

Skin Testing in the Evaluation and Management of Carboplatin-Related Hypersensitivity Reactions

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Carboplatin-induced hypersensitivity reactions (HSRs) are a frequent occurrence in patients being retreated for malignancy. The most common and severe reactions are thought to be IgE mediated. Currently, skin testing is the only method used clinically to identify individuals sensitized to carboplatin. Despite almost 20 years of clinical use, a standardized approach to skin testing and its use in the management of carboplatin HSRs has not been well established. We review the utility of carboplatin skin testing and discuss factors that influence the interpretation of skin testing results. A risk stratification strategy using skin testing and desensitization to manage patients with carboplatin HSRs is proposed. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:856-62)

Key words: Carboplatin; Hypersensitivity reaction; Allergy; Skin testing; Predictive value; Timing; Management

Carboplatin is a second-generation platinum agent that induces intra/interstrand DNA cross-links resulting in inhibition of cell growth and apoptosis.¹ It has broad spectrum antineoplastic properties that make it an integral component of both first-line and retreatment regimens for multiple malignancies including ovarian, lung, and breast cancer.²⁻⁴ Given its clinical effectiveness and favorable toxicity profile, factors limiting its use would be detrimental for patients with cancer.⁵

One of the primary barriers in the use of carboplatin has been the development of hypersensitivity reactions (HSRs). HSRs can be defined as “objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose that is tolerated by normal individuals.”⁶ The exact mechanism of carboplatin-induced HSRs is unknown, but has been described as primarily type I (IgE-mediated reactions) and to a lesser extent type IV (T-cell-mediated) HSRs. Evidence supporting an IgE-mediated reaction to platinum agents was first documented in refinery workers with repeated exposure to platinum salts. Sensitized workers developed recurrent sinopulmonary symptoms

(rhinitis, conjunctivitis, bronchospasm) when rechallenged with platinum-containing solutions.⁷ Additionally, passive transfer of skin reactivity by serum of sensitized refinery workers was demonstrated in both human and monkeys.⁸ More recently a carboplatin-specific IgE has been identified in patients who have experienced HSRs to platinum agents.^{9,10}

Acute HSRs, which are thought to be primarily IgE mediated, occur in 8%-16% of patients who receive carboplatin in both the adult and pediatric populations.¹¹⁻¹³ The frequency of HSRs appears directly related to the number of carboplatin exposures. The incidence increases from 1% in individuals who have received 6 or fewer carboplatin infusions during initial therapy to 27% in those who received 7 or more, and up to 46% in patients who have received greater than 15 infusions.^{11,14} 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.^{14,15} Approximately 50% of carboplatin-induced HSRs are associated with moderately severe symptoms that consist of diffuse erythroderma, wheezing, facial swelling, nausea and/or vomiting, diarrhea, dyspnea, or hypotension.^{14,16} Type IV HSRs are less common that occur hours to days after carboplatin administration.^{17,18} These reactions typically consist of mild cutaneous manifestations, but may also result in severe reactions including skin desquamation.¹⁸

As most HSRs are thought to be IgE mediated, the identification of patients who have been sensitized to carboplatin is critical to the avoidance of future or recurrent HSRs. Carboplatin skin testing, specific IgE, and basophil activation test have all been assessed as possible methods to identify sensitized individuals, although skin testing is the only method currently used clinically.^{9,10,19,20} Despite multiple studies evaluating the use of skin testing in carboplatin-induced HSRs, there is no standardized strategy on the timing of skin testing and how to best utilize skin testing results to manage patients with carboplatin HSRs.

BACKGROUND OF CARBOPLATIN SKIN TESTING

Skin testing to carboplatin was first established in the 1990s and includes both an epicutaneous and intradermal component. Early studies utilized 0.05 to 0.1 mg/mL of carboplatin for both epicutaneous and intradermal skin testing with various levels of success in detecting patients at risk for further HSRs.²¹⁻²³ Since that time, there has been a trend toward standardization of carboplatin skin testing. An epicutaneous skin test is typically performed utilizing a standard concentration of 10 mg/mL.^{15,16,20,24,25} Intradermal skin testing is more variable with the carboplatin dose increasing stepwise from an initial 0.2-30 µg (0.02-0.04 mL injection of 0.01-1 mg/mL carboplatin) to a top dose of 20-300 µg (0.02-0.04 mL injection of 1-10 mg/mL

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts.
Received for publication June 25, 2014; revised June 18, 2015; accepted for publication July 9, 2015.

Available online October 1, 2015.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2015.07.003>

Abbreviations used

HSR- Hypersensitivity reaction

NPV- Negative predictive value

PPV- Positive predictive value

carboplatin).^{15-17,20,24-26} In most studies, a positive skin test result is defined as either a wheal that is at least 5 mm in largest diameter with a surrounding flare or a wheal with a largest diameter 3-5 mm longer than that of the negative control.^{15-17,20,24-28} Results are interpreted after 15-30 minutes though there are case reports of skin tests that become positive after 24 hours.^{16,27}

Although skin testing is well tolerated by most patients, systemic reactions can be seen in 0.02%-3.6% of skin tests, most commonly with intradermal testing.^{29,30} Most often symptoms are mild including pruritus and local swelling, but in rare cases, skin testing can lead to more severe reactions such as anaphylaxis and death.^{29,31} Literature addressing the adverse reactions specifically associated with carboplatin skin testing is lacking, including long-term toxicity, but no cases of severe reactions or anaphylaxis have been reported. Despite the minimal risk for severe reactions, it is recommended that skin testing be performed under close supervision of a provider who is proficient in the management of allergic reactions and anaphylaxis.

UTILIZATION OF CARBOPLATIN SKIN TESTING BEFORE HSRs

The use of carboplatin skin testing has been evaluated both before and after the development of HSRs to identify individuals who have been sensitized to carboplatin, determine the risk for future or recurrent reactions, and provide an opportunity for modification of further carboplatin treatment.^{15-17,20,24,25,27,28}

Given the significant increase in the incidence of HSRs after the seventh cycle of carboplatin, one strategy has been to determine the predictive value of skin testing to identify individuals who have been sensitized to carboplatin to prevent future HSRs. Three studies assessed skin testing in patients with recurrent platinum-sensitive gynecologic cancer who were retreated with carboplatin before the development of an HSR.^{20,27,28} Two of the studies performed a single intradermal skin test before retreatment with carboplatin, whereas the third study performed an intradermal skin test before the start of every cycle.^{20,27,28} The frequency of carboplatin positive skin tests ranged from 13% to 36% utilizing a single intradermal injection. The positive skin tests were observed between cycles 8 and 10 of carboplatin.

In all 3 studies, patients with a negative skin test were rechallenged to carboplatin without the use of desensitization. HSRs occurred in 8%-19% of patients with subsequent carboplatin infusions, which indicated that the negative predictive value (NPV) of a single intradermal injection before the development of an HSR was between 81% and 92%. The study by Markman et al was the only study to rechallenge patients to carboplatin after a positive skin test without the use of desensitization.²⁰ Six of the seven skin test positive patients rechallenged had an additional HSR, which indicated a positive predictive value (PPV) of 86% (Table I). Eight patients were felt to have borderline positive skin tests (a wheal less than 5 mm in diameter). All 8 patients were safely rechallenged to carboplatin without desensitization with no HSRs noted. Other than the 7

patients directly rechallenged to carboplatin, all other skin test positive patients were administered carboplatin utilizing a 4-step desensitization protocol or switched to an alternative non-platinum-based chemotherapeutic agent in the 3 studies. Desensitization was well tolerated in most patients, though additional HSRs were noted in 14%-43% of cases.

One risk factor associated with the development of an HSR despite a negative skin test is the presence of atypical symptoms after carboplatin administration. McAlpine et al reviewed 73 patients with gynecologic malignancies who underwent carboplatin skin testing before being retreated with carboplatin.²⁷ Of the 73 patients, 12 subsequently developed unusual, non-IgE-mediated symptoms after carboplatin administration (tingling, rhinitis, abdominal pain) with a delayed presentation (2-14 days after carboplatin administration). Of the 12 patients with delayed reactions, seven (58%) seroconverted to a positive skin test after subsequent carboplatin cycles and 4 (33%) developed classic HSRs despite a negative or delayed (>24 hours) positive skin test.

UTILIZATION OF CARBOPLATIN SKIN TESTING AFTER AN HSR

The second more common approach is to perform carboplatin skin testing after an HSR. Six studies utilizing this approach found that the frequency of positive skin tests ranged from 66% to 93% and were observed to be after a median of 8-9 cycles of carboplatin (Table II).^{9,15-17,24,25} In all of these studies, patients who were skin test positive were either administered carboplatin utilizing a desensitization protocol or provided an alternative non-platinum-based medication. Desensitization was conducted using either a 10- or 12-step/3-dilution-bag protocol. Additional HSRs occurred in 35%-59% of skin test positive patients who underwent desensitization, though one small study noted HSRs in all 3 patients (Table III).^{9,15,24,25} For patients who seroconverted after subsequent carboplatin infusions, the frequency of additional HSRs was comparable to and potentially higher than those with initial positive skin tests.²⁴

After a carboplatin HSR had occurred, there were no skin test positive patients reported in the literature who were rechallenged to carboplatin without the use of desensitization given ethical and/or safety concerns, so the PPV of skin testing after an HSR is unknown. Additionally, little data have been published on patients with negative skin testing to carboplatin who were rechallenged using a standard infusion. Castells et al identified 4 patients with carboplatin-induced HSRs with persistently negative skin tests who were administered carboplatin without desensitization.¹⁶ All 4 patients developed additional mild HSRs, suggesting that although the risk of anaphylaxis is minimal, the NPV of carboplatin skin testing to determine the risk for an additional HSR is low.

EPICUTANEOUS VERSUS INTRADERMAL SKIN TESTING

Carboplatin skin testing has typically been undertaken using an epicutaneous skin prick followed by intradermal injections. Although an epicutaneous skin test was often utilized to minimize the risk for adverse reactions associated with skin testing, the majority of carboplatin positive skin tests (86.4%) were only identified by intradermal skin testing (Table IV).^{9,16,17,24,25} The highest intradermal carboplatin concentration was important in

TABLE I. Predictive value of carboplatin skin testing before the development of a hypersensitivity reaction

Author	No. of patients	No. of steps in desensitization	ST+ patients with HSRs when rechallenged	ST+ patients with HSRs when desensitized	ST- patients with HSRs on standard infusion	NPV	PPV
Markman et al ²⁰	126	4*	6 of 7 (86%)	1 of 7 (14%)	7 of 87 (8%)	92%	86%
McAlpine et al ²⁷	73	4*	NA	6 of 20 (30%)	9 of 47 (19%)	81%	NA
Gomez et al ²⁸	54	4*	NA	3 of 7 (43%)	4 of 47 (8.5%)	91%	NA

HSR, Hypersensitivity reaction; NPV, negative predictive value; PPV, positive predictive value; ST+, skin test positive; ST-, skin test negative.

*Carboplatin 1:1000 dilution for 30 min, 1:100 dilution for 30 min, 1:10 dilution for 30 minutes, undiluted for duration.

TABLE II. Timing of carboplatin skin testing after the development of a hypersensitivity reaction

Author	No. of patients	Intradermal	Initial ST+	ST- who seroconvert	Seroconvert >6 mo after HSR	Seroconvert <6 mo after HSR	Total number of ST+
Lee et al ²⁵	31	0.02 mL (1, 10 mg/mL)	21/26 (81%)	NA	NA	NA	21/26 (81%)
Leguy-Seguin et al ¹⁷	8	0.02 mL (0.01, 0.1, 1 mg/mL)	6/8 (75%)	NA	NA	NA	6/8 (75%)
Castells et al ¹⁶	60	0.03 mL (1, 10 mg/mL)	53/60 (88%)	2/7 (29%)	NA	NA	56/60 (93%)*
Hesterberg et al ¹⁵	38	0.02 mL (0.1, 1, 3 mg/mL)	25/38 (66%)	6/11 (55%)	6/8 (75%)	0/3 (0%)	31/38 (82%)*
Patil et al ²⁴	39	0.02 mL (0.1, 1, 3/5 mg/mL)	16/39 (41%)	12/23 (52%)	11/14 (79%)	1/9 (11%)	28/39 (72%)
Pagani et al ⁹	3	0.02 mL (0.01, 0.1, 1 mg/mL)	2/3 (66%)	NA	NA	NA	2/3 (66%)

HSR, Hypersensitivity reaction; ST+, skin test positive; ST-, skin test negative.

Epicutaneous skin testing performed in each study using 10 mg/mL concentration.

*Includes 1 patient with a delayed (>48 h) positive skin test.

TABLE III. Frequency of hypersensitivity reactions in patients who were desensitized to carboplatin

Author	No. of steps in desensitization	ST+ patients with HSR when desensitized	ST- patients with HSR when desensitized	Total number of patients with HSR when desensitized
Lee et al ²⁵	12	NA	NA	11 of 31 (35%)
Hesterberg et al ¹⁵	8 or 10	7 of 19 (37%)	6 of 11 (55%)	13 of 30 (43%)
Patil et al ²⁴	8 or 12	22 of 28 (79%)	1 of 11 (9.1%)	23 of 39 (59%)
Pagani et al ⁹	12	2 of 2 (100%)	1 of 1 (100%)	3 of 3 (100%)

HSR, Hypersensitivity reaction; ST+, skin test positive; ST-, skin test negative.

determining the sensitivity of skin testing. For carboplatin skin testing performed before the development of an HSR, a higher frequency of positive carboplatin skin tests (31%-36%) was documented when utilizing an intradermal injection of 100 to 240 mcg of carboplatin (0.02 mL of carboplatin concentration between 5 mg/mL and 10 mg/mL) compared with 2 mcg (13%) (0.0002 mL of 10 mg/mL carboplatin concentration). Similarly, in skin testing after a carboplatin-induced HSR, 27.4% of patients identified required a concentration above 1 mg/mL, which was the top dose utilized in a number of studies. The highest percentage of patients (81%-88%) were positive on the initial skin test if a concentration of 10 mg/mL was used for the final intradermal injection (Table II),^{16,25} though skin necrosis has been noted with this higher concentration.^{15,32}

Although carboplatin skin testing is simple to perform, caution should be exercised in the preparation and handling of the drug. Carboplatin skin tests should ideally be prepared in a work space containing a vertical laminar flow hood.³³ At most practices, this would require pharmacy support. Impervious gloves are recommended when handling and performing skin tests to prevent dermal exposure.³⁴ After completion of the skin test, the drug should be disposed of according to the applicable Environmental Protection Agency, state, and local regulations for hazardous waste.³³

TIMING OF CARBOPLATIN SKIN TESTING

In addition to the concentration of the carboplatin utilized for skin testing, the interval of time between skin testing and last carboplatin exposure contributes to the frequency of an initial false negative skin test. Repeat skin testing is recommended if the initial skin testing is conducted within the first 4-6 weeks after an HSR and the results are negative. This recommendation is based on the data from hymenoptera venom skin tests, which suggests that there may be a period of "anergy" for 4-6 weeks after a systemic reaction, during which time the skin testing results may be falsely negative.³⁵ Additionally, there may be a significant number of skin tests that seroconvert from negative to positive if the interval between skin testing and the HSR is greater than 6 months. Two studies by Hesterberg et al¹⁵ and Patil et al²⁴ found an inverse relationship between the likelihood of a positive initial skin test and the time interval between the HSR and skin testing, though a significant percentage would seroconvert to positive skin testing after subsequent carboplatin exposures. Hesterberg et al determined that 83% (20 of 24) of patients who underwent skin testing less than 3 months after a carboplatin-induced HSR were skin test positive as compared with 36% (5 of 14) of those with an interval of greater than 9 months. Six of eight (75%) patients whose initial negative skin test was separated by greater than 6 months from the

TABLE IV. Frequency of positive results in both epicutaneous and intradermal skin testing

Author	Epicutaneous (%)		Intradermal (%)					Total patients (N)
	10 mg/mL	0.01 mg/mL	0.1 mg/mL	1 mg/mL	3 mg/mL	5 mg/mL	10 mg/mL	
Lee et al ²⁵	5%	—	—	57%	—	—	38%	21
Leguy-Seguin et al ¹⁷	33%	17%	50%	—	—	—	—	6
Castells et al ¹⁶	15%	—	—	72%	—	—	13%	53
Patil et al ²⁴	14%	—	29%	18%	18%	21%	—	28
Pagani et al ⁹	—	50%	50%	—	—	—	—	2
Percentage: Epi vs ID	14%			86%				110
Percentage ID: ≤ 1 mg/mL vs > 1 mg/mL			73%			27%		

Epi, Epicutaneous; ID, intradermal.

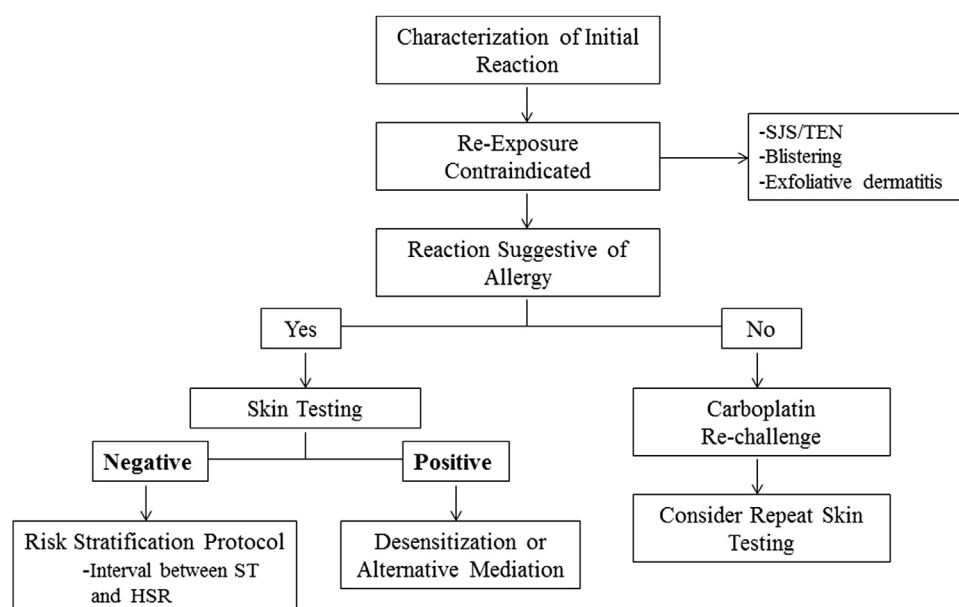


FIGURE 1. Management strategy for carboplatin-induced reactions. HSR, Hypersensitivity reaction; SJS, Stevens-Johnson syndrome; ST, skin test; TEN, toxic epidermal necrolysis.

initial HSR converted to positive skin test after subsequent carboplatin exposure using a desensitization protocol. These findings were supported in a study by Patil et al, in which seroconversion with subsequent carboplatin exposure was documented in 11 of 14 patients (79%) whose initial carboplatin skin test was greater than 6 months from the original HSR. In contrast, combining data from both studies, only 8% (1 of 12) of patients seroconverted after subsequent carboplatin exposure if a negative skin test was obtained less than 6 months from the initial HSR (Table II). These studies highlight the importance of the timing of skin testing in relation to the initial HSR when interpreting an initial negative carboplatin skin test result.

THE USE OF CARBOPLATIN SKIN TESTING IN THE MANAGEMENT OF PATIENTS

Despite the frequency of HSRs related to carboplatin administration, there is no standardized strategy on how to utilize skin testing to evaluate and manage patients who experience

HSRs. When utilized prospectively, a single intradermal injection of 100 to 240 mcg of carboplatin (0.02 mL of carboplatin concentration between 5 mg/mL and 10 mg/mL) identified the majority of patients at risk for the future development of HSRs.^{20,27,28} The frequency of a positive skin test ranging from 31% to 36% is similar to the frequency of HSRs historically observed in patients being retreated with carboplatin. Prospective skin testing before an HSR was determined to have a PPV of 86% and an NPV of 81%-92%, though these data are based on a small number of patients.²⁰ A high PPV indicates that patients with positive skin tests are at risk for additional HSRs if rechallenged with carboplatin and require an intervention such as desensitization or the use of an alternative non-platinum-based medication. A negative skin test does not rule out the possibility of a future HSR, though these reactions are milder with no cases of anaphylaxis reported.¹⁶ Special consideration should be given to patients who experience an atypical or delayed reaction after carboplatin even with a negative skin test as they may still be at risk for future reactions.²⁷ While providing a reliable tool to

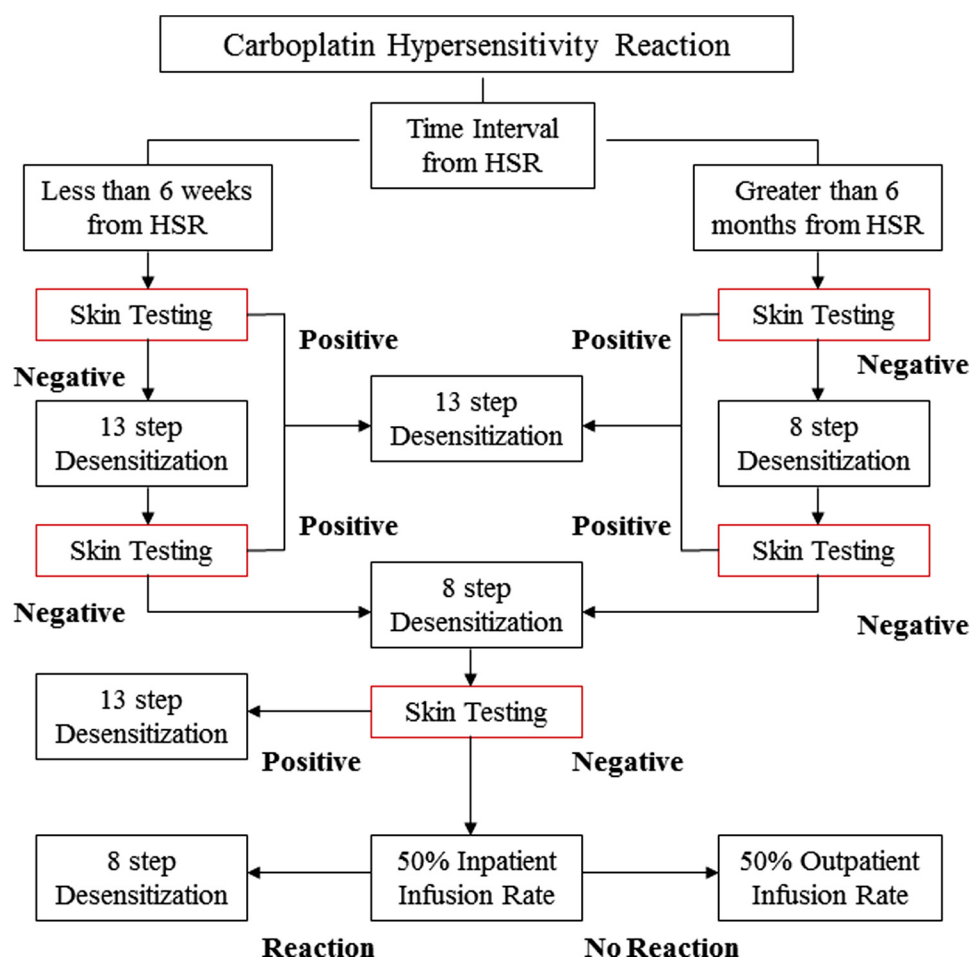


FIGURE 2. Risk stratification for an initial skin test performed less than 6 weeks and greater than 6 months after a carboplatin hypersensitivity reaction. HSR, Hypersensitivity reaction.

identify carboplatin-sensitized individuals, the cost effectiveness and feasibility of routine screening before every infusion is not known and will require an additional study.

For skin testing obtained after an HSR, there is a lack of data to determine the predictive value. Even so, skin testing can contribute to the effective and successful management of these patients. A positive skin test can help identify patients at risk for additional HSRs, even with the use of desensitization, so appropriate therapeutic decisions can be made. A negative skin test must be interpreted carefully as false negatives and/or seroconversion can occur based on a number of factors including the timing of the skin testing in relation to the initial HSR as well as the concentration of carboplatin in the final intradermal skin test. Serial negative skin tests have utility as part of risk stratification to determine which patients are truly not allergic and can safely return to the standard outpatient setting without need for carboplatin desensitization.^{15,24}

At our institution, we have created a successful empiric strategy to incorporate skin testing in the management of patients who have experienced a carboplatin-induced HSR (Figure 1). The first step would characterize the initial HSR. Re-exposure to carboplatin is contraindicated in patients who have experienced symptoms consistent with Stevens-Johnson syndrome, toxic epidermal necrolysis, or an exfoliative and/or

blistering dermatitis. Individuals with other atypical symptoms that are not concerning for an IgE-mediated reaction (hypertension, pain and/or discomfort, and tingling) can be considered for rechallenge to carboplatin. Skin testing may also be considered before and after the next carboplatin exposure as atypical symptoms may herald a future HSR.²⁷

If symptoms are concerning for an IgE-mediated reaction, skin testing is performed. In our experience, if a 10 mg/mL epicutaneous skin prick test is negative, we use increasing concentrations, at 15-minute intervals, of 0.1, 1, and 5 mg/mL of carboplatin for intradermal testing. Individuals who are skin test positive undergo desensitization or are switched to an alternative unrelated medication. If the initial skin test is negative, we recommend risk stratification based on the time interval between the skin test and the original HSR, as outlined in Figure 2. As previously discussed, an initial skin test is more likely to be a false negative and/or seroconvert if performed less than 6 weeks or greater than 6 months from the initial HSR. Therefore, to avoid potential HSRs in an uncontrolled setting, patients undergo 2 consecutive desensitizations in a facility with the resources, health care providers, and nursing staff capable of managing potential severe hypersensitivity reactions. Each desensitization is followed by repeat skin testing. The final skin test should be greater than 6 weeks from the initial HSR. With concern that

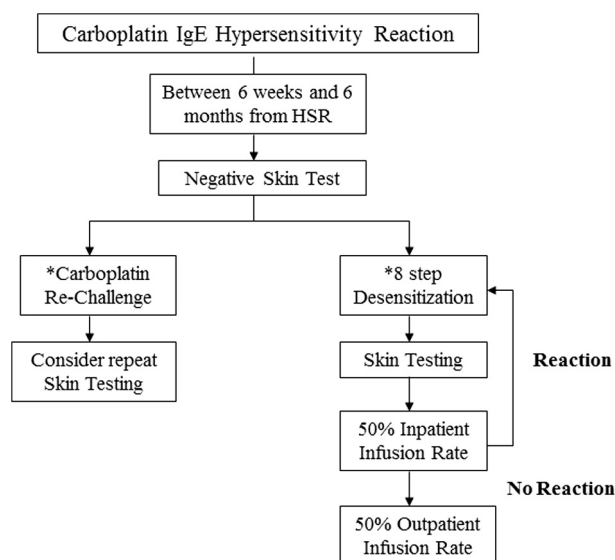


FIGURE 3. Risk stratification for an initial skin test performed between 6 weeks and 6 months after a carboplatin hypersensitivity reaction. Asterisk (*) denotes alternative treatment strategies based on the severity of the reaction and the discretion of the treating physician. HSR, Hypersensitivity reaction.

patients who are less than 6 weeks from their initial HSR are more likely to have a false negative skin test result or seroconvert, a 13-step/3-bag desensitization protocol is used initially as compared with the 8-step/2-bag protocol used in other 2 arms. The 13-step/3-bag desensitization protocol used at our institution is identical to the previously published 12-step protocol with an additional 60 mL/hour step added between steps 11 and 12 in the third bag.²⁵ A 13-step/3-bag desensitization can also be considered for patients with severe initial HSRs (grades 3 and 4) or significant comorbidities (poorly controlled asthma or cardiovascular disease). If there are no adverse reactions observed during desensitization and the skin test remains negative, the carboplatin infusion can be advanced to 50% of the standard infusion rate, which has been safe and successful at our institution in a small number of patients.²⁴ If well tolerated, patients can return to the infusion center to receive carboplatin at 50% of the standard infusion rate for all subsequent infusions.

For negative skin tests that are performed between 6 weeks and 6 months after the initial HSR, there are 2 alternative management strategies (Figure 3). As a carboplatin skin test is less likely to be false negative and/or seroconvert when obtained during this time period, the first strategy is rechallenge to carboplatin and consider additional skin testing to identify patients who may seroconvert. Although this approach allows for the continuation of carboplatin in the standard outpatient setting, there is potential for additional HSRs though none of the few cases reported are described as severe. The second strategy is a more conservative approach that we currently follow at our institution. It consists of an 8-step desensitization followed by a repeat skin test. Similar to the other arms of the risk stratification protocol, patients would return to the infusion center at 50% of the standard infusion speed if the skin test remains negative and treatment is uneventful. Continued desensitization would be recommended if a patient seroconverts or an HSR occurs with

carboplatin administration. This would consist of either an 8- or 13-step protocol depending on what step the HSR developed.

We have found that skin testing in association with a risk stratification protocol allows for the safe administration of carboplatin while ensuring that skin test negative patients who return to the standard infusion center are truly not allergic. Patil et al followed 44 patients with carboplatin-induced HSRs utilizing this risk stratification protocol.²⁴ Six patients were able to return to the outpatient infusion center after tolerating 2 sequential desensitizations while remaining skin test negative with no additional adverse reactions observed. Additionally, we have observed repeat skin testing utilizing our recommended concentrations for epicutaneous skin prick and intradermal injections to be safe. In a retrospective review of 218 carboplatin skin test procedures performed in 104 patients at Massachusetts General Hospital from June 2011 to May 2015, there were no episodes of skin necrosis, systemic symptoms, or anaphylaxis reported. A final intradermal concentration of 10 mg/mL, which has been proposed by other institutions,^{16,25} may be more sensitive and allow for the earlier identification of sensitized individuals, but was omitted from our protocol secondary to concerns of skin necrosis and irritant effects. Further prospective studies will be required to validate the safety of repeat skin testing, the optimal final concentration for intradermal testing, and clinical utility of this risk stratification protocol for the management of carboplatin-induced HSRs.

CONCLUSION

Hypersensitivity reactions are a frequent adverse event associated with the use of carboplatin and are most commonly observed in those retreated for recurrent or progressive cancer. Although an HSR can be related to a number of different immune mechanisms, an IgE-mediated mechanism is the most common and potentially most severe. Currently skin testing is the only modality utilized to identify patients who have been sensitized to carboplatin. Skin testing is easy to perform, provides immediate results, and has a low incidence of adverse events. When employed preemptively in patients being retreated with carboplatin, skin testing has been shown to be valuable in identifying individuals at risk for an HSR, but may not be practical for all providers due to time and resource restraints. The PPV and/or NPV of carboplatin skin testing after the occurrence of a carboplatin-induced HSR is less clear, but has been shown to be the useful part of a risk stratification strategy to identify patients who require desensitization versus those who can safely return to the standard outpatient setting.

REFERENCES

- Blommaert FA, van Dijk-Knijnenburg HC, Dijt FJ, den Engelse L, Baan RA, Berends F, et al. Formation of DNA adducts by the anticancer drug carboplatin: different nucleotide sequence preferences in vitro and in cells. *Biochemistry* 1995;34:8474-80.
- Covens A, Carey M, Bryson P, Verma S, Fung Kee Fung M, Johnston M. Systematic review of first-line chemotherapy for newly diagnosed postoperative patients with stage II, III, or IV epithelial ovarian cancer. *Gynecol Oncol* 2002; 85:71-80.
- Chen XS, Nie XQ, Chen CM, Wu JY, Wu J, Lu JS, et al. Weekly paclitaxel plus carboplatin is an effective nonanthracycline-containing regimen as neoadjuvant chemotherapy for breast cancer. *Ann Oncol* 2010;21:961-7.
- Skarlos DV, Samantas E, Kosmidis P, Fountzilas G, Angelidou M, Palamidas P, et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. *Ann Oncol* 1994;5:601-7.

5. Lorusso D, Petrelli F, Coinu A, Raspagliesi F, Barni S. A systematic review comparing cisplatin and carboplatin plus paclitaxel-based chemotherapy for recurrent or metastatic cervical cancer. *Gynecol Oncol* 2014;133:117-23.
6. Johansson SG, Hourihane JO, Bousquet J, Brujinzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813-24.
7. Pickering CA. Inhalation tests with chemical allergens: complex salts of platinum. *Proc R Soc Med* 1972;65:272-4.
8. Pepys J, Parish WE, Cromwell O, Hughes EG. Passive transfer in man and the monkey of type I allergy due to heat labile and heat stable antibody to complex salts of platinum. *Clin Allergy* 1979;9:99-108.
9. Pagani M, Venemalm L, Bonnadona P, Vescovi PP, Botelho C, Cernadas JR. An experimental biological test to diagnose hypersensitivity reactions to carboplatin: new horizons for an old problem. *Jpn J Clin Oncol* 2012;42:347-50.
10. Caiado J, Venemalm L, Pereira-Santos MC, Costa L, Barbosa MP, Castells M. Carboplatin-, oxaliplatin-, and cisplatin-specific IgE: cross-reactivity and value in the diagnosis of carboplatin and oxaliplatin allergy. *J Allergy Clin Immunol Pract* 2013;1:494-500.
11. Koshiba H, Hosokawa K, Kubo A, Miyagi Y, Oda T, Miyagi Y, et al. Incidence of carboplatin-related hypersensitivity reactions in Japanese patients with gynecologic malignancies. *Int J Gynecol Cancer* 2009;19:460-5.
12. Schiavetti A, Varrasso G, Maurizi P, Castello MA. Hypersensitivity to carboplatin in children. *Med Pediatr Oncol* 1999;32:183-5.
13. Polyzos A, Tsavaris N, Kosmas C, Arnaouti T, Kalahanis N, Tsigris C, et al. Hypersensitivity reactions to carboplatin administration are common but not always severe: a 10-year experience. *Oncology* 2001;61:129-33.
14. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999;17:1141.
15. Hesterberg PE, Banerji A, Oren E, Penson RT, Krasner CN, Seiden MV, et al. Risk stratification for desensitization of patients with carboplatin hypersensitivity: clinical presentation and management. *J Allergy Clin Immunol* 2009;123:1262-7.
16. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-80.
17. Leguy-Seguin V, Jolimoy G, Coudert B, Pernot C, Dalac S, Vabres P, et al. Diagnostic and predictive value of skin testing in platinum salt hypersensitivity. *J Allergy Clin Immunol* 2007;119:726-30.
18. Robinson JB, Singh D, Bodurka-Bevers DC, Wharton JT, Gershenson DM, Wolf JK. Hypersensitivity reactions and the utility of oral and intravenous desensitization in patients with gynecologic malignancies. *Gynecol Oncol* 2001;82:550-8.
19. Iwamoto T, Yuta A, Tabata T, Sugimoto H, Gabazza EC, Hirai H, et al. Evaluation of basophil CD203c as a predictor of carboplatin-related hypersensitivity reaction in patients with gynecologic cancer. *Biol Pharm Bull* 2012;35:1487-95.
20. Markman M, Zanotti K, Peterson G. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003;21:4611-4.
21. Goldberg A, Confino-cohen R, Saba K. A modified, prolonged desensitization protocol in carboplatin allergy. *J Allergy Clin Immunol* 1996;98:841-3.
22. Sood AK, Gelder MS, Huang SW, Morgan LS. Anaphylaxis to carboplatin following multiple previous uncomplicated courses. *Gynecol Oncol* 1995;57:131-2.
23. Broome CB, Schiff RI, Friedman HS. Successful desensitization to carboplatin in patients with systemic hypersensitivity reactions. *Med Pediatr Oncol* 1996;26:105-10.
24. Patil SU, Long AA, Ling M, Wilson MT, Hesterberg P, Wong JT, et al. A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions. *J Allergy Clin Immunol* 2012;129:443-7.
25. Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. *Gynecol Oncol* 2005;99:393-9.
26. Confino-Cohen R, Fishman A, Altaras M, Goldberg A. Successful carboplatin desensitization in patients with proven carboplatin allergy. *Cancer* 2005;104:640-3.
27. McAlpine JN, Kelly MG, O'Malley DM, Azodi M, Coombe K, Schwartz PE, et al. Atypical presentations of carboplatin hypersensitivity reactions: characterization and management in patients with gynecologic malignancies. *Gynecol Oncol* 2006;103:288-92.
28. Gomez R, Harter P, Lück HJ, Traut A, Kommos S, Kandel M, et al. Carboplatin hypersensitivity: does introduction of skin test and desensitization reliably predict and avoid the problem? A prospective single-center study. *Int J Gynecol Cancer* 2009;19:1284-7.
29. Lin MS, Tanner E, Lynn J, Friday GA. Nonfatal systemic allergic reactions induced by skin testing and immunotherapy. *Ann Allergy* 1993;71:557-62.
30. Bagg A, Chacko T, Lockey R. Reactions to prick and intradermal skin tests. *Ann Allergy Asthma Immunol* 2009;102:400-2.
31. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987;79:660-77.
32. Castells MC, editor. *Anaphylaxis and Hypersensitivity Reactions*. Totowa, NJ: Humana Press; 2011.
33. OSHA. Section VI: Chapter 2. Controlling occupational exposure to hazardous drugs. OSHA Technical Manual, TED 1-0.15A. Washington, DC: OSHA; 1999.
34. Carboplatin [package insert]. Irvine, CA: Teva Parenteral Medicines, Inc; 2011.
35. Goldberg A, Confino-Cohen R. Timing of venom skin tests and IgE determinations after insect sting anaphylaxis. *J Allergy Clin Immunol* 1997;100:182-4.

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