

Usefulness of desensitization protocol for a carboplatin hypersensitivity reaction during docetaxel-carboplatin therapy for recurrent ovarian cancer: Case report

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Abstract. We report a case of recurrent ovarian cancer in which desensitization for a carboplatin hypersensitivity reaction proved useful. The patient was a 65-year-old woman who presented with a recurrence of stage IIIc ovarian cancer. The initial chemotherapy consisted of 6 courses of paclitaxel and carboplatin. Recurrence in the pelvis, splenic hilum and para-aortic lymph nodes was detected 19 months after the final day of treatment. The patient was treated with docetaxel-carboplatin therapy for the recurrence, but a Grade 3 hypersensitivity reaction to carboplatin was observed during the second course. Carboplatin desensitization was commenced with the third course and 6 courses were completed with no evidence of hypersensitivity reaction. The antitumor effect showed a complete response and the patient has had a disease-free survival thus far. Desensitization for patients diagnosed with a carboplatin hypersensitivity reaction appeared to be a key method of treatment for prolonging the survival time of patients with recurrent ovarian cancer.

Introduction

Platinum preparations are key drugs for the treatment of platinum-sensitive recurrence of ovarian cancer 6 months or more after the previous treatment (1,2). The therapeutic effect of one such drug, carboplatin, is equivalent to that of cisplatin. It is characterized by not requiring infusion loading during administration and by giving rise to adverse events, including nausea and vomiting, that are adequately managed (3,4), and it is used in combination with paclitaxel or docetaxel. However, it was reported that carboplatin hypersensitivity reactions

develop in response to frequent doses and the patient may lapse into a severe reaction. Additionally, the drug may be difficult to use in routine clinical practice (5). It was recently reported that performing desensitization enables the safe administration of carboplatin (6,7).

We report a case of recurrent ovarian cancer in which it was possible to safely resume carboplatin administration following desensitization in a patient who had developed a hypersensitivity reaction to carboplatin during docetaxel-carboplatin therapy (DC therapy).

Case report

Patient. The patient was a 65-year-old woman. The obstetric history was gravida 4, para 2, while her family history was insignificant. Her past medical history consisted of total abdominal hysterectomy for uterine myoma at 47 years of age and partial transverse colectomy for colon cancer at 61 years of age. She had no history of allergy.

History of the present illness. In July 2007, the patient was referred to us from the Department of Surgery of our hospital for a detailed examination due to the discovery of a pelvic mass. As a result of the examination, a pre-operative diagnosis of ovarian cancer was made and an exploratory laparotomy was performed in August 2007. However, carcinomatous peritonitis was discovered and a bilateral uterine adnexectomy was performed. The diagnosis was stage IIIc ovarian cancer and the histological type was poorly differentiated serous papillary adenocarcinoma. Post-operatively, the patient was treated with 6 courses of paclitaxel-carboplatin therapy (TC therapy). No clinical evidence of disease (NED) was noted in January 2008 and the initial treatment was concluded. The patient received follow-up in the outpatient clinic, but in August 2008 a 4-cm mass in the pelvis, a 2-cm mass in the splenic hilum and a para-aortic lymph node enlargement were detected, and a recurrence was diagnosed. The CA125 value at the time was 67.4 U/ml. Since multiple metastases had been detected, chemotherapy was selected as the treatment modality. Moreover, the patient had experienced Grade 2 peripheral neuropathy during the initial TC therapy and, in accordance with the patient's wishes, it was decided

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to treat the recurrence with DC therapy. The first course of the DC therapy (docetaxel 70 mg/m², carboplatin AUC 6) commenced in the outpatient clinic in September 2009.

Course of the current illness. Adverse events at the completion of the first course consisted of Grade 3 neutropenia, Grade 1 alopecia and Grade 1 peripheral neuropathy.

The second course commenced in October 2009, however, 20 min following the start of carboplatin administration (when 25% of the dose had been administered) facial flushing, sweating and chest discomfort were noted. A carboplatin hypersensitivity reaction was diagnosed and the patient was treated with cortisone, famotidine and chlorpheniramine. Respiratory discomfort also developed and, as SpO₂ had decreased to 87%, 3 l/min of O₂ was administered. The patient later developed generalized eczema and experienced no relief from the symptoms. A Grade 3 allergic reaction was diagnosed and the remainder of the carboplatin dose was not administered.

Based on the CA125 value of 20.7 U/ml and the Gynecologic Cancer Intergroup criteria at the end of the second course, a partial response was recorded. After obtaining sufficient informed consent from the patient, it was decided to continue DC therapy from the third course onwards. Carboplatin was administered using the desensitization method to overcome the carboplatin hypersensitivity reaction.

The patient was admitted in November and the third course of DC therapy was commenced. Following administration of granisetron 3 mg/body and dexamethasone 8 mg/body, docetaxel 100 mg/body was dissolved in 100 ml of physiological saline solution (PSS) and administered over 60 min. A 0.1-ml volume of carboplatin 600 mg/body dissolved in 100 ml of PSS (used as the standard solution) was removed and after being dissolved in 100 ml of PSS, it was administered over 60 min via intravenous drip infusion (i.v. drip). Then, 1 ml of the standard solution was removed and after being dissolved in 100 ml of PSS, it was administered by i.v. drip over 60 min. An additional 10 ml of the standard solution was removed and after being dissolved in 100 ml of PSS, it was administered by i.v. drip over 60 min. Finally, the remainder of the stock solution was administered over 60 min by i.v. drip and this was concluded without any evidence of a hypersensitivity reaction (Table I). The patient was monitored for a number of days, but no serious adverse effects were observed, and she was discharged on day 3 after administration. Treatment was subsequently continued until 6 courses; no hypersensitivity reaction was observed and a complete response of the lesions evaluated was obtained. A state of disease-free survival was confirmed in February 2010.

Follow-up in the outpatient clinic is currently ongoing, but no evidence of recurrence has been detected thus far.

Discussion

Hypersensitivity reactions are one of the rare adverse events associated with chemotherapy and they consist of acute and chronic reactions (8). For example, hypersensitivity reactions to paclitaxel commonly occur immediately after administration of the drug, known as acute hypersensitivity reactions (9). However, chronic hypersensitivity reactions are also noted. These reactions are said not to occur unless repeated courses

Table I. Desensitization protocol.

Step	Carboplatin equivalent (concentration)	Administration time (min)
1	1/1,000	60
2	1/100	60
3	1/10	60
4	1/1 (standard solution)	60

Carboplatin 600 mg/body dissolved in 100 ml of physiological saline solution (PSS) was used as the standard solution. Step 1, a 0.1-ml volume of the standard solution was removed, dissolved in 100 ml of PSS and administered via intravenous drip infusion (i.v. drip) over 60 min. Step 2, a 1-ml volume of the standard solution was removed, dissolved in 100 ml of PSS and administered by i.v. drip over 60 min. Step 3, a 10-ml volume of the standard solution was removed, dissolved in 100 ml of PSS and administered by i.v. drip over 60 min. Step 4, the remainder of the standard solution was administered by i.v. drip over 60 min.

of drugs such as carboplatin are administered (10-13). Acute reactions are type I allergic reactions caused by IgE and, although mast cell involvement has been suggested in chronic reactions, the exact mechanism remains to be elucidated (14). Although such reactions are rare, sufficient caution is crucial due to the possibility of developing serious or fatal anaphylaxis. The incidence of carboplatin hypersensitivity reactions is said to be 12% (5) and it is claimed that these reactions are most common during the 8th or 9th dose (15,16). Shepherd *et al* found that when the number of doses reached 7 or more, the risk of developing a carboplatin hypersensitivity reaction increased to 27% (17), but no clear risk factors or effective methods of prediction have been identified thus far (18-20).

Treatment policies following a hypersensitivity reaction are largely divided into resumption of treatment with a platinum drug in combination with another measure or a switch to a non-platinum drug. A high response rate to treatment that includes a platinum drug is anticipated, particularly in platinum-sensitive recurrent ovarian cancer (1). Moreover, platinum-based chemotherapy has been shown to be superior to chemotherapy with non-platinum drugs (2), and it is preferable to perform platinum-based chemotherapy where possible. Generally cited methods of coping with hypersensitivity when carboplatin administration is resumed are: i) pre-medication enhancement methods, by adding a steroid preparation and antihistaminic (14); ii) switching methods, in which a change is made to another platinum drug, such as cisplatin (14); and iii) desensitization (10,13,18), as used in our patient.

Carboplatin was prepared in four different concentrations: 1/1,000, 1/100, 1/10 and the standard solution. The patient was admitted and her ECG and oxygen saturation were monitored. The dose of paclitaxel was administered, followed by the carboplatin solutions down to the 1/10 concentration each in order over a 1-h period. The final standard solution was administered over 1.5 h. The carboplatin administration time was 4.5 h, a shorter time period than in earlier reports (9,12,14), and even when the docetaxel administration time was added, administration was possible within 6 h. All of the

courses down to the 6th course were administered following patient admission. However, administration also appeared to be possible in the outpatient clinic, if the facility was appropriately equipped.

A study showed that when a carboplatin hypersensitivity reaction occurred prior to the completion of drug administration, it was possible to resume administration by temporarily ceasing administration, and after the patient had recovered, resuming administration by reducing the flow rate to 1/4, then gradually increasing it to 1/2 and finally to the original flow rate (20).

We treated a patient with recurrent ovarian cancer in whom it was possible to resume carboplatin administration safely by desensitization in order to overcome a carboplatin hypersensitivity reaction. If the regimen is altered without selecting desensitization, the drug may not induce a response. Since taxanes and platinum preparations are key drugs for platinum-sensitive cases of recurrent ovarian cancer, even if administration of carboplatin alone becomes impossible, there is concern that fewer drugs may be available for the third and fourth line. Moreover, none of the response rates to the drugs that are used as salvage chemotherapy, with the exception of platinum preparations, are high. Thus, carboplatin desensitization is considered a key method of treatment in order to prolong the patient survival time.

In conclusion, we reported a carboplatin hypersensitivity reaction during DC therapy of recurrent ovarian cancer. Carboplatin desensitization enabled 6 courses to be completed, and disease-free survival was achieved. Carboplatin desensitization is also a useful method of treatment in order to prolong patient survival time in platinum-sensitive cases of recurrent ovarian cancer.

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