

Use of cisplatin without desensitization after carboplatin hypersensitivity reaction in epithelial ovarian and primary peritoneal cancer

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OBJECTIVE: The purpose of this study was to evaluate the results of substituting cisplatin for carboplatin in women who experienced a carboplatin-associated hypersensitivity reaction while undergoing treatment for gynecologic cancers.

STUDY DESIGN: Using a comprehensive data repository, we identified all epithelial ovarian cancer and primary peritoneal cancer patients who experienced a documented significant hypersensitivity reaction to carboplatin and were subsequently treated with cisplatin at our institution from 1995 to the present. We also performed a review of published case reports of similar patient management.

RESULTS: We identified a total of 24 patients who met inclusion criteria. Eighteen patients (75%) tolerated cisplatin without any adverse

events. Six patients (25%) eventually developed a reaction to cisplatin; none was life threatening, and only 1 required hospitalization. Twenty-three of the 24 patients (96%) tolerated at least 1 cycle of cisplatin. Of the 5 patients who initially tolerated cisplatin but eventually experienced a reaction, the mean number of cycles tolerated was 3.4.

CONCLUSION: The use of cisplatin without desensitization is a reasonable approach for continuing platinum-based chemotherapy in patients with a significant carboplatin hypersensitivity reaction. Patients should be advised of risks and closely monitored, given published case reports of anaphylaxis.

Key words: carboplatin, cisplatin, hypersensitivity, ovarian cancer

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Platinum-based agents are a standard component of initial chemotherapy for ovarian cancer and a first choice in second-line chemotherapy for patients who are platinum sensitive.^{1,2} Carboplatin has been shown to be equally efficacious to cisplatin in the treatment of

advanced-stage ovarian cancer. Additionally, carboplatin is the preferred drug in this setting, given its relatively favorable toxicity profile.³

Repeated carboplatin use has been associated with an increasing incidence of carboplatin hypersensitivity reactions,⁴⁻⁶ with cumulative risk <1% with initial treatment to as high as 27% with repeated exposures because of recurrence.^{5,7} Carboplatin hypersensitivity reactions can range from mild, including rash and facial flushing, to more severe, including anaphylaxis, bronchospasm, hypotension, and death.^{5,7} Given the widespread use of platinum agents in the treatment of ovarian cancer, the ability to continue to use these agents is very important.

Several management strategies are available to deal with the complication of a carboplatin hypersensitivity reaction. Some would advocate discontinuation of further therapy with platinum agents and suggest proceeding with alternative chemotherapeutic regimens. Other authors^{6,8-11} have published experience utilizing desensitization protocols in-

volving prolonged premedication regimens, slow infusion protocols, or dose escalation schema.

One alternative approach is the substitution of cisplatin for carboplatin without additional desensitization.¹²⁻¹⁶ Cisplatin has a long and proven track record in the treatment of ovarian cancer but was replaced with carboplatin when the latter agent demonstrated a more favorable toxicity profile.^{3,17} Given comparable efficacy, this substitution approach would allow for continued utilization of platinum-based agents in platinum-sensitive patients who cannot tolerate additional carboplatin without requiring repeated high doses of steroids. This retrospective study reports on our institution's experience with the substitution of cisplatin for carboplatin after a carboplatin hypersensitivity reaction and reviews other reports in the literature on the same approach.

MATERIALS AND METHODS

Following institutional review board approval, all patients with an epithelial

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TABLE 1
Demographics of participants (n = 24)

	n	Initial treatment (n)
Age, y (range)	50 (31-70)	
Stage (n)		Neoadjuvant (4)
II	1	Surgery (20)
IIIA	1	Debulking (n)
IIIB	2	Optimal (15)
IIIC	18	Suboptimal (9)
IV	2	Initial agents (n)
Histology (n)		Taxol/carboplatin (22)
Papillary serous	21	Carboplatin/cytosan (1)
Endometrioid	1	Carboplatin/gemzar (1)
Clear cell	1	
Papillary peritoneal	1	
Grade (n)		
1	4	
2	3	
3	12	

ovarian or primary peritoneal cancer who experienced a significant hypersensitivity reaction to carboplatin and subsequently received cisplatin from January 1995-June 2006 were included in this study. We reviewed medical records for occurrence, medical management, and outcomes of carboplatin-associated hypersensitivity reactions. In this study, significant hypersensitivity reactions were classified as mild or severe. Mild reactions were characterized by cutaneous manifestations alone without alteration in pulse or blood pressure and no evidence of bronchospasm, which persisted despite administration of additional doses of histamine blockers and steroids (typically, 25 mg of diphenhydramine, 20 mg of famotidine, and 20 mg of dexamethasone administered intravenously). Severe reactions included any alteration in pulse or blood pressure or the occurrence of bronchospasm. All patients who experienced a significant carboplatin hypersensitivity reaction were rechallenged with cisplatin infused over 1.5 hours, with standard premedications, consisting of 16 mg of ondansetron and 20 mg of dexamethasone. Demographic and clinical data were abstracted from the pa-

tients' records and evaluated with descriptive statistics.

RESULTS

Twenty-four patients experienced a severe carboplatin hypersensitivity reaction at our institution and subsequently received cisplatin chemotherapy. The median age at diagnosis was 50 years (range, 31-70). Eighteen of 24 patients were stage IIIC at diagnosis, and the majority (88%) had papillary serous histology. All grades were represented in our study, with 12 of 24 having grade III pathology at the time of diagnosis. Four patients were treated with neoadjuvant chemotherapy before cytoreductive surgery after biopsy confirmed diagnosis, whereas 20 underwent primary cytoreductive surgery with tumor debulking. Twenty-two of 24 patients (92%) had paclitaxel and carboplatin as their initial chemotherapy, with 2 other patients receiving either carboplatin and gemzar or carboplatin and cytoxan. The demographics of this cohort are represented in Table 1.

The mean and median number of cycles at which a carboplatin hypersensitivity reaction occurred were 12 and 10, re-

spectively. Reactions to carboplatin included erythema, pruritus, nausea, chest pain, increased blood pressure, increased heart rate, or bronchospasm. Twelve patients had a mild reaction to carboplatin as defined by inclusion criteria, and 12 patients had a severe reaction (Table 2). All patients were evaluated and treated at the time of the initial reaction. Additional treatment for the hypersensitivity reaction depended on the severity and type of symptom. Treatment included immediate discontinuation of the infusion in all patients. Patients were administered a combination of steroids, antihistamines, histamine-2 blockers, intravenous hydration, and epinephrine when medically indicated at the discretion of the treating oncologist.

Patients selected for this study then went on to receive cisplatin alone, cisplatin and paclitaxel, cisplatin with taxotere, or cisplatin with gemzar. Standard premedications, without additional steroids, were administered before exposure to cisplatin. Eighteen of the 24 patients (75%) completed cisplatin therapy without experiencing any adverse events.

Six patients (25%) experienced a reaction to cisplatin at some point during this treatment. One patient (4%) experienced a cisplatin hypersensitivity reaction during her first exposure to cisplatin. The reaction consisted of severe itching, hoarseness, and swollen eyes.

TABLE 2
Characteristics of carboplatin hypersensitivity reactions (n = 24)

Symptoms	Number of patients
Mild	
Erythema	24
Pruritus	20
Nausea	4
Severe	
Increase in blood pressure	7
Tachycardia	4
Chest pain	1
Bronchospasms	6

TABLE 3
Summary of cisplatin rechallenge studies

Study	n	Successful	Allergic	Deaths
Present study	24	18	6	0
Dizon et al ²⁴	7	5	1	1
Kandel et al ¹²	5	5	0	0
Libra et al ²⁶	3	3	0	0
Ottaiano et al ¹³	10	9	1	0
Polyzos et al ¹⁴	4	4	0	0
Porzio et al ¹⁶	1	1	0	0
Shlebak et al ²⁷	1	0	1	0
Shukunami et al ¹⁵	1	1	0	0
Weidman et al ²⁸	2	2	0	0
Zweizig et al ²⁵	1	0	0	1
Total	59	48 (81%)	9 (15%)	2 (3%)

The infusion was discontinued, and the patient received dexamethasone and benadryl with resolution of her symptoms. Of the remaining 5 patients who initially tolerated cisplatin but eventually experienced a hypersensitivity reaction, the mean number of cycles tolerated was 3.4 (range, 1-4 cycles). Three of the cisplatin hypersensitivity reactions were mild (cutaneous manifestations alone) and 3 were severe. The severe reactions included an increase in blood pressure and pulse and/or evidence of bronchospasm including subjective shortness of breath/chest tightness or decreased oxygen saturation. None of the reactions was life threatening, and only 1 required hospitalization for overnight observation with no further event. The severity of these patients' initial hypersensitivity reactions to carboplatin did not correlate with their subsequent cisplatin hypersensitivity reactions. Overall, 23 of 24 patients (96%) tolerated at least 1 cycle of cisplatin.

COMMENT

It is well recognized that the incidence of carboplatin hypersensitivity reactions is correlated with the number of carboplatin cycles administered.⁵ Thus, the reexposure to carboplatin during treatment for recurrences results in an increase in the incidence of carboplatin hypersensitivity reactions. Reinduction with plati-

num in patients with platinum-sensitive ovarian cancer results in a 50-77% response rate.^{18,19} Although there are other agents available for second-line therapy, the response rate to other agents is substantially lower.²⁰

The role of continued treatment with platinum agents after a carboplatin hypersensitivity reaction is controversial. Published reports have demonstrated that desensitization protocols to allow the administration of platinum therapy can be successful.^{8,21,22} Other case reports have demonstrated that cisplatin can be used after a carboplatin hypersensitivity reaction, although the incidence of cross-reaction is unknown.²³

This series represents the largest compilation of patients with carboplatin hypersensitivity reactions who were treated with cisplatin without desensitization. Of the 24 patients who received cisplatin, 6 experienced a cisplatin hypersensitivity reaction. By adding our data to previously published reports,^{9,10} we identified a total of 59 reported patients who have received cisplatin without desensitization after experiencing a carboplatin hypersensitivity reaction (Table 3). Forty-eight patients (81%) completed cisplatin chemotherapy without hypersensitivity reaction, and 9 (15%) had a cisplatin hypersensitivity reaction during the course of their treatment. Fifty-four of the 59 patients (92%) were able to tolerate at

least 1 cycle of cisplatin. Five patients (8%) were unable to tolerate their first cycle of cisplatin. One of our patients had a serious allergic reaction during her first cycle of cisplatin, and she went on to receive other chemotherapy. Among other reported series, 1 patient developed fascial swelling and dyspnea²⁴ and 1 patient developed urticaria.¹¹ Two patients (3%) suffered fatal anaphylactic reactions.^{24,25}

The use of cisplatin after a carboplatin hypersensitivity reaction is a reasonable approach for continuing platinum-based therapy without the use of extended steroid premedication regimens. This approach may be beneficial for patients with poor glucose control or other relative contraindications to prolonged steroid exposure. Given that there have been 2 reported deaths, patients should be advised of potential risks and should be closely monitored. ■

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DISCUSSION

David Griffin, MD. Dr Callahan et al have reported their experience in treating patients with cisplatin after a hypersensitivity reaction to carboplatin. The role of platinum agents in primary and recurrent ovarian and primary peritoneal adenocarcinomas cannot be overstated, making this article an important contribution.

The objective of the study was to evaluate the results of substituting cisplatin for carboplatin in patients who had experienced carboplatin sensitivity. The authors performed a retrospective chart review using their institutional database, identifying patients with ovarian or primary peritoneal cancer who displayed a documented hypersensitivity reaction during a defined period.

The patients suffered a significant reaction, defined by the authors as one that did not subside sufficiently to allow resumption of carboplatin despite treatment with histamine blockers (H1 and H2) and an intravenous steroid. The reactions were further classified as mild (cutaneous alone) or severe (any reaction that included an alteration in pulse, blood pressure, or bronchospasm). The patients were subsequently challenged with cisplatin using a standard infusion regimen without premedication specific for a previous hypersensitivity reaction.

The study has potential problems inherent in most retrospective reviews, especially in regard to documentation of a reaction in this case. However, the availability of a comprehensive institutional database has allowed this group to evaluate a large number of patients and provide the largest single report to date addressing an important problem encountered in patients with recurrent ovarian and primary peritoneal cancer.

Platinum agents are an essential component in the treatment of epithelial ovarian and primary peritoneal cancers. The introduction of cisplatin in the 1970s resulted in an improvement in survival for these malignancies with clinical response rates of nearly 80% and clinical complete response rates of 40-50%. A metaanalysis in 1991 demonstrated an improved outcome in patients treated with platinum-containing regimens.¹ The toxicity associated with cisplatin led to the introduction and eventual substitution with carboplatin in the current intravenous regimens most commonly utilized.

The role of platinum-based chemotherapy in recurrent disease is also well established in platinum-sensitive disease, generally recognized as at least a 6-month interval from completion of platinum-based chemotherapy until recurrence. This corresponds to an expected response rate to platinum retreatment of greater than 30%, with correspondingly higher response rates with longer treatment-free intervals.

Reports of platinum hypersensitivity are rare during primary treatment in ovarian-type malignancies. The first reports of platinum hypersensitivity reactions were with the use of cisplatin in the 1970s and typically occurred in patients who had previously received the drug. Markman et al² subsequently reported at least a 12% rate of carboplatin hypersensitivity reactions occurring after an average of about 8 cycles of platinum-containing therapy in a large series from MD Anderson Cancer Center. Other reports have generally corroborated these findings with reported rates of hypersensitivity reactions up to 20% as the others stated in their introduction.

The exact nature of platinum hypersensitivity is still debated but usually includes prior exposure. Although IgE mediated immediate hypersensitivity reactions (type I) may occur in special populations (patients previously exposed to platinum dust in industry); most patients' hypersensitivity seems to include activation of previously sensitized T cells and a delayed hypersensitivity reaction (type IV hypersensitivity).³

This article confirms previous studies with the mean number of cycles received before carboplatin sensitivity being 12. The 24 patients reported here by Callahan et al were evenly divided between mild and severe reactions to carboplatin.

Eighteen patients were successfully treated with cisplatin after their carboplatin hypersensitivity reaction. Only 1 patient had an immediate reaction to cisplatin, with the other 5 tolerating 1-4 cycles of cisplatin chemotherapy before a hypersensitivity reaction occurred.

This study provides the largest number of patients to date of cisplatin treatment after hypersensitivity to carboplatin. There were no deaths or life-threatening reactions and only 3 of 24 severe reactions, with 1 patient requiring observation overnight after her hypersensitivity reaction. These data provide a basis for another option in treating the patient with carboplatin sensitivity along with premedication, which is often unsuccessful, and desensitization, which is complicated, time consuming, and difficult to accomplish as an outpatient.¹⁻³

I would like to ask several questions in regard to this article:

1. What dose of cisplatin was used?

2. Did the severity of the carboplatin reaction predict subsequent cisplatin hypersensitivity?
3. Might histamine blockade lead to less or later cisplatin sensitivity?
4. Which patients would qualify for cisplatin challenge, given the potential for severe reactions and 3% mortality according to pooled data (patient characteristics, potential platinum response, etc) along with the morbidity associated with cisplatin?
5. Has your group any results regarding skin testing and/or desensitization in patients after a hypersensitivity reaction to carboplatin?

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Dr Callahan (Closing). In our study, the dose of cisplatin used was 75 mg/m². The severity of the initial carboplatin reaction did not predict the subsequent cisplatin hypersensitivity reaction.

Currently the exact mechanism(s) of carboplatin hypersensitivity reactions not fully understood. Given that most patients do not exhibit cross-sensitization to cisplatin, but a minority do, one may speculate that multiple biological

mechanisms may be at work. Histamine release is a well-recognized downstream result of type I reactions, but whether premedication with an antihistamine might be useful in preventing subsequent development of hypersensitivity to cisplatin remains unknown.

Our current practice is to consider all patients who did not experience an anaphylactic reaction to carboplatin as potential candidates for cisplatin challenge. Patients should be informed of the risks and benefits of cisplatin rechallenge, especially given the 2 case reports of fatal reactions. For patients with anaphylactic reactions to carboplatin, inpatient or outpatient prolonged desensitization protocols (over 24 hours) may be reasonable options.

Our group does not perform routine skin testing because the overwhelming portion of patients with documented carboplatin hypersensitivity are able to tolerate at least 1 dose of cisplatin without a serious reaction. This observation may explain the high negative predictive values associated with skin testing reported by several authors. However, in our opinion, to be truly valuable, a skin test must also possess a high positive predictive value. In other words, a positive skin test would be concerning enough for a life-threatening reaction that would preclude the clinician from administering a platinum agent, regardless of tumor response considerations. To our knowledge there have been no reports documenting such a high positive predictive value for skin testing, and such studies are unlikely to be performed because of ethical considerations.