# Chemotherapy-related hypersensitivity reaction in Japanese patients with gynecologic malignancy

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**Summary**

*Purpose of investigation:* Chemotherapy-related hypersensitivity reaction seems to be problematic in the safe management of chemotherapy. In this study we investigated chemotherapy-related hypersensitivity reaction in patients with gynecologic malignancy. *Methods:* Between January 2009 and December 2010, we examined hypersensitivity reaction (≥ grade2) using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. We analyzed the incidence, clinical features, management, and outcome. *Results:* We administered over 1,057 infusions (24 regimens) to 205 patients. We found a total of four hypersensitivity reactions (≥ grade 2) cases (carboplatin: 2; nedaplatin: 1; docetaxel: 1). Signs and symptoms were varied. In two cases, the same regimen was rechallenged by using anti-allergic drugs. The docetaxel case was successful. The carboplatin case was not successful. *Conclusion:* Chemotherapy-related hypersensitivity reaction (≥ grade2) does not occur frequently. In the case of platinum, especially, carboplatin, re-administering after hypersensitivity reaction should be done carefully though platinum is a key drug in patients with gynecologic malignancies.

*Key words:* Hypersensitivity reaction; Chemotherapy; Gynecologic malignancy.

## Introduction

Gynecologic malignancies are usually more sensitive to systemic chemotherapy than other malignancies, and patients receive more kinds of chemotherapy and more frequently per patient than other malignancies. Moreover, new drugs (pegylated liposomal doxorubicin, gemcitabine, etc.) have been used recently in gynecologic malignancies [1, 2].

On the other hand, it is assumed that hypersensitivity reactions of chemotherapy seem to be more problematic in the safe management of chemotherapy as outpatient chemotherapy is performed more frequently in Japan. Hypersensitivity reaction is a known source of great stress to patients, their families, nurses, other patients, and physicians; 52% of a nursing staff have reported that infusion reactions are draining and frightening to them. Around 88% of outpatient and 62% of inpatient nurses consider infusion reactions frightening to other patients, with the potential to cause anxiety and confusion [3, 4].

It is very difficult to estimate incidents of hypersensitivity reaction [5]. There are a wide variety of grading scales for hypersensitivity reaction. We examined our reported hypersensitivity reaction (≥ grade2) using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0.

In this study, we investigated chemotherapy-related hypersensitivity reaction in patients with gynecologic malignancies.

## Materials and Methods

This retrospective study was approved by the Osaka City University, Graduate School of Medicine Institutional Review Board. Using the available electronic medical record data between January 2009 and December 2010, we examined our reported hypersensitivity reaction using the CTCAE v.4.0. We analyzed the incidence, clinical features, management, and outcome of chemotherapy-related hypersensitivity reaction (≥ grade 2) in patients with gynecologic malignancy, and the possibility of rechallenge with the drug.

## Results

### *Incidence of hypersensitivity reaction*

We administered over 1,057 infusions (24 regimens) to 205 patients with gynecologic malignancies between January 2009 and December 2010. Median age was 60 years (24-84). Diseases of gynecologic malignancy were as follows: ovarian cancer: 78; endometrial cancer: 53; cervical cancer: 45; peritoneal cancer: 13; uterine carcinosarcoma: 4; vaginal cancer: 3; choriocarcinoma and uterine sarcoma: 2; etc. (Table 1). Courses of chemotherapy performed were as follows: TC (paclitaxel+carboplatin): 479; nedaplatin: 84; cisplatin: 83; DC (docetaxel+carboplatin): 72; doxil: 61; AP (adriamycin+cisplatin): 26; CPT-11+nedaplatin: 25; docetaxel+nedaplatin: 23; etc. (Table 2). We found a total of four hypersensitivity reactions (≥ grade 2) cases. Three cases occurred in patients with ovarian cancer and one case was in a patient with cervical cancer. Three cases were treated by platinum (two cases: carboplatin; one case: nedaplatin) and one case was by taxane (docetaxel).

### *Clinical features and management of hypersensitivity reaction*

All cases were grade 2 hypersensitivity reaction. Signs and symptoms varied: thoracic symptoms: chest tightness, hypotension; respiratory symptoms: dyspnea,

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Table 1. — *Number of patients with gynecologic malignancies*.

| Gynecologic malignancy | No. of patients | No. of HSR (≥ grade2) |
|---|---|---|
| Ovarian cancer | 78 | 3 |
| Endometrial cancer | 53 | 0 |
| Cervical cancer | 45 | 1 |
| Peritoneal cancer | 13 | 0 |
| Uterine carcinosarcoma | 4 | 0 |
| Vaginal cancer | 3 | 0 |
| Choriocarcinoma | 2 | 0 |
| Uterine sarcoma | 2 | 0 |
| Tubal cancer | 1 | 0 |
| Endometrial stromal sarcoma | 1 | 0 |
| Vaginal melanoma | 1 | 0 |
| Bartholin gland carcinoma | 1 | 0 |
| Ovarian cancer & endometrial cancer (double cancers) | 1 | 0 |

HSR: hypersensitivity reaction.

Table 2. — *Regimen of chemotherapy*.

| Regimen | No. of courses | No. of HSR (≥ grade 2) |
|---|---|---|
| TC (PTX+CBDCA) | 479 | 1 |
| CDGP | 84 | 1 |
| CDDP | 83 | 0 |
| CPT-11+CDDP | 82 | 0 |
| DC (DTX+CBDCA) | 72 | 2 |
| PLD | 61 | 0 |
| AP (ADR+CDDP) | 26 | 0 |
| CPT-11+CDGP | 25 | 0 |
| DTX+CDGP | 23 | 0 |
| THP-ADR+CDDP | 19 | 0 |
| CPT-11 | 18 | 0 |
| PTX | 17 | 0 |
| EMA/CO (VP-16+MTX+ACD+CPA+VCR) | 16 | 0 |
| CDDP+S-1 | 10 | 0 |
| DTX | 10 | 0 |
| EP/MEA (VP-16+CDDP+MTX+ACD) | 8 | 0 |
| DAVFeron (DTIC+ACNU+VCR+IFN-beta) | 5 | 0 |
| ADR | 5 | 0 |
| CPT-11+MMC | 4 | 0 |
| BEP (BLM+VP-16+CDDP) | 3 | 0 |
| DTX+GEM | 3 | 0 |
| CAP (CPA+ADR+CDDP) | 2 | 0 |
| TP (PTX+CDDP) | 1 | 0 |
| CPT-11+PTX | 1 | 0 |

HSR: hypersensitivity reaction; PTX: Paclitaxel; CBDCA: Carboplatin; CDGP: Nedaplatin; CDDP: Cisplatin; DTX: Docetaxel; PLD: Pegylated liposomal doxorubicin; ADR: Adriamycin; THP-ADR: Tetrahydropyranyladriamycin; VP-16: Etoposide; MTX: Methotrexate; ACD: Actinomycin D; CPA: Cyclophosphamide; VCR: Vincristine; DTIC: Dacarbazine; ACNU: Nitrosourea; IFN-beta: Interferon-beta; MMC: Mitomycin C; BLM: Bleomycin; GEM: Gemcitabine.

wheezing, desaturation; dermatological symptoms: erythema, flushing, etc. The treatment methods for hypersensitivity reaction to each drug were very similar in the four cases, utilizing mainly diphenhydramine (2 cases), and intravenous hydrocortisone (3 cases) and supplemental nasal oxygen (2 cases) (Table 3).

*Rechallenge of the drug following hypersensitivity reaction*

In two cases (carboplatin and docetaxel) of four hypersensitivity reaction cases, the same regimen was rechallenged by using anti-allergic drugs on the same day following hypersensitivity reaction. The docetaxel case was successful. The carboplatin case was not successful and we changed the regimen. In the other two cases, we changed the regimen without rechallenge of the drug.

Table 3. — *Clinical features and management of hypersensitivity reaction (HSR)*.

| | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Drug of HSR | Carboplatin | Carboplatin | Nedaplatin | Docetaxel |
| Regimen of HSR | DC | TC | Nedaplatin | DC |
| Allergy history | Alcohol | Pyrine | (–) | (–) |
| Prior chemotherapy | TC×8 CDDP+CPT-11×6 GEM×1 | CDDP+CPT-11×6 | CDDP×3 | (–) |
| Cycle no. of 1st HSR | 5 | 9 | 2 | 1 |
| Grade of HSR | 2 | 2 | 2 | 2 |
| Signs and symptoms | | | | |
| Thoracic | (–) | Hypotension | (–) | Chest tightness |
| Respiratory | (–) | Dyspnea, Desaturation | Wheezing, Desaturation | Dyspnea |
| Dermatological | Erythema, Frushing | (–) | (–) | (–) |
| Treatment methods | | | | |
| Diphenhydramine | (–) | (+) | (–) | (+) |
| Hydrocortisone | (+) | (+) | (–) | (+) |
| Oxygen | (–) | (+) | (+) | (–) |
| Rechallenge | not successful | (–) | (–) | successful |

## Discussion

Hypersensitivity reaction is common in clinical practice, and most cases are mild or moderate. For example, hypersensitivity reaction to paclitaxel has been reported to occur in inapproximately 10% of patients, however, less than 1% of patients experience severe hypersensitivity reaction [6]. There have been several reports investigating hypersensitivity reaction in patients with gynecologic cancer [6-9]. Most reports included mild hypersensitivity reaction cases. Moreover, new drugs (pegylated liposomal doxorubicin, gemcitabine, etc.) have been used recently in patients with gynecologic malignancy [1, 2]. In this study, we investigated hypersensitivity reaction (≥ grade 2) of chemotherapy performed recently.

We administered over 1,057 infusions (24 regimens) to 205 patients with gynecologic malignancies between January 2009 and December 2010. We found a total of four hypersensitivity reaction (≥ grade 2) cases. Three cases occurred in patients with ovarian cancer and one case was in a patient with cervical cancer. Three cases were treated by platinum and one case by taxane. Two cases of platinum were carboplatin (2 of 551 courses) and one case was nedaplatin (1 of 132 courses). One taxane case was docetaxel (1 of 98 courses).

It is very difficult to estimate our incidents of hypersensitivity reaction, although there have been many reports of hypersensitivity reaction [6-9]. There are a wide variety of grading scales for hypersensitivity reaction. The CTCAE itself has undergone several revisions (v.4.0 was

released in May 2009). In clinical trials, these scales for grading allergic reactions have been used frequently. Some studies graded each sign and symptom of hypersensitivity reaction separately using the CTCAE [5]. We examined our reported hypersensitivity reaction (≥ grade 2) using the CTCAE (v.4.0). This grading scale seemed to be a relatively new and ideal tool for hypersensitivity reaction.

Major drugs as a hypersensitivity reaction-causing agent are platinum and taxane. Using the CTCAE (v.4.0), incidents of hypersensitivity reaction (≥ grade 2) to carboplatin have not been so frequent. Hypersensitivity reaction to carboplatin is considered to be an IgE-mediated immune response. The incidence of hypersensitivity reaction per patient increases with the number of doses given, and in cases of documented occupational exposure to the drug. However, a longer platinum-free interval between courses of drugs has been correlated with an increased incidence of hypersensitivity reaction [7-9]. In our study, the first hypersensitivity reaction was during the 5th course of DC therapy after eight courses of TC therapy and six courses of CDDP+CPT-11 therapy, and in the 9th course of TC therapy after six courses of CDDP+CPT-11 therapy. We could not rechallenge carboplatin by using anti-allergic drugs on the same day following hypersensitivity reaction because of a re-hypersensitivity reaction. This is in accord with previous reports. The number of chemotherapies including platinum have decreased for platinum-resistant cancer. Moreover, new drugs (pegylated liposomal doxorubicin, gemcitabine, etc.) have been used recently in gynecologic malignancy, and seemed to be the reason for lower incidents of hypersensitivity reaction to carboplatin. Our study included one case of hypersensitivity reaction to nedaplatin. There has been no report for hypersensitivity reaction to nedaplatin and some reports included a few hypersensitivity reaction cases [10]. In our case, the first hypersensitivity reaction was during the 2nd course of nedaplatin therapy after three courses of cisplatin therapy, in accord with previous reports.

Hypersensitivity reaction to taxane is considered as a non-IgE-mediated immune response. Therefore, hypersensitivity reaction occurs most frequently during the first or second exposure and is severe only during these administrations. Nearly all patients rechallenged after the first administration were able to tolerate subsequent cycles [6, 11, 12]. Our study included one case of hypersensitivity reaction to docetaxel. There have been many reports of hypersensitivity reaction to docetaxel [12]. In our case, the first hypersensitivity reaction was during the first course of DC therapy without prior chemotherapy. We were able to rechallenge docetaxel by using anti-allergic drugs on the same day following hypersensitivity reaction in accordance with previous reports. There was no hypersensitivity reaction to paclitaxel (0 of 498 courses). In most cases of alcohol allergy, we used docetaxel instead of paclitaxel, for example, DC therapy instead of TC therapy. This seemed to be the reason for no case of hypersensitivity reaction to paclitaxel.

There was no case of hypersensitivity reaction to new drugs, for example, pegylated liposomal doxorubicin, gemcitabine, etc., which may be because of the small number of courses of regimen performed.

In two cases (carboplatin and docetaxel) of four hypersensitivity reaction cases, the same regimen was rechallenged by using anti-allergic drugs on the same day following hypersensitivity reaction. The docetaxel case was successful, whereas the carboplatin case was not successful so we changed the regimen.

In conclusion, chemotherapy-related hypersensitivity reaction (≥ grade 2) does not occur frequently in patients with gynecologic malignancies. In the case of platinum, especially carboplatin, re-administering after hypersensitivity reaction should be done carefully though platinum is a key drug in patients with gynecologic malignancy.

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