Introduction

The incidence of hypersensitivity reactions (HSRs) to carboplatin and oxaliplatin has increased with the increasing use of platinum-based chemotherapies.¹ The incidence of HSR increases with repeat exposure and reaches 27% in patients receiving more than 6 cycles of carboplatin and 24% in patients receiving oxaliplatin.^{2,3} Skin testing remains the diagnostic standard for evaluating carboplatin- and oxaliplatin-induced HSRs, and desensitization allows patients who require additional cycles of these agents to receive treatment despite an allergy.⁴

One-time skin testing has a high negative predictive value but is problematic, with up to an 8.5% false-negative rate.^{5–8} In addition, chemotherapy desensitization is highly specialized, resource

intensive, and available only at a limited number of academic centers with experienced physicians and nurses.^{4,9} The authors previously published a novel protocol for patients with a history of carboplatin-induced HSR that used repeat skin testing before each desensitization, and they used this protocol in a small cohort of patients to safely identify those who were not allergic to carboplatin despite presumed HSR.¹⁰

Accurate identification of nonallergic patients despite presumed HSR allows patients who are referred to tertiary centers for desensitizations to return to outpatient infusion centers, decreases unnecessary desensitizations, and improves patient care. Since the development of the risk-stratification protocol, the allergy and immunology service at Massachusetts General Hospital (Boston, Massachusetts) has expanded this protocol to all patients referred with carboplatin- and oxaliplatin-induced HSR. The authors reviewed the safety, efficacy, and outcomes of this risk-stratification protocol in managing a large group of patients with carboplatin- and oxaliplatin-induced HSRs.

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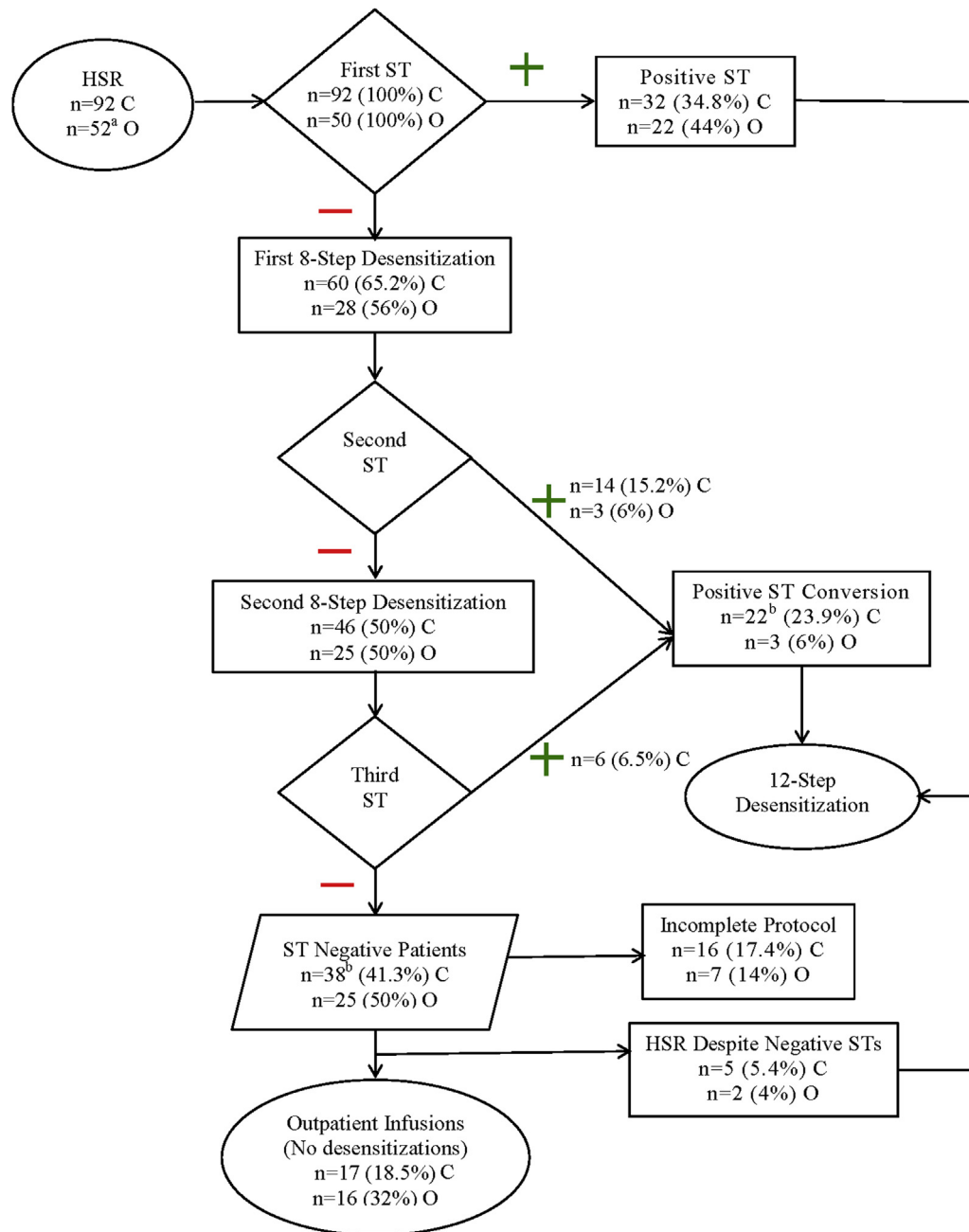


Figure 1. Risk-stratification protocol for carboplatin (C) and oxaliplatin (O) hypersensitivity reactions (HSRs). ^aTwo patients received emergency desensitization without initial skin testing (ST) and were excluded from subsequent analysis. ^bTwo carboplatin-treated patients had positive ST conversion at the fourth and fifth STs, respectively, that were performed outside the standard protocol owing to symptoms of HSR during desensitizations despite negative ST results.

Methods

A 5-year retrospective review was performed of all patients referred to the allergy and immunology service at Massachusetts General Hospital with carboplatin- or oxaliplatin-induced HSR. Patients were included if they (1) were older than 18 years, (2) had a history of HSR to carboplatin or oxaliplatin, (3) could provide informed consent, and (4) underwent desensitization to carboplatin or oxaliplatin from January 1, 2008 through December 31, 2012. Patients were excluded if skin testing to carboplatin or oxaliplatin was not performed. Patient demographics and clinical characteristics, including history of atopy, cancer diagnosis, chemotherapy cycle number, initial HSR severity grade, and initial HSR symptoms, were reviewed.

Approval was obtained from the Massachusetts General Hospital institutional review board.

Evaluation of Initial HSRs

Initial HSRs were graded on a previously reported 4-point scale.¹¹ Reactions were grade 0 (absent) if there was no reaction; grade 1 (mild) if less than 50% of the skin was involved in a cutaneous reaction (flushing, hives, 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.¹¹ Symptoms of initial HSR were recorded and classified by organ system.

Table 1

Demographics and characteristics of patients with carboplatin- and oxaliplatin-induced hypersensitivity reaction who underwent desensitization from 2008 to 2012

	Carboplatin (n = 92, 64.8%)	Oxaliplatin (n = 50, 35.2%)	Total (N = 142, 100.0%)
Age (y), mean $\pm$ SD	58.2 $\pm$ 9.3	58.0 $\pm$ 10.3	58.1 $\pm$ 9.3
Race, n (%)			
White	86 (93.5)	44 (88.0)	130 (91.5)
Black	2 (2.2)	2 (4.0)	4 (2.8)
Asian or Pacific Islander	2 (2.2)	3 (6.0)	5 (3.5)
Hispanic	2 (2.2)	1 (2.0)	3 (2.1)
Gender, n (%)			
Women	91 (98.9)	29 (58.0)	120 (84.5)
Men	1 (1.1)	21 (42.0)	22 (15.5)
History of atopy, n (%)			
Positive	65 (70.7)	26 (52.0)	91 (64.1)
Negative	27 (29.3)	24 (48.0)	51 (35.9)
Cancer, n (%)			
Ovarian	87 (94.6)	0 (0.0)	87 (61.4)
Colorectal	0 (0.0)	48 (96.0)	48 (33.8)
SCC	3 (3.3)	0 (0.0)	3 (2.1)
NSCLC	2 (2.2)	0 (0.0)	2 (1.4)
Metastatic adenocarcinoma of unknown primary	0 (0.0)	2 (4.0)	2 (1.4)
Chemotherapy cycle number, median (IQR)	9 (8–11)	8 (5–13)	9 (7–11)
Initial HSR severity grade, median (IQR)	2.0 (1.0–3.0)	3.0 (2.0–3.0)	3.0 (1.0–3.0)

Abbreviations: IQR, interquartile range; NSCLC, non-small cell lung cancer; SCC, small cell carcinoma.

Skin Testing

Standard skin prick and intradermal skin testing procedures and equipment were used. Saline was used as a negative control, and histamine (1 mg/mL percutaneously and 0.1 mg/mL intradermally) was used as a positive control. For skin prick testing, 10 mg/mL of carboplatin or 5 mg/mL of oxaliplatin was applied. If the reaction was negative, 3-step intradermal testing was performed for carboplatin (0.1, 1, and 5 mg/mL) or oxaliplatin (0.05, 0.5, and 5 mg/mL) with 0.02 mL of each dilution. These concentrations are consistent with previously published protocols.^{4–7,9,12} In the authors' experience, maximizing the carboplatin intradermal testing concentration at 5 mg/mL is adequate for detecting allergic sensitization, and higher concentrations induce local skin necrosis and skin irritation. A positive skin test reaction was defined as a wheal diameter at least 3 mm larger than the saline control. Patients presented for skin testing during the week before their next platinum-based chemotherapy infusion.

Risk-Stratification Protocol

The authors expanded on their previously described risk-stratification protocol for patients with carboplatin-induced HSR to include patients with carboplatin-induced HSR and those with oxaliplatin-induced HSR.¹⁰ Patients with a history suggestive of a carboplatin- or oxaliplatin-induced HSR first underwent skin testing (Fig 1). Patients whose first skin test results were positive were deemed to be allergic to carboplatin or oxaliplatin, respectively, and were managed by a 12-step desensitization procedure for each subsequent carboplatin or oxaliplatin treatment.⁴ Patients with negative skin test results were managed using an 8-step desensitization for their next carboplatin or oxaliplatin treatment, followed by repeat skin tests before each desensitization.⁹ If the repeat skin test result remained negative, the 8-step desensitization was used for the subsequent carboplatin or oxaliplatin treatment.⁹ If repeat skin test results remained negative 3 times with uneventful intervening desensitization treatments, these patients were determined not to be allergic to carboplatin or oxaliplatin and

received all subsequent carboplatin or oxaliplatin infusions at a 50% infusion rate without further desensitization. In patients whose skin test results converted from negative to positive during the risk-stratification protocol, a 12-step desensitization was used for all subsequent carboplatin or oxaliplatin treatments, and no further skin tests were performed.

Patients were categorized as having a positive reaction if their first skin test reaction was positive, a conversion if their first skin test result was negative but converted to positive at repeat skin testing, or a negative reaction if their skin test result remained negative.

Desensitizations

Patients received a standard pretreatment medication regimen of 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- or 12-step desensitization procedures were used.^{4,9} All desensitization procedures were supervised by the allergy and immunology service and conducted at the inpatient oncology service with trained nursing staff.

If an HSR developed during desensitization, the infusion was stopped and 50 mg of intravenous diphenhydramine was administered. Oxygen, ranitidine (50 mg intravenously), and methylprednisolone (60 mg intravenously) were added, if necessary, for severe or recurrent reactions. Intramuscular epinephrine was used for grade 3 reactions. Once symptoms resolved, the desensitization was resumed at the previously tolerated step. If a patient developed an HSR and required repeat desensitization with the same drug, the desensitization procedure was modified with the addition of prophylactic medications or additional steps to slow the desensitization.

Data Analysis

The χ^2 , 2-sided Mann-Whitney *U*, and Kruskal-Wallis tests with post hoc Bonferroni correction were used to compare history of atopy, chemotherapy cycle number, HSR severity, and interval from the HSR to first skin test between skin test categories. Logistic regression analysis using history of atopy, chemotherapy cycle number, HSR severity grade, and symptoms of initial immediate HSR to predict skin test category was planned a priori. Statistical analysis was performed with SPSS 18.0 (SPSS, Inc, Chicago, Illinois).

Results

Patient Characteristics

A total of 144 patients (92 treated with carboplatin and 52 treated with oxaliplatin) were referred to the allergy and immunology service (Fig 1). Two patients with a history of oxaliplatin-induced HSR underwent emergency desensitization without undergoing further skin testing and were excluded. Ninety-two patients with carboplatin-induced HSR and 50 with oxaliplatin-induced HSR were included in the study. The mean age $\pm$ SD was 58.1 $\pm$ 9.3 years (Table 1). Of the 142 patients, 130 (91.5%) were white, 120 (84.5%) were women, and 91 (64.1%) had a history of atopy. The most frequent malignancy in carboplatin-treated patients was ovarian cancer (n = 87, 94.6%) and that in oxaliplatin-treated patients was colorectal cancer (n = 48, 96%). The HSRs occurred after a median of 9 cycles (interquartile range [IQR] 8–11) of carboplatin and 8 cycles (IQR 5–13) of oxaliplatin. History of atopy and chemotherapy cycle were not associated with the skin test result for carboplatin or oxaliplatin.

Table 2

Symptoms of initial hypersensitivity reaction to carboplatin and oxaliplatin

	Carboplatin (n = 92)	Oxaliplatin (n = 50)	Total (N = 142)
Systemic			
Fever	0 (0.0%)	1 (2.0%)	3 (2.1%)
Rigors	2 (2.2%)	4 (8.0%)	6 (4.2%)
Generalized weakness or malaise	1 (1.1%)	1 (2.0%)	2 (1.4%)
Chills	0 (0.0%)	5 (10.0%)	5 (3.5%)
Cutaneous			
Pruritus	47 (51.1%)	22 (44.0%)	69 (48.6%)
Erythema or flushing	52 (56.5%)	26 (52.0%)	78 (54.9%)
Urticaria	14 (15.2%)	7 (14.0%)	21 (14.8%)
Diaphoresis	4 (4.3%)	2 (4.0%)	6 (4.2%)
Angioedema	3 (3.3%)	4 (8.0%)	7 (4.9%)
Oropharynx			
Oral or perioral tingling or pruritus	3 (3.3%)	3 (6.0%)	6 (4.2%)
Throat tightness or swelling	5 (5.4%)	7 (14.0%)	12 (8.5%)
Hoarseness	2 (2.2%)	1 (2.0%)	3 (2.1%)
Throat pain	3 (3.3%)	0 (0.0%)	3 (2.1%)
Throat tingling or pruritus	6 (6.5%)	1 (2.0%)	7 (4.9%)
Cardiovascular			
Lightheadedness	3 (3.3%)	1 (2.0%)	4 (2.8%)
Chest pain	6 (6.5%)	2 (4.0%)	8 (5.6%)
Tachycardia	4 (4.3%)	7 (14.0%)	11 (7.7%)
Change in blood pressure	16 (17.4%)	12 (24.0%)	28 (19.7%)
Pulmonary			
Chest tightness	8 (8.7%)	5 (10.0%)	13 (9.2%)
Dyspnea	14 (15.2%)	9 (18.0%)	23 (16.2%)
Cough	3 (3.3%)	5 (10.0%)	8 (5.6%)
Wheeze	3 (3.3%)	3 (6.0%)	6 (4.2%)
Rhinitis	9 (9.8%)	1 (2.0%)	10 (7.0%)
Hypoxemia	2 (2.2%)	5 (10.0%)	7 (4.9%)
Gastrointestinal			
Nausea or vomiting	18 (19.6%)	11 (22.0%)	29 (20.4%)
Esophageal spasm	1 (1.1%)	0 (0.0%)	1 (0.7%)
Abdominal pain	9 (9.8%)	2 (4.0%)	11 (7.7%)
Diarrhea	1 (1.1%)	5 (10.0%)	6 (4.2%)
Genitourinary			
Vaginal pain	0 (0.0%)	1 (2.0%)	1 (0.7%)
Musculoskeletal			
Musculoskeletal pain	2 (2.2%)	2 (4.0%)	4 (2.8%)
Neurologic			
Paresthesias	4 (4.3%)	2 (4.0%)	6 (4.2%)
Tinnitus	1 (1.1%)	0 (0.0%)	1 (0.7%)
Visual changes	1 (1.1%)	4 (8.0%)	5 (3.5%)
Dizziness	1 (1.1%)	1 (2.0%)	2 (1.4%)
Altered mental status	1 (1.1%)	1 (2.0%)	2 (1.4%)
Facial paralysis	1 (1.1%)	0 (0.0%)	1 (0.7%)
Headache	4 (4.3%)	0 (0.0%)	4 (2.8%)
Dysarthria	1 (1.1%)	0 (0.0%)	1 (0.7%)
Seizure	0 (0.0%)	1 (2.0%)	1 (0.7%)
Hematologic			
Thrombocytopenia	0 (0.0%)	1 (2.0%)	1 (0.7%)

Symptoms and Severity of Initial HSR

For the initial HSR to carboplatin, erythema or flushing (n = 52, 56.5%) was the most frequent symptom, followed by pruritus (n = 47, 51.1%), nausea or vomiting (n = 18, 19.6%), and a change in blood pressure (n = 16, 17.4%; Table 2). Median initial HSR severity grade was 2 (IQR 1–3). Carboplatin-treated patients with positive skin test results, including those with positive and converted results, had more severe initial HSRs (3, IQR 2–3) than those with negative results (2, IQR 1–3, $P = .029$), and a change in blood pressure during initial HSR was associated with a positive skin test result ($P = .015$).

For the initial HSR to oxaliplatin, erythema or flushing (n = 26, 52%) was the most frequent symptom, followed by pruritus (n = 22, 44%), a change in blood pressure (n = 12, 24%), and nausea or vomiting (n = 11, 22%; Table 2). Median initial HSR severity grade was 3 (IQR 2–3). Severity of the initial HSR did not differ between skin test results for oxaliplatin ($P = .578$), and erythema or flushing during the initial HSR was associated with a positive skin test result ($P = .003$).

Carboplatin Risk-Stratification Protocol

Of the 92 carboplatin-treated patients, 32 (34.8%) had positive and 60 (65.2%) had negative reactions at the first skin test (Fig 1). With repeat skin testing, 22 patients (23.9%) showed conversion from negative to positive reactions, and 38 patients (41.3%) still showed negative reactions. Fourteen (63.6%) of those with conversion showed a conversion to a positive reaction at the second skin test, and 6 patients (27.3%) showed a conversion to a positive reactions at the third skin test. Two patients continued to receive skin testing outside the standard protocol owing to symptoms of HSR during desensitizations despite 3 negative skin test results, and they subsequently showed a conversion to a positive skin test reaction. The first patient developed flushing during the third desensitization and showed a conversion to a positive skin test reaction at the fourth skin test. The second patient had recurrent pruritus during desensitizations and showed conversion to a positive skin test reaction at the fifth skin test. Five patients with conversion had HSRs during the desensitization immediately before their conversion. Four of the HSRs were grade 1, and 1 was grade 3. All were safely managed with antihistamines alone.

Of the 38 patients with negative skin test reactions, 16 (42.1%) did not complete 3 skin tests with intervening desensitizations owing to the completion of the chemotherapy regimen, treatment change, or death. Twenty-two patients (57.9%) had 3 negative skin test results and required additional carboplatin treatment. Seventeen (77.3%) of the 22 patients continued their carboplatin treatment regimens through 59 outpatient infusions without complications. The median number of outpatient infusions was 2 (IQR 1–5) during the study period.

Three (13.6%) of the 22 patients who continued their carboplatin treatments through outpatient infusions developed HSRs during their first infusion that resolved with antihistamine treatment alone. The first patient had a grade 3 reaction with rhinitis, oral pruritus, and abdominal pain. The second patient had a grade 1 reaction with hand erythema and pruritus, and the third patient had a grade 1 reaction with facial flushing. All 3 patients safely returned to inpatient desensitizations for further carboplatin treatments. Two (9.1%) of the 22 patients who qualified for outpatient carboplatin infusions without desensitizations were not referred to outpatient infusions owing to severe adverse reactions during desensitizations, including anaphylaxis.

Oxaliplatin Risk-Stratification Protocol

Of the 50 oxaliplatin-treated patients, 22 (44%) had a positive reaction and 28 (56%) had a negative reaction at the first skin test (Fig 1). Three patients (6%) showed conversion from a negative to a positive reaction with repeat skin testing, and 25 (50%) patients still showed a negative reaction. All 3 patients with converted reactions showed a positive reaction at the second skin test. None of these patients with conversion had HSRs during desensitizations before their conversion.

Of the 25 patients with negative skin test results, 7 (28%) left the protocol owing to completion of chemotherapy regimen, treatment change, or death. Eighteen patients (72%) had 3 negative skin test results and required additional oxaliplatin treatment. Sixteen (88.9%) of the 18 patients continued their oxaliplatin treatment regimens through 95 outpatient infusions at the authors' institution without complications. The median number of outpatient infusions was 5 (IQR 1–8) at the authors' institution during the study period. Three (18.8%) of the 16 patients started outpatient oxaliplatin infusions at the authors' institution and transferred to their local hospitals and oncologists for additional cycles of therapy.

Two (11.1%) of the 18 patients who qualified for outpatient oxaliplatin infusions without desensitizations were not referred to outpatient infusions owing to a history of severe adverse reactions,

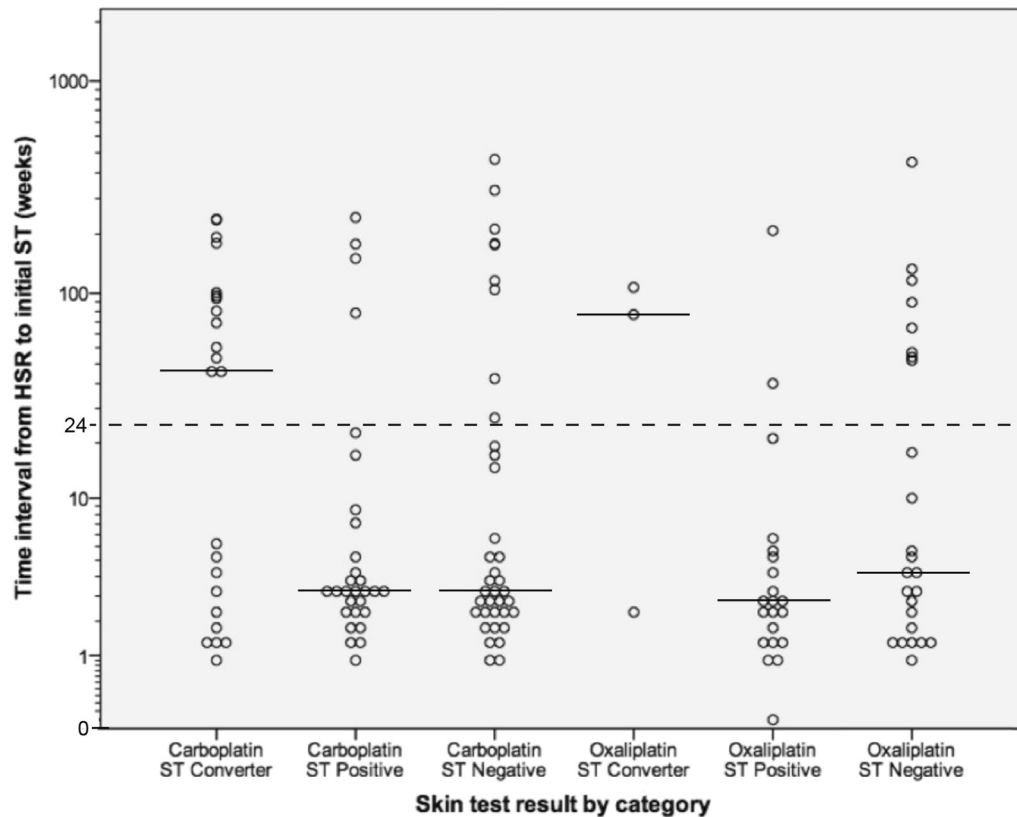


Figure 2. Median interval in weeks (solid line) from initial hypersensitivity reaction (HSR) to skin testing (ST) for carboplatin and oxaliplatin by skin test result.

unlikely mediated by IgE, during desensitizations. One patient had immune-mediated thrombocytopenia, and oxaliplatin treatment was discontinued. The second patient had recurrent dyspnea and hypoxemia and received modified desensitizations safely.

Interval from Initial HSR to First Skin Test

The median interval from the initial HSR to the first skin test evaluation was 3.5 weeks (IQR 2.2–42.2) for carboplatin-treated patients and 3 weeks (IQR 1.7–20) for oxaliplatin-treated patients. Three carboplatin-treated patients and 1 oxaliplatin-treated patient did not undergo skin testing until after their first desensitization and were excluded specifically from the interval from the initial HSR to the first skin test analysis. For carboplatin- and oxaliplatin-treated patients, those with conversion were more likely to have an interval of at least 6 months elapse from the initial HSR to the first skin test (carboplatin, $P = .002$; oxaliplatin, $P = .045$). In carboplatin-treated patients, the median time from the HSR to the first skin test was 42.2 weeks (IQR 2.2–97) for those with conversion, 3.0 weeks (IQR 2.2–8.3) for those with positive skin test reactions, and 3.0 weeks (IQR 2.2–21.7) for those with negative reactions (Fig 2). In oxaliplatin-treated patients, the median time from the HSR to the first skin test was 79.1 weeks (IQR 40.9–93) for those with conversion, 2.6 weeks (IQR 1.3–5.2) for those with positive reactions, and 3.9 weeks (1.7–50.9) for those with negative reactions.

Four carboplatin-treated patients with conversion and 1 oxaliplatin-treated with conversion had a longer than 6-month delay from the initial HSR to the first skin test evaluation. Two carboplatin-treated patients were in cancer remission after their initial HSR and had recurrence of malignancy necessitating further carboplatin treatments. Another 2 carboplatin-treated patients and 1 oxaliplatin-treated patient were switched off platinum-based

chemotherapy after the initial HSR but had progression of cancer and were restarting platinum-based chemotherapy.

Discussion

The authors previously developed a novel risk-stratification protocol and found it safe and effective in managing a small number of patients with carboplatin-induced HSR.¹⁰ In the present study, this protocol was used in a large number of patients with carboplatin-induced HSR and patients with oxaliplatin-induced HSR. The protocol not only was safe and effective in distinguishing allergic from nonallergic patients but also found high rates of nonallergic patients after presumed HSR and avoided 154 unnecessary carboplatin and oxaliplatin desensitizations at the authors' institution. Patients who were initially referred to the allergy and immunology service at Massachusetts General Hospital for presumed carboplatin- or oxaliplatin-induced HSR but determined not to be allergic could return to their referring local physicians for continued outpatient infusions without desensitization. The authors further confirmed their previous finding that patients who presented at least 6 months from the initial HSR for skin test evaluation were at greater risk of having an initial false-negative skin test result.¹⁰ Therefore, repeat skin testing is even more important in patients with delayed initial skin test evaluation.

The authors identified a larger than expected proportion of patients with a history of presumed HSR to not be allergic to their respective chemotherapies (18.5% for carboplatin and 32% for oxaliplatin) and who could tolerate outpatient infusions without desensitizations. A small cohort of patients from the initial publication of the risk-stratification protocol by Patil et al¹⁰ was included in this retrospective review to present a comprehensive examination of all cases over a 5-year period and to track cases over time to determine the validity of the risk-stratification protocol. Most

patients in the study maintained their negative skin test reaction status, but there were high attrition rates owing to completion of chemotherapy treatment or change in chemotherapy regimen. Therefore, the percentage of nonallergic patients who could tolerate infusions without desensitizations were likely underestimated. In the present study, 17 patients safely completed 59 outpatient carboplatin infusions without desensitizations, and 16 patients safely completed 95 outpatient oxaliplatin infusions without desensitizations. The reported numbers of desensitizations saved also were underestimated, because they included only outpatient infusions at the authors' institution and did not include outpatient chemotherapy infusions completed at local hospitals or chemotherapy infusions completed after the study period for this patient cohort.

The accurate diagnosis of drug allergy is associated with fewer hospital days and decreased health care expenditures.¹³ Sparse data exist on the cost effectiveness of drug desensitization because cost-effectiveness analysis is used to aid decision making in the face of meaningful tradeoffs, and there are often few alternatives to desensitization.¹⁴ Currently, there is no standard protocol to manage patients with a history of carboplatin- or oxaliplatin-induced HSR. The present risk-stratification protocol can safely provide the accurate diagnosis of drug allergy for patients with presumed carboplatin- or oxaliplatin-induced HSR. Patients who were diagnosed as nonallergic not only could avoid desensitizations with less time and resources but also return to local health care providers for infusions with less travel and improved quality of life. The risk-stratification protocol balances safety with improved quality of life and avoidance of resource-intensive desensitizations by better defining a clinical population in need of special services.

The present data further demonstrated that patients with a history of carboplatin- or oxaliplatin-induced HSR who present at least 6 months after initial the HSR for skin test evaluation are at greater risk of a false-negative skin test result. The interval from the initial HSR to the skin test evaluation also was shown to be a significant factor in a prior study in carboplatin-treated patients by Hesterberg et al⁹ in a nonoverlapping cohort. The authors hypothesize that in patients with false-negative skin test results, the hypersensitivity state declines over time to a level lower than the threshold detectable by skin testing. Patients become resensitized through their first desensitization and show a conversion to a positive reaction at their second skin test. One-time skin testing has high false-negative rates but has remained the diagnostic standard for carboplatin- and oxaliplatin-induced HSR.^{5–8} The present study demonstrated that repeat skin testing with intervening desensitizations can detect false-negative skin test results and is superior to 1-time skin testing.

Patients with carboplatin- and oxaliplatin-induced HSR presented with predominantly cutaneous IgE-mediated symptoms, although noncutaneous symptoms involving the gastrointestinal and cardiovascular systems also were common. Two patients with oxaliplatin-induced HSR had non-IgE-mediated symptoms that were safely detected and managed by the risk-stratification protocol. One patient had type II immune-mediated thrombocytopenia, and oxaliplatin was stopped, with the reversal of HSR. A second patient had recurrent dyspnea and hypoxemia and was continued on desensitizations successfully. Oxaliplatin has been hypothesized to directly activate T cells as an antigen and trigger cytokine release, and premedication with steroids has been associated with symptom regression and decreased cytokine levels.¹⁵ The symptoms described in this report were similar to those in prior studies.^{1–4,9,16}

Two symptoms were associated with positive skin test results—change in blood pressure in patients with presumed

carboplatin-induced HSR and erythema or flushing in patients with presumed oxaliplatin-induced HSR. However, these symptoms are commonly reported with carboplatin- and oxaliplatin-induced HSRs and using them to differentiate or risk stratify patients at presentation would be difficult.^{1–3,17} Few other studies have investigated clinical predictors of hypersensitivity to carboplatin and oxaliplatin, with variable results. History of atopy and treatment as salvage therapy have been reported as positive clinical predictors.^{18,19} The present study did not find an association with history of atopy, and treatment as salvage therapy was not examined. Without consistent clinical predictors of HSR, the importance of systematically evaluating each patient using a diagnostic and management framework using the risk-stratification protocol becomes even more paramount.

Prior investigators have rechallenged patients with a history of carboplatin- or oxaliplatin-induced HSR, but the authors are the first to focus on diagnosis and risk stratification. Rechallenging patients without a diagnostic framework can lead to unpredictable and suboptimal outcomes. Polyzos et al¹⁷ reported on a series of 32 patients with carboplatin-induced HSR and successfully rechallenged 20 patients with mild HSR using premedication, but carboplatin needed to be discontinued in 12 patients with severe initial HSR. Siu et al²⁰ rechallenged 14 patients with mild HSR to oxaliplatin, but 4 patients developed a HSR on re-exposure, with 2 patients developing even more severe reactions than their initial HSRs. The present risk-stratification protocol mitigates the risk of an adverse event occurring during outpatient infusion rechallenge by monitoring serial skin test reactions and desensitizations before rechallenge. Two carboplatin-treated patients received additional skin tests outside the standard protocol owing to symptoms of HSR during desensitizations despite 3 prior negative skin test reactions. These patients were assessed to be at greater risk owing to a history of adverse reactions during desensitizations and were clinically judged by the allergy and immunology service to need further monitoring by extension of the risk-stratification protocol.

In the present study, only 3 patients with carboplatin-induced HSR maintained a negative skin test reaction without symptoms during the risk-stratification protocol until exposed to their first outpatient infusions. All 3 patients had non-life-threatening HSRs that were safely managed with antihistamine treatment. However, this is a reminder that patients can become allergic and develop HSRs after being deemed initially not allergic, likely related to continued repeat exposure to the drug. Patients with high-risk features such as anaphylaxis during desensitization and non-IgE-mediated HSRs were detected early and prevented from referral to outpatient infusions even with negative repeat skin test results.

This study had a few limitations. This was a single-center study at a tertiary care center with a large population of patients with ovarian cancer. There were high attrition rates for the carboplatin- and oxaliplatin-treated patients with negative skin test reactions owing to completion of the chemotherapy regimen or a change in treatment regimen. This limited the number of patients who qualified for outpatient infusions. Despite this limitation, a significant percentage of patients in the risk-stratification protocol were found not to be allergic and a large number of desensitizations were prevented despite presumed HSR. Wong et al²¹ reviewed the presentation and management of HSRs using 3 desensitization protocols in oxaliplatin-treated patients at Massachusetts General Hospital from July 2007 to June 2012, with some overlap with the present cohort. Although there is some overlap in the oxaliplatin-treated patient population, the present study examined a very different question and aspect of the population, specifically the outcomes of the risk-stratification protocol.

In conclusion, some patients with a history of a presumed carboplatin- and oxaliplatin-induced HSR are not allergic to the drug.

This risk-stratification protocol can safely identify nonallergic patients, allowing them to return to the local outpatient setting for further treatment without desensitization. The risk-stratification protocol requires the expertise of an allergist and immunologist with repeat skin testing but improves overall quality of life with decreased usage of health care resources.

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