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Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions

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Abstract

Objectives. The incidence of hypersensitivity reactions (HR) is increased in patients treated with multiple courses of carboplatin. The purposes of this investigation were to evaluate the effectiveness of a 12-step desensitization protocol and to characterize the immune mechanism of carboplatin HR.

Methods. We analyzed 10 consecutive patients who had documented HR to carboplatin and in whom continued treatment with carboplatin was considered advantageous. The patients were treated with carboplatin using a 6-h, 12-step desensitization protocol with a 30-min premedication regimen. Skin tests were performed on five patients.

Results. Ten patients successfully completed 35 planned courses of desensitizations to carboplatin, 31 of which were without reactions. Four patients had symptoms during their first ($n = 3$) and third ($n = 1$) desensitizations but tolerated the re-administration of infusions without further reactions. For subsequent courses, the protocol was modified for two patients who had extracutaneous symptoms during desensitization and was unchanged for the patient who had mild urticaria. These three patients tolerated subsequent courses of desensitizations without reactions. The fourth patient with symptoms during desensitization no longer required carboplatin due to progressive disease. Of the five patients who were skin tested to carboplatin, four had positive wheal and flare reactions. In one patient, the skin test response to carboplatin became negative after desensitization.

Conclusion. The 6-h, 12-step desensitization protocol is safe and effective for treating patients with carboplatin HR. Positive skin tests to carboplatin suggest a mast cell/IgE-mediated mechanism. Conversion of the positive skin test to a negative response after desensitization supports antigen-specific mast cell desensitization.

Keywords: Carboplatin hypersensitivity; Carboplatin desensitization; Carboplatin skin test

Introduction

Carboplatin is an effective and well-tolerated cytotoxic agent used as standard front-line chemotherapy for ovarian cancer [1–5]. Many patients achieve a clinical complete remission with the platinum-based regimen but later develop recurrent disease within 3 years of diagnosis [6]. For patients with platinum-sensitive recurrent cancer, disease relapsing after at least a 6-month disease-free interval, platinum-based chemotherapy remains the most active regimen [6,7]. In addition to its clinical effectiveness, carboplatin has a low incidence of toxicity and limited nausea or vomiting with anti-emetic therapy [8]. Therefore, the ability to administer carboplatin safely as front-line therapy and in the relapse setting provides a significant clinical benefit to the patient.

Patients treated with multiple courses of carboplatin experience increased incidence of hypersensitivity reac-

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tions (HR) [9–11]. HR are uncommon during the initial courses, but the incidence of reactions increases to 27% in patients receiving more than seven cycles of carboplatin [9]. Thus, most cases of carboplatin HR are observed during the re-treatment for relapsed disease [12]. Symptoms of HR vary from cutaneous reactions such as flushing and urticaria to life-threatening respiratory and cardiovascular compromise including bronchospasm, chest pain, and hypotension [13], with more than 50% of patients developing at least moderately severe symptoms [9]. HR to carboplatin often prompts its permanent discontinuation [10]. Given that a carboplatin-based regimen is the standard second-line therapy for platinum-sensitive recurrent ovarian cancer, eliminating carboplatin as a treatment option presents a significant disadvantage for the patient.

Several authors have outlined re-treatment methods including oral and intravenous desensitizations to carboplatin with variable success [10,11,14–16]. We present a strategy that uses a 6-h, 12-step desensitization protocol with a simple 30-min premedication regimen without the use of corticosteroids. The protocol was uniformly successful for the ten patients who received a total of 35 planned courses of carboplatin. Four of the five patients skin tested to carboplatin had positive results. In one patient, the skin test response to carboplatin became negative after desensitization. We present here the summary of our experience.

Methods

Patients

This study was a cooperative effort between the Medical Oncology service at Dana-Farber Cancer Institute and the Allergy/Immunology service at Brigham and Women's Hospital. The study was approved by the Human Research Committee at Brigham and Women's Hospital. Between April 2002 and February 2004, patients who had documented HR to carboplatin and in whom continued treatment with carboplatin was considered advantageous were evaluated for carboplatin desensitization. A patient's reactions were considered mild if she had localized cutaneous manifestations alone including localized urticaria or pruritus. The reactions were considered moderate to severe if the patient had diffuse erythroderma, dyspnea, laryngeal edema, bronchospasm, oxygen desaturation, chest pain, and/or significant alterations in blood pressure.

Carboplatin skin test

Skin tests to carboplatin were conducted with saline and histamine used as negative and positive controls, respectively. No intradermal histamine skin test was performed if the prick histamine result was positive. The sizes of wheal and flare reactions were recorded. The prick test was performed on the volar surface of the forearm with a drop of carboplatin at 10 mg/ml. If the prick test was negative, the intradermal test was applied with 0.02 ml of carboplatin at 0.1 mg/ml. The concentration was increased progressively by 10-fold, as long as the intradermal results remained negative, to a maximal concentration of 10 mg/ml, which represented a maximum of four injections in different locations. All skin tests were interpreted 15 min after application. A prick test was considered positive if the diameter of the wheal was at least half of that produced by the histamine control and at least 3 mm greater than that of the negative control. An intradermal test result was considered positive if the wheal was greater than 5 mm with a surrounding flare.

Six-hour, 12-step desensitization protocol

The first desensitization for each patient was conducted in the medical intensive care unit according to the safety guidelines established at the Brigham and Women's Hospital. Subsequent desensitizations were performed in the inpatient oncology unit with a chemotherapy nurse in one-to-one attendance. Patients taking beta-blocker medications were instructed to hold their beta-blockers 1 day before the desensitization. Medical and nursing instructions for desensitization included the following. First, informed consent regarding the potential risks as well as the benefits was obtained before all desensitizations. Second, rescue medications including epinephrine, antihistamines, bronchodilators, and supplemental oxygen were placed by the bedside to ensure rapid administration. Third, patients were premedicated with diphenhydramine 25 mg and famotidine 20 mg administered intravenously 30 min before the initiation of the carboplatin infusion. Lorazepam 1 mg were offered to patients to alleviate anxiety.

The standard 12-step desensitization protocol combined gradual increases in the rate of infusion and concentration of carboplatin, administering the total carboplatin dose over 5.82 h. The standard protocol was used for all patients receiving desensitizations for the first time. The total carboplatin dose (X mg) was determined using the Calvert formula for a target area under the curve of 5 on the basis of the calculated creatinine clearance. The three infusion solutions—A, B, and C—contained $X/100$, $X/10$, X mg of carboplatin, respectively, diluted in 250 ml of D5 water. The concentration of solutions A, B, and C were $(X/100)/250$, $(X/10)/250$, and $(X)/250$ mg/ml, respectively. Solution A was used for Steps 1 to 4, Solution B for Steps 5 to 8, and Solution C for Steps 9 to 12. The rate of the infusion was adjusted every 15 min with each step delivering approximately twice the dose of the previous step. The final Step 12 maintained a constant rate of infusion to deliver the remainder of the total carboplatin dose. The standard

Table 1
Standard desensitization protocol using a total dose of 500 mg as an example

Total dose	500 mg	Solution concentration	Total dose in each solution (mg)
Solution A	250 ml	0.02 mg/ml	5.0*
Solution B	250 ml	0.20 mg/ml	50.0*
Solution C	250 ml	2.00 mg/ml	500.0*

Step	Solution	Rate (ml/h)	Time (min)	Administered dose (mg)	Cumulative dose infused (mg)
1	A	2	15	0.010	0.010
2	A	5	15	0.025	0.035
3	A	10	15	0.050	0.085
4	A	20	15	0.100	0.185
5	B	5	15	0.250	0.435
6	B	10	15	0.500	0.935
7	B	20	15	1.000	1.935
8	B	40	15	2.000	3.935
9	C	10	15	5.000	8.935
10	C	20	15	10.000	18.935
11	C	40	15	20.000	38.935
12	C	75	184.4	461.065	500.000
			Total time = 5.82 h		Total dose infused = 500 mg*

* The sum of the doses in Solutions A, B, and C equals 555 mg. Total dose infused is 500 mg.

protocol, with an infusion of 500 mg of carboplatin as an example, is shown in Table 1.

Results

From April 2002 to February 2004, ten consecutive patients with ovarian (n = 8), peritoneal (n = 1), and endometrial (n = 1) cancer who had documented HR to carboplatin and required continuing treatment with a platinum agent were evaluated for carboplatin desensitization (Table 2). The patients' mean age was 53 (range 38 to 74). They had received a median of eight courses of carboplatin (range 5–10) before developing their first HR. Eight patients had moderate to severe reactions to carboplatin, and the other two had mild reactions. All reactions occurred during the infusion, and no patients reported delayed reactions. Five of the ten patients had a history of

Table 2
Characteristics of patients with carboplatin hypersensitivity and skin test results

Patient*	Age	Tumor type	No. of courses to first HR	Reaction during first HR (severity)**	Total no. of desensitizations	HR during desensitizations	Carboplatin skin test results
1	53	ovarian	9	pruritus, flushing, lightheadedness (ms)**	1	none	not done
2	44	ovarian	8	flushing, dyspnea, chest tightness (ms)**	3	none	not done
3	47	ovarian	8	flushing, dyspnea, tachycardia (ms)**	5	none	positive at intradermal 10 mg/ml
4	52	ovarian	6	pruritus, nausea, tachycardia (ms)**	1	anxiety, tachycardia during 1st desensitization	not done
5	53	peritoneal	8	flushing, chest pain, hypertension (ms)**	5	none	not done
6	40	ovarian	10	back pain, pruritus, Flushing (m)**	5	pruritus during 3rd desensitization	not done
7	74	ovarian	8	pruritus of hands and feet (m)**	4	none	negative
8	38	ovarian	5	total body urticaria (ms)**	4***	two hives during 1st desensitization	positive at intradermal 1 mg/ml
9	63	endometrial	8	flushing, diffuse urticaria (ms)**	4	none	positive at intradermal 10 mg/ml
10	66	ovarian	9	flushing, dyspnea, desaturation, chest pain (ms)**	3***	dyspnea, desaturation during 1st desensitization	positive at intradermal 10 mg/ml

* Patients are numbered according to the date of initial desensitization.
** Severity of reactions: m—mild; ms—moderate to severe.
*** Number of desensitizations as of submission of manuscript.

allergic rhinitis. No patient had asthma, atopic dermatitis, or food allergies.

All ten patients were treated with carboplatin by the 6-h, 12-step desensitization protocol. The patients received a median number of five courses of desensitizations (range 1–5). The 10 patients successfully completed 35 planned courses of desensitizations to carboplatin, 31 of which were without reactions. Four patients had symptoms during their first ($n = 3$) and third ($n = 1$) desensitizations that were less severe than their original reactions. These symptoms were classified as mild ($n = 2$) and moderate to severe ($n = 2$) reactions (Table 3). All four patients successfully completed the planned infusions in their entirety. Three of the four patients had subsequent desensitizations without HR. The fourth patient no longer received carboplatin due to progressive disease.

Patient 4 developed anxiety and sinus tachycardia (low 100s) with a stable blood pressure 10 min into Step 7 of her first desensitization. The infusion was held, and she was treated with diphenhydramine 50 mg intravenously. Her symptoms resolved within 30 min. The infusion was re-administered at Step 7, and she tolerated the rest of the infusion without further reactions. Because of progressive disease, Patient 4 no longer received carboplatin.

Patient 6 developed hand pruritus and facial flushing 15 min into Step 12 of her third desensitization. She had tolerated the first two desensitizations without any reactions. The infusion was held, and she was given diphenhydramine 50 mg intravenously. Her symptoms resolved within 15 min, and the infusion was restarted at Step 12. She tolerated the rest of the infusion without further reactions. Her protocol was subsequently modified by decreasing the rate of Step 12 to 60 ml/h instead of the original 75 ml/h. This modification increased the duration of the infusion from 5.82 to 6.6 h. She had no HR during subsequent courses on the modified desensitization protocol.

Patient 8 had two small hives 15 min into Step 12 of her first desensitization. The infusion was continued while she was closely observed for further cutaneous manifestations. She tolerated the rest of the infusion without further reactions. The hives resolved several hours after the completion of the infusion. Her desensitization protocol remained unchanged, and she had no HR during subsequent desensitizations.

Patient 10 developed facial flushing, dyspnea, and desaturation to 88% on room air 20 min into Step 12 of her first desensitization. She did not have any wheezing, and her blood pressure remained stable. She was treated with diphenhydramine 50 mg intravenously and received supplemental oxygen. Her symptoms resolved within 30 min after the infusion was stopped. After another hour, the infusion was resumed at Step 12. She tolerated the rest of the infusion without reactions. The protocol was modified for her subsequent desensitization by adding two intermediate steps between Steps 11 and 12. Intermediate Step 1 consisted of the administration of solution C at a rate of 50 ml/h for 15 min. Intermediate Step 2 was the administration of solution C at a rate of 60 ml/h for 15 min. Step 11 remained unchanged. The duration of Step 12 was decreased from 3.07 to 2.7 h to maintain the same total carboplatin dose. These modifications increased the duration of the protocol from the standard 5.82 to 5.96 h. Patient 10 successfully completed her subsequent courses without any HR with the modified desensitization protocol.

Skin tests were performed on five patients (Table 2). Patients 3, 9, and 10 had positive skin tests to carboplatin

Table 3
Characteristics of patients who had reactions during carboplatin desensitization

Patient	Reactions (severity)*	Step	Treatment of symptoms during desensitizations	Protocol modification	Total no. of desensitizations**
4	Anxiety, tachycardia (ms)*	1st desensitization Step 7 (at 10 min)	Stopped infusion. Treated with diphenhydramine. Restarted infusion at Step 7. No further HR during rest of infusion.	Carboplatin no longer required because of change in treatment regimen.	1
6	Pruritus (m)*	3rd desensitization Step 12 (at 15 min)	Stopped infusion. Treated with diphenhydramine. Restarted infusion at Step 12. No further HR during rest of infusion.	Decrease rate of Step 12 to 60 ml/h for 4th desensitization. No HR during subsequent desensitizations.	5
8	Two hives (m)*	1st desensitization Step 12 (at 15 min)	Continued infusion of Step 12 until completion. Urticaria did not worsen during infusion.	No change in protocol. No HR during subsequent desensitizations.	4**
10	Dyspnea, desaturation (ms)*	1st desensitization Step 12 (at 20 min)	Stopped infusion. Treated with diphenhydramine and supplemental O2. Restarted infusion at Step 12. No further HR during infusion.	Added two intermediate steps between Steps 11 and 12 for 2nd desensitization. No HR during subsequent desensitizations.	3**

* Severity of reactions: m—mild; ms—moderate to severe.
** Number of desensitizations as of submission of manuscript.

at 10 mg/ml injected intradermally, and Patient 8 had positive response at 1 mg/ml injected intradermally. Patient 7 had a negative skin test. Saline and histamine were used as negative and positive controls, respectively. The effect of desensitization on skin test response was determined by skin testing Patient 10 before and after her second course of desensitization (Table 4). Before desensitization, her skin reactivity to carboplatin was positive at 10 mg/ml injected intradermally. The skin response to carboplatin became negative 2 h after desensitization was completed. Histamine responses were preserved before and after the infusion. The wheal ratio—defined as the ratio of the wheal produced by carboplatin (intradermal) versus the wheal produced by histamine (prick)—diminished from 1.6 to 1 after desensitization.

Discussion

This study outlines the 6-h, 12-step desensitization protocol used at our institution over a two year period for the treatment of patients who presented with HR to carboplatin secondary to mast cell/IgE-mediated reactions. All 10 patients successfully received 35 planned courses of desensitizations to carboplatin, 31 of which were without reactions. Four patients had symptoms during their first (n = 3) and third (n = 1) desensitizations but tolerated the re-administration of the infusions and subsequent courses of desensitizations without HR. The 6-h, 12-step protocol with a simple premedication regimen represents a significant advance in the treatment of patients with carboplatin HR.

Hypersensitivity of refinery workers to platinum salts has been well described in the literature. The mechanism of platinum HR in these workers is thought to be an IgE-mediated reaction with low molecular weight platinum salts acting as haptenic compounds [17]. Repeated exposure through inhalation of platinum is required for sensitization, and the symptoms that develop in sensitized individuals upon exposure are consistent with type I reactions—rhinitis, conjunctivitis, and bronchospasm [18]. Furthermore, the positive passive transfer in human and monkey [19] and the demonstration of platinum-specific IgE antibody by the radioallergosorbent test [17] confirm the type I immunologic nature of sensitivity to platinum compounds in refinery workers.

The mechanism of carboplatin hypersensitivity in cancer patients is also likely to be mast cell/IgE-mediated reactions [20,21]. In our patient population, HR to carboplatin did not occur during the initial courses of therapy. Most patients had reactions during their second-line therapy for recurrent cancer. The median total number of courses of carboplatin our patients received before the initial HR were observed was eight courses (range 5 to 10), correlating with published results [9,10]. In general, patients with carboplatin hypersensitivity are likely sensitized during the initial six courses of the carboplatin-based regimen. After recurrence of their disease, they are re-exposed to carboplatin during the seventh cycle and develop reactions during the eighth cycle. This observation suggests that a prolonged period of sensitization is required before the onset of HR.

The reaction profile of our patients, consistent with type I reactions, was similar to that reported [9,13]. Initial symptoms included flushing, pruritus, urticaria, nausea, dyspnea, tachycardia, hypertension, and chest pain. These reactions were consistent with symptoms caused by the release of mast cell mediators including histamine, proteases (tryptase and chymase), and eicosanoids [22]. Eight patients had moderate to severe symptoms, and two had mild reactions during their initial HR to carboplatin. All 10 patients had their initial HR during the infusion with six patients experiencing symptoms within 15 min of starting the infusion. None of our patients exhibited delayed reactions, although delayed reactions to carboplatin have been reported [9,10].

In addition, four of the five patients skin tested to carboplatin had positive wheal and flare reactions. The four patients who had positive skin tests had moderate to severe initial HR. The patient who had negative skin test had mild initial HR-localized pruritus of the hands and feet—suggesting that skin test response may correlate with clinically significant reactions to carboplatin. The maximal intradermal concentration of 10 mg/ml was used. This carboplatin concentration was within the range of 5 to 12 mg/ml used in two studies that gave negative intradermal results in 836 of 898 skin tests combined [23,24]. The concentration of 10 mg/ml used in our study was not likely to provoke a nonspecific skin reactivity or a direct mast cell activating effect. The positive skin responses in most of our patients who were tested suggest that cutaneous mast cells were sensitized with IgE antibodies to carboplatin. With exposure to carboplatin injected intradermally, cross-linking of carboplatin-specific IgE antibodies triggered the release of mast cell mediators, producing the wheal and flare reactions.

Table 4
Effect of desensitization on skin test reactivity: wheal/flare (mm) response for Patient 10

	Controls		Carboplatin	
	Histamine (prick)	Diluent (intradermal)	10 mg/ml (intradermal)	Wheal ratio*
Before desensitization	positive (5/15)	negative (4/0)	positive (8/15)	1.6
After desensitization	positive (4/13)	negative (4/0)	negative (4/1)	1

* Wheal produced by carboplatin (intradermal) versus wheal produced by histamine (prick).

To determine the effect of desensitization on cutaneous mast cell reactivity, we performed skin test on Patient 10 before and after her second course of desensitization. The result of the skin test to carboplatin was positive before desensitization but became negative after the infusion, demonstrating the inhibition of cutaneous mast cell reactivity. This result is consistent with findings by Goldberg et al. [15] where skin responses to intradermal carboplatin diminished after desensitization. Indeed, the prolonged period required for sensitization, the symptoms consistent with the release of mast cell mediators, and the positive skin test results implicate an IgE-mediated mechanism in carboplatin HR. The observation of diminished skin test response after desensitization in Patient 10 supports the contribution of an antigen-specific mast cell inhibition to the protection against HR.

On the basis of our experiences with paclitaxel and carboplatin desensitizations, we made several observations regarding the protocol. First, starting the infusion at low concentrations and at slow infusion rates reduced the probability of reactions during the desensitization. If a reaction did occur, the symptoms were less severe than those of the initial HR. Second, most patients who had HR during desensitization had the reactions during their first desensitization. If the patient experienced no HR during the first desensitizations, she was less likely to have reactions during subsequent protocols. Third, patients with HR during desensitizations had a specific desensitization step at which their reactions occurred. The step at which the reactions were elicited was different among patients but was consistent for each patient.

For patients with carboplatin hypersensitivity, many re-treatment strategies including desensitization to carboplatin with variable success are presented in the literature [10,11,14–16]. The 6-h, 12-step desensitization protocol has several significant features. First, the premedication regimen included only a one-time administration of diphenhydramine 25 mg and famotidine 20 mg given 30 min before the carboplatin infusion. Corticosteroids were not used as premedication. Anecdotally, premedication with corticosteroids for desensitization to antibiotics does not prevent mast cell/IgE-mediated anaphylactic reactions [25]. Furthermore, in published protocols for penicillin desensitization, corticosteroids are not used as premedication [26,27]. Many premedication regimens for carboplatin desensitization reported require the administration of several doses of corticosteroids over 12 to 24 h [10,14–16]. Our 30-min regimen using only H1 and H2 antihistamines represents a significant advantage in terms of time, cost, and other resource utilization.

In addition, the rate of the carboplatin infusion was adjusted every 15 min with each step delivering approximately twice the dose of the previous step. If there were no reactions during the desensitization, the protocol took a little less than 6 h to complete. Furthermore, once HR occurred during desensitization, our management strategies were to stop the infusion, treat the symptoms, and restart the infusion once symptoms had resolved. In this study, re-administration of the infusion was safe and well tolerated in four desensitizations. Finally, we used a generic 12-step protocol for all first desensitizations. Based on the step at which the HR was elicited during the desensitization, we modified the protocol for subsequent treatments. Neither of the two patients whose protocol was modified had reactions during subsequent desensitizations. Inclusion of more patients is needed to confirm these observations.

There are two cases in the literature of fatal outcome to platinum chemotherapy, highlighting the potential for severe life-threatening reactions to carboplatin [28,29]. To provide maximal safety for our patients, we have enacted multidisciplinary desensitization guidelines for the housestaff, nursing, pharmacy, and medical staff from the intensive care unit, oncology, and allergy services. First, all initial desensitizations were conducted in the medical intensive care unit with subsequent protocols administered in the inpatient oncology unit. Second, the chemotherapy nurses administering the infusion and the housestaff participating in the care were trained to recognize and respond immediately to the symptoms of HR. Third, patients were educated regarding the early symptoms of HR and instructed to notify the nursing staff immediately at the onset of symptoms. Finally, emergency medications including epinephrine, antihistamines, bronchodilators, and supplemental oxygen were by the bedside to ensure rapid administration. The guidelines for desensitizations were routinely reevaluated to improve the safety margin for the patients undergoing desensitizations.

Carboplatin hypersensitivity is likely to be a mast cell/IgE-mediated mechanism, given the prolonged period required for sensitizations, the clinical presentation consistent with mast cell mediator release, and the positive skin tests to carboplatin. The conversion of a positive skin test to a negative response after desensitization supports an antigen-specific mast cell desensitization. Future management and treatment strategies may include the use of anti-IgE therapy for those patients with positive skin tests to carboplatin. The 6-h, 12-step desensitization protocol with a 30-min premedication regimen is a safe and effective method for the treatment of carboplatin in patients with prior HR consistent with mast cell/IgE-mediated reactions. The protocol was uniformly successful in the 10 patients who underwent a total of 35 desensitizations. Using the multidisciplinary approach, we have achieved a high margin of safety for our patients undergoing desensitization. This study provides considerable support to the efficacy and feasibility of re-treatment of carboplatin in patients with prior hypersensitivity and warrants the consideration for the incorporation of this desensitization protocol as standard clinical practice in tertiary care centers.

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