CASE REPORT

Desensitization treatment with cisplatin after carboplatin hypersensitivity reaction in gynecologic cancer

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Abstract : Platinum-based chemotherapy is the standard regimen for the treatment of gynecologic cancers ; however, hypersensitivity reactions (HR) to platinum often lead to discontinuation of this effective treatment. Here we performed a desensitization protocol for platinum infusion in 3 patients who required platinum re-administration after developing HR. Two patients (Case 1 and 2) were treated with the desensitization protocol successfully without developing HR during the subsequent 3 courses. Case 3 tolerated desensitization well for 2 courses, but in the 3rd course, she developed severe HR immediately after the initiation of cisplatin infusion because the desensitization protocol was unintentionally omitted. These cases show the usefulness and effectiveness of the desensitization protocol for the continuation of platinum treatment in patients who have undergone an extended number of treatments. J. Med. Invest. 57 : 163-167, February, 2010

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INTRODUCTION

Platinum-based chemotherapy is the standard treatment for gynecologic cancers. Carboplatin has less neurotoxicity, nephrotoxicity, gastrointestinal toxicity, and more myelosuppression than cisplatin and is considered therapeutically equivalent to cisplatin in patients with ovarian cancer (1) ; therefore, carboplatin has become a very useful agent, which is easier to administer and can be managed even in the outpatient clinic. All clinicians should warn patients about myelosuppression, although it is acceptable in most cases. However, as the use of carboplatin has become greater, an unfavorable side effect has been noticed more frequently : hypersensitivity reactions (HR), which represents a potentially lethal complication of chemotherapy (2).

The incidence of HR with carboplatin increases with repeated drug exposure, and is reported to occur usually from six to 21 courses of treatment (3) ; therefore, HR is a serious problem when an extended number of courses are attempted to manage disease recurrence. Several preventive procedures have been proposed : premedication with antihistamines or corticosteroids, substitution with a different platinum salt, and a desensitization protocol. Several desensitization protocols using platinum agents have been reported (2, 4-6).

Here we successfully performed a desensitization protocol using cisplatin for three patients who developed HR to carboplatin.

PATIENTS

We retrospectively evaluated and characterized patients with gynecologic cancers who experienced HR associated with carboplatin administration at our hospital from 2001 to 2007. During this period, 73 patients were treated with carboplatin-based chemotherapy, and we identified 17 patients (22%) with cervical (n=2), endometrial (n=4), and ovarian

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(n=11) cancer who developed a broad range of HR attributed to carboplatin. The characteristics of the patients are presented in Table 1. Ten patients were

Table 1 Characteristics of the patients (N=17)

Median age (range)		56.5 (45-69)
	Stage	No of the patients
Cervical cancer	IIb	2
Endometrial cancer	Ic	1
	IIIc	2
	IV	1
Ovarian cancer	Ic	1
	IIIa	1
	IIIc	8
	IV	1
Initial treatment		No of the patients
Neoadjuvant chemotherapy		10
Surgery-adjuvant chemotherapy		7
Initial agents		No of the patients
Taxane/platinum		17
Courses of carboplatin		5-27
Cumulative dose of carboplatin		3600-12750

treated with neoadjuvant chemotherapy and seven with adjuvant chemotherapy. None of these patients had an allergic response to carboplatin during the initial treatments. HR was classified as mild or severe, as reported previously (6). Reactions were considered mild if they consisted of cutaneous manifestations alone, or there was no associated alteration in pulse or blood pressure, and no evidence of bronchospasm. Reactions were considered severe or anaphylactic if symptom complexes included any alteration in pulse or blood pressure. A mild allergic reaction was recorded in 9 cases. Eight patients developed severe symptoms (Table 2). The number of prior platinum treatments before the first HR observation varied from five to 27. All reactions occurred during platinum infusion, and no patients developed delayed reactions. None of the eight patients with

Table 2 Characteristics of carboplatin hypersensitivity reactions (N=17)

Symptoms		Number of patients
Mild	erythema, pruritus	17
	Nausea	3
Severe	decrease in blood pressure	6
	Tachycardia	2
	Chest pain, bronchospasms	5

severe HR was rechallenged with platinum.

Three patients who had experienced mild HR were rechallenged with carboplatin after providing informed consent. Without desensitization, rechallenge was not successful in these three patients, who all experienced HR recurrence. The symptoms of HR did not occur immediately after rechallenge, but at a mean of 40 min (range 30 to 60 min) after the initiation of infusion. Two patients developed severe HR and the other mild HR. At the onset of HR, carboplatin infusion was interrupted immediately and patients were treated with oxygen and hydrocortisone. Two patients who had experienced severe HR discontinued carboplatin chemotherapy, which led to a poorer prognosis as this agent is the key drug in the treatment of gynecologic cancers.

To continue platinum treatment, the other three of 17 patients who had experienced mild HR were treated with a desensitization protocol, substituting cisplatin (60 mg/m^2) for carboplatin (Table 3). This regimen was performed with reference to the Windom HH report (8). Briefly, paclitaxel (175 mg/m^2) infusion was followed by cisplatin 60 μg/m^2 in 100 ml saline (1 : 1000 dilution of the final therapeutic dose (60 mg/m^2)), 100 ml/hr × 1 hr, and changed to cisplatin 600 μg/m^2 in 100 ml saline (1 : 100 dilution) subsequently for 60 min. 1 : 10 dilution infusion (cisplatin 6000 μg/m^2 in 100 ml saline) was administrated subsequently for 60 min, and then infusion was temporarily interrupted. On the 2nd day, treatment was initiated by cisplatin infusion at 1 : 10 dilution (cisplatin 6000 μg/m^2 in 100 ml saline) for

Table 3 Summary of the patients who underwent the desensitization protocol (N=3)

Case	No. of the prior carboplatin (cisplatin) courses	Cumulative dose of carboplatin (cisplatin) before desensitization (mg)	Grade of HR	Cisplatin dose at desensitization (mg/m2)	HR at desensitization	No of courses with desensitisation
1	22	11800	mild	60 (90 mg/body)	no reaction	2
2	20	7050	mild	60 (80 mg/body)	no reaction	6
3	12 (3)	5450 (240)	mild	60 (80 mg/body)	no reaction	2

60 min, and the remainder of the cisplatin at the therapeutic dose was infused over eight hours.

Patients were premedicated with 50 mg promethazine, 20 mg dexamethasone and 50 mg ranitidine administered 30 min before the initiation of paclitaxel infusion.

CASE REPORTS

Case 1.

The patient was a 57-year-old woman diagnosed with FIGO stage IIIc ovarian cancer of endometrioid adenocarcinoma. She was treated with neoadjuvant chemotherapy, TC (paclitaxel and carboplatin) therapy for three courses, followed by debulking surgery. After the operation, she received adjuvant TC therapy for 16 courses. In the sixteenth course, sniffles and chest pain developed during paclitaxel administration. Mild HR to paclitaxel was considered and adjuvant chemotherapy was temporarily interrupted. Three months later she developed recurrence, diagnosed as a pelvic mass, and DC (docetaxel and carboplatin) therapy was started. In the third course of DC therapy (cumulative dose of carboplatin was 11800 mg), she had mild HR (erythema and chest pain) during carboplatin infusion and infusion was stopped. Carboplatin was discontinued and DP therapy (docetaxel and cisplatin) with the desensitization protocol was performed. She received the full therapeutic dose of cisplatin successfully without developing HR for 2 courses ; however, further treatment was discontinued because of disease progression.

Case 2.

The patient was a 62-year-old woman diagnosed with FIGO stage IV endometrial cancer with multiple lung metastases. She was treated with debulking surgery followed by adjuvant chemotherapy (DC therapy). In the twentieth course (cumulative dose of carboplatin was 7050 mg), sniffles and erythema developed during carboplatin infusion and mild HR to carboplatin was diagnosed. Therapy included immediate discontinuation of the infusion and administration of a combination of antihistamines and steroids. Carboplatin was discontinued and single-agent chemotherapy with docetaxel was given for three additional courses. After the third course, chest CT revealed possible drug-induced interstitial pneumonitis although the lung metastatic lesion was clearly reduced. These findings led us to discontinue further treatment.

After two-year observation without treatment, the metastatic lesions in the lung began to spread. After obtaining informed consent with regard to the risk for progression of interstitial pneumonia and critical anaphylaxis, TP therapy with the desensitization protocol was started. This therapy was successfully carried out for six courses without developing HR. Fortunately, interstitial pneumonitis did not occur and the lung metastatic lesion disappeared. Currently, she has in sustained remission.

Case 3.

The patient was a 52-year-old woman diagnosed with FIGO stage IIIc serous epithelial ovarian cancer. She initially had a huge pelvic tumor and presented with peritonitis carcinomatosa. She was treated with neoadjuvant chemotherapy (TC therapy) for two courses followed by debulking surgery. After the operation she received adjuvant chemotherapy (TC therapy) for six courses which resulted in sustained remission. Nineteen months later, the serum CA125 level began to elevate and multiple recurrent tumors in the intraperitoneal cavity caused small intestinal ileus. She then underwent surgical small intestinal bypass. After this operation, TC therapy was restarted because of its high sensitivity at initial therapy. In the third course she developed erythema and pruritus during carboplatin infusion. Mild HR was diagnosed and the carboplatin infusion rate was reduced. In the next course (cumulative dose of carboplatin of 5450 mg), rechallenge was carried out, but mild HR occurred again. For the additional treatments, carboplatin was discontinued and single-agent chemotherapy with paclitaxel was administered ; however, the serum CA125 level elevated again after several courses and treatment was replaced by a gemcitabine plus docetaxel regimen. This therapy failed to suppress disease progression. As she seemed to be platinum sensitive, TP therapy was challenged in the following courses after obtaining informed consent with regard to the risk for critical anaphylaxis. She was able to receive TP therapy for two courses without developing HR. In the third course (cumulative dose of cisplatin was 240 mg) she had mild HR (pruritus). Although the potential risk of critical HR was strongly considered, we decided to perform TP therapy with the desensitization protocol after obtaining her agreement. TP therapy with desensitization was successfully carried out for two courses without developing HR. In the third course, she was accidently treated with TP therapy

without the desensitization protocol. Serious HR (tachycardia, wheezing, and decreased oxygen saturation) occurred during cisplatin infusion at full therapeutic concentration, and she was rescued with immediate hydrocortisone and epinephrine injection. She seemed to be sensitized to cisplatin completely and TP therapy was discontinued. She is currently receiving palliative care.

DISCUSSION

Carboplatin is very useful for gynecologic cancers which had responded to prior platinum-based chemotherapy and relapsed after more than six-month progression-free survival (PFS). In those cases, an extended number of courses are performed and the cumulative dose of carboplatin is likely to be higher ; however, the prolonged use of carboplatin increases the incidence of HR. Markman, *et al.* reported that HR was seen in 27% of patients who had received more than seven courses of this drug therapy. The median number of courses of carboplatin before observation of the first HR was eight. In particular, carboplatin treatment beyond 15 cycles and/or 8000 mg increased the risk of severe HR (7).

The severity of the symptoms varied. Occasionally, HR is recognized as a subtle itching or erythema, and in most cases (54%) more severe reactions, including anaphylaxis, are observed (3). Once HR is established, rechallenge should not be attempted because approximately 50% of cases will experience anaphylaxis. Case 3 was rechallenged with carboplatin after mild HR. Fortunately, she did not develop anaphylaxis but mild HR. Zanotti, *et al.* reported that the skin test is useful for identifying patients for whom the risk of reappearance of an allergic reaction is low (8-10).

Once patients have developed HR, they are forced to discontinue carboplatin treatment, resulting in a poorer prognosis because carboplatin is the key drug for the treatment of gynecologic cancer. Thus, it is important to suppress HR development for extended courses of carboplatin treatment.

The mechanism of HR to carboplatin remains unclear. It has been suggested that multiple use of this drug is involved in the development of allergy (2, 3, 11). Repeated administration of platinum may serve as a hapten and bind to proteins to form complexes, which act as allergens. This can be classified as type 1 IgE-mediated allergy. Castells, *et al.* reported that carboplatin skin testing was a helpful predictor of reactivity (12). Several attempts have been made to prevent HR by suppressing type 1 allergy (e.g., premedication with histamine or corticosteroid, treatment with carboplatin at lower concentrations). Switch carboplatin to an alternative platinum agent is another good option (10, 11, 13).

Cisplatin is comparable to carboplatin in terms of anti-tumor activity in gynecologic cancers. Although cross-reactivity between carboplatin and cisplatin should be considered, antigenicity may differ between these two platinum preparations. Occasionally, the absence of HR to cisplatin is reported in patients who have experienced HR to carboplatin in previous treatment. Callahan, *et al.* reported that among patients who have developed HR to carboplatin in initial treatment, only 8% were unable to complete cisplatin therapy without prior desensitization (6) ; therefore, substituting cisplatin for carboplatin after HR development is a good strategy if continuation of platinum-based chemotherapy is highly desirable.

Another method for preventing HR to carboplatin is a desensitization protocol by gradual re-introduction of small amounts of drug antigens to full therapeutic doses (2, 4). In our three patients, all had undergone many more than seven courses of carboplatin chemotherapy ; therefore, further treatments with platinum were much more likely to result in HR. Thus, we attempted a desensitization protocol by replacing carboplatin with cisplatin with eight-hour prolonged infusion at a therapeutic dose. This protocol was successful in all three patients, except for one treatment course. Generally, alteration of the successful protocol (*e.g.* to render them faster or to significantly change the time interval between doses) should be avoided. In the one failed treatment course, the desensitization protocol was erroneously skipped and the patient rapidly developed anaphylaxis just after the initiation of cisplatin infusion at the full therapeutic dose, although she had undergone successful desensitization protocols until the previous treatment. This result supports the usefulness of our approach to HR prevention.

However, further continuation of cisplatin treatment with our desensitization protocol is barely successful for suppressing HR (5). Jones, *et al.* reported the outcome of five patients treated for ovarian cancer with cisplatin after HR to carboplatin. Three of five patients were successfully re-treated, but one patients once again developed HR during the second cycle. The other patient developed recurrent symptoms during the 4th cycle. Further investigations

are needed to define the cellular and molecular mechanisms underlying desensitization. One possible method may be to switch cisplatin for another platinum treatment (e.g. oxalliplatin or nedaplatin) while the desensitization protocol shows potential to continue platinum-based chemotherapy. Another method may be to switch intravenous infusion to intraperitoneal administration (IP). Fujiwara, *et al.* reported that IP therapy with low toxicity might reduce the risk of HR (14).

We reported the usefulness and effectiveness of the desensitization protocol for the continuation of platinum treatment in patients who had undergone an extended number of carboplatin treatments. It is important to state that the aim of this report is not to negate the potential utility of carboplatin in patients with ovarian cancer who have experienced an allergic reaction to the agent.

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