

Platinum Chemotherapy Hypersensitivity

Prevalence and Management



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KEYWORDS

- Platinum agent • Carboplatin • Cisplatin • Oxaliplatin • Chemotherapy allergy
- Chemotherapy hypersensitivity • Chemotherapy desensitization

KEY POINTS

- Hypersensitivity reactions to platinum agents are common. For carboplatin and cisplatin, the incidence of the first hypersensitivity reaction is typically clustered around the second and third reexposure during the second line of therapy (eighth and ninth courses overall). For oxaliplatin, the first hypersensitivity reactions occurred throughout the treatment course.
- Skin testing is helpful for risk stratification to choose desensitization protocols and assess risk for breakthrough hypersensitivity reactions during the desensitization.
- A risk-stratification protocol using 3 serial skin tests has been shown to be safe and effective in managing patients with a history of hypersensitivity reactions to platinum-based chemotherapeutic agents.
- The most widely accepted desensitization protocols for platinum agents are the 8-step and 12-step (or modified 13-step) protocols.
- With appropriate clinical history and evaluation, patients can receive first-line chemotherapy treatment safely despite a history of hypersensitivity reactions to platinum-based chemotherapeutic agents.

INTRODUCTION

Cancer is a leading cause of death worldwide and although the incidence continues to rise, cancer mortality has declined over the past decade in large part due to more efficacious chemotherapeutic regimens.¹ The ability to use first-line chemotherapeutic

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agents in the treatment of patients with cancer is critical to good patient outcomes. However, hypersensitivity reactions (HSRs) have emerged as a significant complication to therapy and an increasing incidence of HSRs to first-line chemotherapeutic agents are limiting their use.

As an example, it is well-described that ovarian cancer is the most fatal gynecologic malignancy.² The standard treatment approach for newly diagnosed ovarian cancer involves multidisciplinary treatment, including surgical cytoreduction followed by a platinum-based therapy.^{3,4} Despite achieving initial complete clinical remission, the vast majority will go on to develop recurrent ovarian cancer.⁵ For women with recurrent ovarian cancer, repeat treatment with carboplatin is the treatment of choice. However, carboplatin retreatment in these patients is associated with a high rate of HSRs ranging from 21% to 47%.^{6–8} Unfortunately, patients with recurrent ovarian cancer presenting with drug HSRs are frequently and irreversibly labeled as allergic, preventing the use of first-line therapies. The lack of understanding the standard approach to management after an initial HSR leads to suboptimal outcomes, including needless avoidance of first-line chemotherapeutic agents in patients who could tolerate rechallenge without desensitization or intentional rechallenge with a drug that may cause a recurrent and severe HSR. However, there is significant research and experience showing that an accurate clinical history and proper management can improve patient outcomes despite a reported HSR.

This review focuses on HSRs induced by platinum-based chemotherapeutic agents. We review the epidemiology, clinical presentation, and management of HSRs to platinum-based chemotherapeutic agents.

BACKGROUND AND EPIDEMIOLOGY

Carboplatin and cisplatin are platinum-based chemotherapeutic agents commonly used for ovarian, lung, and head and neck cancers. Carboplatin and cisplatin are classified as DNA alkylating agents. Carboplatin was introduced in the late 1980s and has since gained popularity in clinical treatment due to its vastly reduced side effects compared with its parent compound cisplatin. HSRs are rarely reported during the initial treatment and the frequency of HSRs appears directly related to the number of exposures. HSRs are typically noted after multiple cycles have been administered and occur most frequently with the second line of treatment.

With carboplatin, the incidence increases from 1% in individuals who have received 6 or fewer carboplatin infusions to 27% in those who received 7 or more, and up to 46% in patients who have received more than 15 infusions.^{6,9} The peak incidence of HSRs occurs with the eighth or ninth exposure, which generally corresponds to the second or third cycle of retreatment after recurrence of malignancy.⁹ It is important to note that women with inherited mutations in BRCA 1 or 2 appear to have a higher risk for carboplatin infusion reactions and reactions occur at a lower cumulative exposure.^{10,11} Patients with a BRCA 1 or 2 mutation are also at higher risk for reacting during desensitization.¹¹

Cisplatin was the first of the platinum drugs to be used but is often limited by side effects, including neurotoxicity, nephrotoxicity, and ototoxicity. These side effects are less common with equal efficacy, making carboplatin a better treatment option for most patients with cancer requiring platinum-based therapy. The incidence of cisplatin hypersensitivity exhibits similar characteristics to those observed with carboplatin. One of the first publications on cisplatin as a treatment for lung cancer described that, among patients receiving 6 or more cycles of combination chemotherapy, 5 of 21 patients experienced “anaphylaxis.”¹² In general, the frequency of

cisplatin HSRs ranges from 5% to 20% and increases with concomitant radiation therapy.¹³

Oxaliplatin is another platinum-based chemotherapy drug in the same family as carboplatin and cisplatin and is similarly a DNA alkylating agent. It is typically administered in combination with other agents for the treatment of colorectal cancer. Colorectal cancer is the third-leading cause of cancer death in the United States. Initial reports of HSRs to oxaliplatin were low, but more recent data suggest the incidence of HSRs to oxaliplatin is similar to that of the earlier-generation platinum agents. This rising incidence of HSRs to oxaliplatin is likely the result of increasing clinical use. The reported incidence of HSRs associated with oxaliplatin in patients with colorectal cancer is approximately 12%, with 1% to 2% of patients developing moderate to severe reactions.¹⁴

MECHANISMS AND CLINICAL PRESENTATION

HSRs to platinum agents are likely primarily mast cell mediated, although the exact mechanism remains unclear. HSRs to platinum agents are thought to be primarily immunoglobulin (Ig)E-mediated, because a period of sensitization and/or re-sensitization is required, skin tests are often positive, skin test reactivity correlates with the risk of reaction during desensitization, and skin test conversion from negative to positive is seen following reexposure and after developing a reaction.^{15–19} A different mechanism may be responsible for a subgroup that remains skin test negative despite repeat testing, although mechanistic studies are needed to investigate this hypothesis.

IgE-mediated mechanisms were first observed in workers who were repeatedly exposed to platinum salts. Workers sensitized to platinum agents developed sinopulmonary symptoms (rhinitis, conjunctivitis, bronchospasm) when challenged with platinum-containing solutions.²⁰ IgE-mediated mechanisms were also supported by the fact that skin reactivity can be passively transferred via serum of sensitized workers.²¹ Specific IgE has been identified in patients who experienced HSRs to platinum agents (this is discussed further in the section on diagnostic testing).^{22–24}

It has been observed that approximately half of HSRs due to carboplatin present with moderately severe symptoms, including diffuse erythroderma, wheezing, facial swelling, nausea and/or vomiting, diarrhea, dyspnea, and hypotension.^{9,19} The distribution of clinical characteristics of HSRs to carboplatin and oxaliplatin observed in our original studies are summarized in [Table 1](#).^{16,18}

Delayed HSRs that are likely due to T-cell-mediated mechanisms may also occur after platinum agent administration.^{25,26} These HSRs range from mild to severe cutaneous manifestations, with mild reactions being more common, and severe cutaneous reactions including desquamation.²⁶

DIAGNOSTIC TESTING

Carboplatin Skin Testing

Carboplatin skin testing was first developed in the 1990s. Initial studies used 0.05 to 0.1 mg/mL of carboplatin for epicutaneous and intradermal skin testing.^{27–29} Subsequent studies investigating carboplatin skin testing have established a standard concentration of 10 mg/mL for the epicutaneous step followed by increasing stepwise concentrations from 0.2 to 30.0 μ g (0.02–0.04-mL injection of 0.01–1 mg/mL carboplatin) to 20.0 to 300.0 μ g (0.02–0.04-mL injection of 1–10 mg/mL carboplatin) for the intradermal steps.^{15,16,19,25,30–32} At our institution, we perform skin testing at the nonirritating concentrations listed in [Table 2](#).

Table 1 Clinical characteristics of hypersensitivity reactions		
Clinical Characteristics	Carboplatin (n = 38) No. of Patients (%) ¹⁵	Oxaliplatin (n = 48) No. of Patients (%) ¹⁷
Oropharynx	6 (16)	9 (19)
Throat tightness		
Tongue swelling		
Hoarseness		
Cardiovascular	11 (29)	16 (33)
Tachycardia/bradycardia		
Hypertension/hypotension		
Chest pain		
Dizziness		
Light-headed		
Pulmonary	11 (29)	17 (35)
Chest tightness		
Shortness of breath		
Cough		
Nasal symptoms		
Gastrointestinal	14 (37)	14 (29)
Nausea/vomiting/diarrhea		
Abdominal pain		
Genitourinary	2 (5)	0 (0)
Urethral burning		
Musculoskeletal	0 (0)	3 (6)
Arthralgia		
Spasm		
Pain		
Cutaneous	30 (79)	38 (78)
Erythema/flushing pruritus		
Urticarial		
Palmar erythema		
Delayed cutaneous	3 (8)	1 (2)
Rash		
Erythema/flushing		
Pruritus		
Neurologic	0 (0)	6 (13)
Tingling		
Dizziness		
Tunnel vision		
Jittery		
Seizure		
Difficulty focusing ^a		
Systemic	0 (0)	9 (19)
Fever		
Chills/rigors		
Somnolence		
Drug-induced immune-mediated	0 (0)	1 (6) ^b
Thrombocytopenia (DITP)		
Hemolytic anemia (DIHA)		

^a One patient had tunnel vision, jitters, seizure, difficulty focusing, and tingling.
^b One additional patient developed DITP and DIHA after undergoing additional desensitization among the original 48 patients with oxaliplatin HSRs.

Table 2
Nonirritating concentrations for platinum agent skin testing

Platinum Agent	Skin Prick Test Dilutions, mg/mL	Intradermal Test Dilutions, mg/mL
Carboplatin	10	0.1
		1
		5 ^a
Oxaliplatin	5	0.05
		0.5
		5
Cisplatin	1	0.01
		0.1
		1

Abbreviation: ID, intradermal.

^a Higher 10 mg/mL ID concentration has been reported to cause local skin necrosis, and is therefore not used.

Epicutaneous and intradermal steps are both important for carboplatin skin testing. Performing the epicutaneous step can decrease the risk of inducing HSRs with skin testing, whereas the intradermal step is needed to achieve adequate sensitivity, as 86.4% of positive skin testing is elicited during the intradermal step.³³ The final concentration for intradermal skin testing also affects skin-testing results. Among patients who had a history of HSR, using a final step of 0.02 to 0.03 mL of a 10-mg/mL dilution resulted in positive skin testing for 81% to 88% of patients,^{19,31} whereas using 0.02 mL of 1 to 5 mg/mL dilutions resulted in positive skin testing for 41% to 75% of patients (83% among patients who experienced recent HSRs within the past 3 months).^{15,16,22,25} However, skin necrosis has been reported with the higher concentration of 10 mg/mL.¹⁶ The rate of positive skin testing also may depend on the severity of the HSR. A cohort of 23 patients with moderate to severe carboplatin-induced HSRs had a 100% positive skin-testing rate.³²

The length of time between last exposure to carboplatin (typically when the carboplatin-induced HSR occurred) and initial skin testing must be taken into consideration when interpreting carboplatin skin testing.

Data from hymenoptera venom skin testing suggest that the risk for false-negative skin testing is higher due to “anergy” during the first 4 to 6 weeks following a systemic reaction.³⁴ We have similarly seen a small number of patients who experienced HSRs less than 6 weeks before the initial skin test, who initially had negative skin testing that later converted to positive when the skin testing was repeated outside the 6-week window (unpublished observation). Therefore, if skin testing performed during the first 4 to 6 weeks following carboplatin-induced HSR is negative, it is typically repeated outside of the 4-week to 6-week window.

We have found that a longer interval of time (ie, >6 months) between carboplatin-induced HSRs and skin testing is associated with a higher frequency of an initial false-negative skin test. The frequency of positive skin testing has been shown to be significantly lower among patients who experienced recent HSRs within the past 3 months (83%, 20/24) compared with patients who experienced a remote HSR more than 9 months before (36%, 5/14).¹⁶ Most of the latter group, 71% (5/7) converted to positive skin testing on retesting after 1 reexposure to carboplatin via desensitization.¹⁶ Two other studies have also shown that patients who converted from negative to positive skin testing after reexposure to carboplatin via desensitization were more likely to have a time interval of at least 6 months between the carboplatin-induced HSR and initial skin testing compared with patients with

persistently negative skin testing.^{15,17} In our experience, 3 repeat skin tests before each desensitization was adequate for risk stratification for patients who undergo initial skin testing more than 6 months after the initial carboplatin-induced HSR.^{15–18,33}

Predictive values of carboplatin skin testing are discussed further in the “Risk Stratification and Desensitization” section.

Cisplatin Skin Testing

Nonirritating concentrations have been reported for both epicutaneous (highest 10 mg/mL) and intradermal skin-testing steps (highest 1 mg/mL).^{19,25,35}

Predictive values for skin testing have been the least studied for cisplatin out of the 3 platinum agents. In 1 report, 2 patients with cisplatin-induced HSR had positive skin testing and subsequently received cisplatin via desensitization.¹⁹ In another report, of 2 patients with cisplatin-induced HSRs, 1 patient had positive skin testing and subsequently did not receive any platinum agent, and 1 patient had negative skin testing and subsequently tolerated carboplatin without reaction.²⁵

Oxaliplatin Skin Testing

Skin testing has been performed at 0.01 to 5 mg/mL for the epicutaneous step, 0.001 to 0.05 mg/mL for the initial intradermal step, and 0.5 to 5 mg/mL for the final intradermal step.^{18,24,25,36,37} At our institution, we perform skin testing at the nonirritating concentrations listed in [Table 2](#).

Skin testing following oxaliplatin-induced HSR has a reported 26% to 100% positive rate.^{18,24,25,36,37} Skin testing in patients who tolerated infusions of oxaliplatin and in oxaliplatin-naïve patients has a reported 100% negative rate. Pagani and colleagues³⁷ reported that oxaliplatin skin testing was negative for 100% (15/15) of patients never exposed to platinum agents and 100% (18/18) of patients who had received oxaliplatin therapy without reactions.

The negative predictive value of oxaliplatin skin testing remains unclear. Although a prospective study of 101 patients reported a 5% false-negative rate,³⁸ another study reported 70% (7/10) of patients with negative skin testing who subsequently received oxaliplatin via graded challenge had a positive reaction.²⁴

Therefore, as with carboplatin skin testing, the main utility of oxaliplatin skin testing appears to be risk stratification of patients who have experienced oxaliplatin-induced HSRs (see section on risk stratification).

Specific IgE

Specific IgE to platinum agents has been investigated as a diagnostic tool.

In a report of only 3 patients with carboplatin-induced HSR, 100% (3/3) had specific IgE to carboplatin (Carbo-sIgE) ≥ 0.35 kU/L and 33% (1/3) had specific IgE to cisplatin (Cis-sIgE) ≥ 0.35 kU/L. Interestingly, the 2 patients with undetectable Cis-sIgE had breakthrough HSRs during the initial carboplatin desensitizations that were mild enough to allow completion of the desensitization protocol, and tolerated carboplatin subsequent desensitizations without breakthrough HSRs. The 1 patient with Cis-sIgE elevated at 4.2 kU/L experienced a severe breakthrough HSR (anaphylaxis) during the initial carboplatin desensitization and subsequent administration of platinum agents was deferred.²²

In a much larger study, Caiado and colleagues,²³ measured Carbo-sIgE and specific IgE to oxaliplatin (Oxali-sIgE) in 24 patients who had experienced HSRs due to platinum agents (carboplatin, 12; oxaliplatin 12). Cis-sIgE was measured in 21 of these patients. Of the 12 patients who had experienced HSRs due to carboplatin, 59% (7/12) had positive Carbo-sIgE, 17% (2/12) also had positive Cis-sIgE, and all had negative

Oxali-slgE. Of the 12 patients with oxaliplatin-induced HSRs, 75% (9/12) had positive Oxali-slgE, 67% (8/12) had positive Carbo-slgE and Cis-slgE. Carbo-slgE and Oxali-slgE were measured in 17 control patients who had been exposed to platinum agents and did not experience HSRs (carboplatin, 5; oxaliplatin, 12). All 5 carboplatin-exposed, nonreactive controls had negative Carbo-slgE and Oxali-slgE. Of the 12 oxaliplatin-exposed, nonreactive controls, 25% (3/12) had positive Carbo-slgE and 2 had positive Oxali-slgE. Based on these results, the investigators concluded that Carbo-slgE likely had higher specificity and lower sensitivity compared with Oxali-slgE, and that oxaliplatin was more immunogenic (given the positive Carbo-slgE and Cis-slgE observed in patients exposed only to oxaliplatin).

In a separate study, Oxali-slgE was reported to have a sensitivity of 38% to 54% depending on the cutoff (0.10–0.35 kU/L).²⁴

Basophil Activation Test

The basophil activation test, or BAT, has been evaluated as a diagnostic test for platinum-induced HSRs. Basophil CD63 and CD203c expression were compared between patients with history of carboplatin-induced HSRs ($n = 12$) and oxaliplatin-induced HSRs ($n = 3$), control patients who had previously tolerated carboplatin ($n = 6$), and control patients who had never been exposed to platinum agents ($n = 6$). BAT was positive for 67% (8/12) of patients with carboplatin-induced HSRs and 100% (3/3) of patients with oxaliplatin-induced HSRs. All 15 patients with history of platinum-induced HSRs had positive skin testing results. Patients from both control groups had negative BAT results. Based on these results, the Giavina-Bianchi and colleagues³⁹ calculated that BAT has a sensitivity of 73% and specificity of 100% for platinum-induced HSRs.

The same investigators also correlated BAT with breakthrough reactions during 27 desensitization procedures. Nine patients experienced 13 breakthrough reactions during desensitization, and BAT was positive in 92% (12/13) with increased CD203c expression in 92% (12/13) and increased CD63 expression in 69% (9/13). Although BAT was also positive in 50% (7/14) of desensitization procedures without breakthrough reactions, there was a statistically significant difference in BAT positivity between desensitization procedures with and without breakthrough reactions ($P = .02$). The 13 breakthrough reactions during desensitization ranged in severity from grade 1 ($n = 10$), grade 2 ($n = 2$), to grade 3 ($n = 1$). The grade 2 and 3 breakthrough reactions ($n = 3$) had positive BAT for both markers (100%), suggesting that positive BAT for both activation markers could possibly be a biomarker predictive of higher risk of grade 2 to 3 breakthrough reactions during desensitization.³⁹

RISK STRATIFICATION AND DESENSITIZATION

Carboplatin

Predictive values before hypersensitivity reaction

Carboplatin skin testing has been investigated as a predictive tool for the development of HSRs in patients with recurrent platinum-sensitive gynecologic cancer who required retreatment with carboplatin before HSR.^{30,40,41} The overall frequency of positive skin testing (31%–36%) is similar to the frequency of HSR observed in patients being retreated with carboplatin.³³ Carboplatin skin testing was shown to have a negative predictive value between 81% and 92% and a positive predictive value of 86%.³³ Further studies are needed to investigate the clinical utility of skin testing before retreatment.

Predictive values after hypersensitivity reaction: utilization for risk stratification with desensitization

The positive predictive value of skin testing after HSR without desensitization is unknown, as carboplatin rechallenge without desensitization in patients with positive skin testing has not been reported in the literature. The negative predictive value of skin testing after HSR is also unclear, although data from 4 patients suggest that the negative predictive value is low. These 4 patients had negative skin testing after carboplatin-induced HSR but developed mild HSRs when they received carboplatin without desensitization.¹⁹

Skin testing appears to have the most utility in risk stratification of patients who have experienced carboplatin-induced HSR. Positive skin testing indicates a risk for additional HSRs during reexposure even if desensitization is used (37% of patients and 17% of desensitizations).¹⁶ This is true for both patients with initial positive skin testing and patients who convert from negative to positive skin testing after reexposure. The percentage of desensitizations complicated by HSRs are comparable between patients with initial positive skin testing and patients who convert from negative to positive skin testing after reexposure (58.5% vs 56.1%, $P = 5.87$).¹⁵ Serial negative skin testing can help identify patients who can safely return to receiving carboplatin in the outpatient setting without desensitization. Patients with serial negative skin testing are significantly less likely to have desensitizations complicated by HSRs compared with patients who convert from negative to positive skin testing after reexposure (4.5% vs 56.1%, $P < .001$).¹⁵

A risk-stratification protocol using 3 serial skin tests has been shown to be safe and effective in managing patients with carboplatin-induced HSRs.^{15,17} This protocol safely differentiates allergic from nonallergic patients and helps prevent unnecessary desensitizations.¹⁷

Cisplatin

Multiple studies have shown that desensitization is a safe and effective way to reintroduce cisplatin to patients who have experienced cisplatin-induced HSRs.^{19,42} At our institution, we have been following the same risk-stratification protocol for cisplatin as carboplatin and oxaliplatin with success.

Oxaliplatin

Multiple studies have shown that desensitization is a safe and effective way to reintroduce oxaliplatin to patients who have experienced oxaliplatin-induced HSRs.^{17–19,43}

As with carboplatin skin testing, oxaliplatin skin testing is useful for risk stratification of patients who have experienced oxaliplatin-induced HSRs. We have shown that patients with positive skin testing are more likely to experience HSRs during desensitization compared with patients with negative skin testing. Among the 25 patients who had positive initial skin test, 48% (12/25 patients) developed an HSR during at least 1 of their desensitizations, with 24% (34/144) of the desensitizations complicated by HSRs. In contrast, the respective incidences for patients who were initially skin test negative were 24% (5/21 patients) and 11% (6/54 desensitizations), respectively, despite using a more rapid desensitization protocol. When considering the results of repeat skin testing, a higher percentage of patients had breakthrough reactions if their initial skin testing was positive and remained positive (45%, 10/22) or if their skin testing converted from negative to positive (50%, 1/2), than if their skin testing remained negative (21%, 4/19).¹⁸

As with carboplatin, the timing of skin testing is important in determining the interpretation of the results for risk stratification and management.^{17,18} The risk-stratification

protocol used for carboplatin has been investigated and found to be safe and effective for oxaliplatin as well, and is described in the following section.¹⁷

It has also been found that HSRs are less common when oxaliplatin is administered using a slowed, stepwise infusion (one-fifth of the total dose over 1 hour followed by the remaining four-fifths of the total dose over 6 hours vs the total dose over 2 hours) (3.4% vs 13.6%, $P < .01$).⁴⁴

Desensitization Protocols Based on Risk Stratification

The most widely accepted desensitization protocols for platinum agents are the 8-step and 12-step (or modified 13-step) protocols.^{15–17,19,31,45} The 8-step and modified 13-step protocols are outlined in [Table 3](#).

The choice of protocol for a particular desensitization is based on risk stratification from the skin-testing results. Based on our studies, patients with positive skin testing are considered allergic and are reintroduced to the platinum agent using a 13-step desensitization procedure.^{15,17} The 13-step desensitization procedure is identical to a previously published 12-step procedure with the addition of a 60-mL/h step between steps 11 and 12 in the third bag.⁴⁵ Patients with initial negative skin testing are reintroduced to the platinum agent using an 8-step desensitization procedure,¹⁶ followed by repeat skin testing before each subsequent desensitization. If repeat skin testing is negative, subsequent desensitizations are performed using the 8-step desensitization procedure. After 3 consecutive negative skin tests and 8-step desensitizations tolerated without breakthrough reactions, patients are considered not allergic to the platinum agent and receive subsequent treatments in the outpatient setting at a 50% infusion rate. If skin tests convert from negative to positive, or if an HSR is experienced during an 8-step desensitization, a 12-step desensitization is used for subsequent treatments and skin testing is not repeated.¹⁷

Taking into consideration data regarding skin-testing anergy during the first 4 to 6 weeks after an HSR and data suggesting that most false-negative initial skin testing occurs when the time interval between the initial HSR and the initial skin test is at least 6 months, we have updated the risk-stratification protocol at our institution to risk stratify patients with 1 skin test only if the time interval between the initial HSR and the initial skin test is at least 6 weeks but less than 6 months ([Fig. 1](#)).

Desensitization also has been shown to be effective from both a medical and health care cost perspective. Sloane and colleagues⁴⁶ investigated health care costs and outcomes in carboplatin-allergic patients (patients with a history of carboplatin-induced HSRs) compared with nonallergic control patients (patients who tolerated carboplatin via standard administration). The investigators found that average hospital costs were 31% higher for nonallergic control patients ($n = 186$) than carboplatin-allergic patients ($n = 171$). Desensitization costs were not included in this calculation. The investigators also found that there was a trend toward increased life expectancy in the carboplatin-allergic patients ($n = 155$) with recurrent ovarian cancer who received carboplatin via desensitization compared with nonallergic control patients ($n = 81$) with recurrent ovarian cancer who received carboplatin via standard administration.

Cross-Reactivity Between Platinum Agents

Studies have investigated the use of oxaliplatin and/or cisplatin as alternative agents following carboplatin-induced HSRs.

Studies investigating the use of cisplatin as an alternative agent following carboplatin-induced HSRs suggest that although many carboplatin-allergic patients tolerate cisplatin, there is some degree of potentially fatal cross-reactivity between carboplatin and cisplatin. In 1 study, 100% (19/19) of patients were able to tolerate

Table 3 Desensitization protocols for carboplatin (target dose 297.6 mg)							
13-Step Protocol							
Solution		Concentration, mg/mL			Amount Infused, mL		
1		0.011904			9.375		
2		0.11904			18.75		
3		1.1810256			250		
Step	Solution	Infusion Duration, min	Cumulative Time, min	Infusion Rate, mL/h	Volume Infused per Step, mL	Dose per Step, mg	Cumulative Dose, mg
1	1	15	15	2.5	0.625	0.00744	0.00744
2	1	15	30	5	1.25	0.01488	0.02232
3	1	15	45	10	2.5	0.02976	0.05208
4	1	15	60	20	5	0.05952	0.1116
5	2	15	75	5	1.25	0.1488	0.2604
6	2	15	90	10	2.5	0.2976	0.558
7	2	15	105	20	5	0.5952	1.1532
8	2	15	120	40	10	1.1904	2.3436
9	3	15	135	10	2.5	2.952564	5.296164
0	3	15	150	20	5	5.905128	11.201292
11	3	15	165	40	10	11.810256	23.011548
12	3	15	180	60	15	17.715384	40.726932
13	3	163	343	80	217.5	256.873068	297.6
8-Step Protocol							
Solution		Concentration, mg/mL			Amount Infused, mL		
1		0.011904			18.75		
2		1.1895072			250		
Step	Solution	Infusion Duration, min	Cumulative Time, min	Infusion Rate, mL/h	Volume Infused per Step, mL	Dose per Step, mg	Cumulative Dose, mg
1	1	15	15	5	1.25	0.01488	0.0435
2	1	15	30	10	2.5	0.02976	0.1305
3	1	15	45	20	5	0.05952	0.3045
4	1	15	60	40	10	0.11904	0.6525
5	2	15	75	10	2.5	2.973768	1.516
6	2	15	90	20	5	5.947536	3.2429
7	2	15	105	40	10	11.895072	6.6968
8	2	15	120	80	232.5	276.560424	87

cisplatin after carboplatin-induced HSRs.⁴⁷ In another case series of 6 patients who received cisplatin after developing a carboplatin-induced HSR, 5 patients were able to tolerate cisplatin with premedication, but 1 patient developed a cisplatin-induced HSR that precluded further treatment with cisplatin.⁴⁸ In a case series of 24 patients who received cisplatin without desensitization after experiencing carboplatin-induced HSRs, 6 (24%) developed cisplatin-induced HSRs at some point during cisplatin therapy.⁴⁹ Furthermore, there have been 2 cases reported of patients with

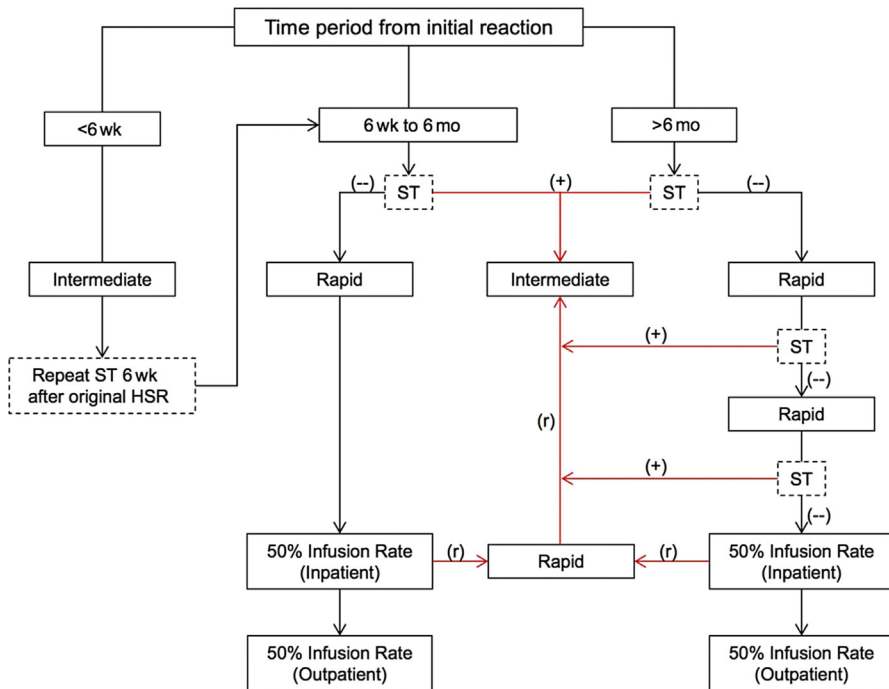


Fig. 1. Risk stratification protocol for platinum agents. (–), negative skin test; (+), positive skin test; Intermediate, 13-step protocol as outlined in [Table 3](#); (r), reaction; Rapid, 8-step protocol as outlined in [Table 3](#); ST, skin test.

carboplatin-induced HSRs who were switched to cisplatin and developed fatal HSRs.^{48,50}

Studies investigating the use of oxaliplatin as an alternative agent following carboplatin-induced HSRs suggest that there is some degree of potentially fatal cross-reactivity between carboplatin and oxaliplatin. In one study, 27 patients received oxaliplatin after experiencing carboplatin-induced HSRs, and 7% (2/27) of patients experienced HSRs to oxaliplatin.⁴⁷ Another study reported that 2 of 11 patients who received oxaliplatin via desensitization after experiencing an HSR during carboplatin desensitization also developed an HSR during oxaliplatin desensitization.⁵¹

The results of specific IgE testing for carboplatin, oxaliplatin, and cisplatin among patients with and without a history of platin-induced HSRs suggest that the risk of patients sensitized to oxaliplatin also being sensitized to carboplatin and cisplatin is higher than the risk of patients sensitized to carboplatin also being sensitized to oxaliplatin. Patients who experienced carboplatin-induced HSRs had positive Carbo-sIgE (59%, 7/12) and negative Oxali-sIgE (100%, 12/12), but patients who experienced oxaliplatin-induced HSRs had not only positive Oxali-sIgE (75%, 9/12), but positive Carbo-sIgE and Cis-sIgE as well (67%, 8/12).²³

Negative skin testing may be helpful in selecting an alternative platinum agent. Leguy-Seguin and colleagues²⁵ found that 100% (8/8) of patients who had negative skin testing to an alternative platinum agent were able to tolerate that alternative platinum agent (4/4 with carboplatin-induced HSRs tolerated cisplatin, 1/1 with a cisplatin-induced HSR tolerated carboplatin, 2/2 with oxaliplatin-induced HSRs

tolerated cisplatin, and 1/1 with an oxaliplatin-induced HSR tolerated carboplatin). Elligers and colleagues⁵² reported 1 patient with an oxaliplatin-induced HSR and negative cisplatin skin testing subsequently tolerated cisplatin. Enrique and colleagues⁵³ reported 2 patients with carboplatin-induced HSRs who had negative cisplatin skin testing and subsequently tolerated cisplatin. Syrigou and colleagues⁵⁴ reported 3 patients with carboplatin-induced HSRs who had negative cisplatin skin testing and subsequently tolerated cisplatin. Taken together, 100% (14/14) of patients who had negative skin testing to an alternative platinum agent were able to tolerate that alternative platinum agent.

SUMMARY

HSRs to platinum agents are common. For carboplatin and cisplatin, the first HSR typically occurs around the second and third re-exposure during the second line of therapy (eighth and ninth courses overall). For oxaliplatin, the first HSR can occur throughout the treatment course. Skin testing helps risk stratify patients to appropriate desensitization protocols and assess risk for breakthrough HSRs during desensitization. Patients with platinum agent hypersensitivity may be managed with a risk-stratification protocol using 3 serial skin tests and desensitization protocols. Patients with a negative result on the initial skin test should be retested if their HSRs were less than 6 weeks or more than 6 months from the initial skin test, as they are at risk for converting to a positive result on subsequent skin testing. Those who convert to a positive skin test result should be treated with a slower desensitization protocol. Those who have 3 consecutive negative skin test results may progress to outpatient slowed infusion protocols. Specific IgE to platinum agents are promising as a diagnostic tool, but remain investigational. In summary, with appropriate clinical history and management, patients can receive first-line chemotherapy treatment safely despite a history of HSRs to platinum-based chemotherapeutic agents.

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