Risk stratification for desensitization of patients with carboplatin hypersensitivity: Clinical presentation and management

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Background: Women with ovarian cancer treated with chemotherapeutic platinum agents frequently develop hypersensitivity reactions (HSRs). How best to risk-stratify patients for desensitization is uncertain.
Objectives: To evaluate skin test (ST) reactivity to carboplatin in patients with recent and remote histories of carboplatin HSR and to review the relationship between skin test reactivity and tolerance of subsequent carboplatin desensitization.
Methods: Thirty-eight women with carboplatin HSR were evaluated by ST to carboplatin. Thirty women subsequently underwent 106 desensitizations to carboplatin.
Results: Carboplatin ST was positive in 25 of 38 patients (66%). Of patients with recent HSR (<3 months), 20 of 24 (83%) tested positive, whereas 5 of 14 (36%) with remote HSR (>9 months) tested positive ($P < .01$). Nineteen carboplatin ST^+ and 11 ST^- patients underwent desensitization to carboplatin. Seven ST^+ patients (37%) had mild HSR during desensitization but completed the desensitization with additional treatment or protocol modification. ST^- patients with a recent history of HSR (n = 3) tolerated a rapid protocol without HSR and remained ST^- with repeated testing. Six of 8 ST^- patients (75%) with remote HSR reacted during desensitization. The HSRs were more severe and often associated with an elevated tryptase level. Five of 7 patients retested became ST^+ before the second desensitization. Carboplatin desensitization was successfully completed in 105 of 106 (99%) treatment courses.
Conclusions: The timing of carboplatin ST in relation to initial HSR is vital for risk stratification and subsequent desensitization. Initial ST^- patients with a remote history of HSR are at high risk for conversion to ST^+ and can develop more severe HSR. (J Allergy Clin Immunol 2009;123:1262-7.)

Key words: *Desensitization, drug allergy, carboplatin, ovarian cancer, skin testing, hypersensitivity*

Ovarian cancer is responsible for more deaths than any other cancer of the female reproductive system and ranks as the fifth most lethal cancer in women in the United States.[1] The current first-line treatment of recurrent ovarian cancer involves the use of carboplatin in combination with paclitaxel. Carboplatin has comparable efficacy to cisplatin with a preferable side-effect profile.[2,3]

The increased frequency of carboplatin use in the treatment of ovarian cancer has resulted in an increased prevalence of hypersensitivity reactions (HSRs).[4,5] A 1% incidence of HSR is documented in patients receiving fewer than 5 courses of treatment, but this increases to 27% in patients receiving more than 7 treatments.[4,6,7] At least 50% of the HSRs are described as moderately severe with symptoms of diffuse erythroderma, wheezing, facial swelling, dyspnea, and hypotension.[4] Anaphylaxis, respiratory arrest, and even death have been reported as a result of HSRs to platinum agents.[5,8,9]

The emergence of HSR to carboplatin has limited the use of this agent. Previously, the use of carboplatin was abandoned in favor of alternative agents to avoid the potentially severe complications associated with these reactions.[10] Attempts have been made to reinfuse carboplatin with slower infusion rates and a variety of pretreatment regimens.[4,11-15] Other investigators have used alternative platinum agents (cisplatin or oxaliplatin).[7,12,14,16-21] Unfortunately, the results have been mixed and have included a high rate of HSR. More recently, several groups have attempted carboplatin desensitization using a variety of protocols.[22-29]

The value of skin testing (ST) in predicting HSR to carboplatin has been examined. In prospective studies, the negative predictive value of carboplatin ST was found to be 98% to 99% in patients who had received multiple previous courses of carboplatin.[7,30] Markman et al[30] prospectively evaluated the predictive value of ST in 126 women with ovarian cancer and no history of HSR during infusions. Of 87 ST^- women, 7 experienced a HSR during subsequent infusions, giving a false-negative rate of 8%. Lee et al[24] reported their ST experience in 26 women with a known history of HSR to carboplatin. ST results were positive in 81% of patients tested.

At our institution, we have used ST in combination with a desensitization protocol to treat women with HSR to carboplatin successfully. Our experience and findings are described.

METHODS

Patient recruitment

Between November 2003 and August 2005, 38 patients were referred to the Allergy Service by the Gynecologic Oncology Service at Massachusetts

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Abbreviations used
HSR: Hypersensitivity reaction
ST: Skin test

General Hospital. All patients had a history of recurrent ovarian cancer and a HSR to carboplatin during a previous infusion. Institutional review board approval was obtained for this study.

Hypersensitivity reactions

Clinical symptoms associated with the initial hypersensitivity reaction were categorized by organ system involvement, and as immediate or delayed (Table I). Immediate reactions were defined as occurring during the course of carboplatin administration, whereas delayed reactions occurred at any point after completion of carboplatin infusion.

Skin testing

All 38 patients were skin tested to carboplatin. Skin prick testing was performed at doses equivalent to the standard infusion concentrations used at Massachusetts General Hospital for carboplatin (1.0 mg/mL). If skin prick testing was negative, intradermal skin testing was performed, using 0.02 cc of 0.1 mg/mL dilution, and proceeding to 1.0 mg/mL and 3.0 mg/mL dilutions if ST^- at the lower concentration. The dose range for intradermal skin testing was consistent with previously published protocols.[7,24,27,28,30] In our experience, 10 mg/mL was highly irritating and induced necrosis at the site of use during initial skin testing attempts in several patients. Five patients were tested at the 10 mg/mL dose. The highest intradermal skin testing concentration used was reduced to 3 mg/mL in all subsequent patients. Tests were considered positive if the wheal diameter was 3 mm greater than the negative control and had a surrounding flare. Histamine (1 mg/mL percutaneous and 0.01 mg/mL intradermal) and saline were used as positive and negative controls, respectively. The χ^2 test was used in all statistical analyses. A P value of .05 was considered statistically significant.

Carboplatin desensitization

Thirty patients subsequently underwent a total of 106 desensitization procedures. Eight patients did not proceed to desensitization on the basis of individual treatment decisions by the oncology staff. All desensitizations were performed through the oncology inpatient service by trained nursing staff with physician supervision. Informed consent was obtained from each patient before all ST and desensitization procedures. A standard pretreatment medication regimen was given: Allegra 180 mg (Sanofi-Aventis) and/or Clarinex 5 mg (Schering-Plough Corp) the evening before desensitization and the morning of desensitization, and an additional dose immediately before initiation of desensitization. Dexamethasone 10 mg was administered orally before initiation of chemotherapy as standard emesis prophylaxis. A 10-step desensitization protocol was used if carboplatin skin testing was positive (Fig 1). The protocol was modified from the vancomycin desensitization protocol published previously.[31] If skin testing was negative, a more rapid 8-step protocol was used (see this article's Fig E1 in the Online Repository at www.jacionline.org). If a hypersensitivity reaction occurred during the desensitization procedure, the infusion was stopped, the patient was evaluated, and symptoms were treated as needed with antihistamines and/or steroids. Epinephrine was available for use but was not required for treatment. A tryptase level was obtained if possible within 4 hours of any HSR. Once symptoms resolved, the infusion was restarted at the last tolerated step. If patients developed HSR during desensitization, subsequent desensitizations were modified by using a slower protocol with additional steps. Patients who were ST^- initially had repeat skin testing before any further desensitization procedures. If carboplatin ST was then positive, the protocol was modified from the more rapid 8-step protocol to the standard 10-step protocol (Fig 2). Once a patient tested positive on skin testing, no further skin testing was performed.

TABLE I. Initial hypersensitivity reactions in the study population (N = 38)

Immediate reactions	N	Percent
Oropharynx	6	15.8
Throat tightness	5	13.2
Tongue swelling	2	5.3
Cardiovascular	11	28.9
Tachycardia/bradycardia	3	7.9
Blood pressure alterations	4	10.5
Chest pain	1	2.6
Dizzy/lightheaded	4	10.5
Pulmonary	11	28.9
Chest tightness	3	7.9
Shortness of breath	5	13.2
Cough	1	2.6
Nasal symptoms	5	13.2
Gastrointestinal	14	36.8
Nausea/vomiting	14	36.8
Genitourinary	2	5.3
Urethral burning	2	5.3
Cutaneous	30	78.9
Erythema/flushing	23	60.5
Pruritus	21	55.3
Urticaria	5	13.2
Palmar erythema	19	50.0
Delayed reactions		
Cutaneous	3	7.9
Rash	1	2.6
Pruritus	2	5.3
Erythema	1	2.6
Combined cutaneous reactions	33	86.8

RESULTS

Demographics

All patients were white women ranging in age from 40 to 81 years at the time of presentation to the Allergy Service. Mean age was 58 (SD, ±9) years with a median of 59 years.

Initial hypersensitivity reactions to carboplatin

Hypersensitivity reactions to carboplatin most commonly occurred during the second (42%) and third (21%) cycles of the second line of treatment. In standard treatment protocols, these are commonly the eighth and ninth overall cycles of carboplatin. A minor additional peak occurred during the third cycle (8%) of the third line of treatment (Fig 3).

Clinical symptoms

Cutaneous manifestations (pruritus, urticaria, flushing) were the most prominent presenting HSRs (87%), with palmar erythema noted in 50% of patients. Gastrointestinal (37%), cardiovascular (29%), and respiratory (29%) symptoms were also common (Table I).

Skin testing

Carboplatin ST was positive in 25 of 38 patients (66%). In patients with a recent history of a HSR (<3 months), 20 of 24 (83%) patients were ST^+, whereas only 5 of 14 (36%) patients with a distant history of a HSR (>9 months) tested positive ($P < .01$) with initial testing (Table II).