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ORIGINAL ARTICLE

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Incidence and risk factors for paclitaxel hypersensitivity during ovarian cancer chemotherapy

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Abstract Hypersensitivity reaction (HSR) is still a major concern during cancer chemotherapy with paclitaxel. In the present study, we investigated retrospectively the incidence of HSRs to paclitaxel and the risk factors in 105 patients (553 courses) who received adjuvant chemotherapy (paclitaxel and carboplatin) for ovarian cancer. Moderate to severe HSRs that led to cessation or discontinuation of the chemotherapy, including respiratory distress and hypotension, were observed in 14 patients (13.3%) and 16 courses (2.9%), regardless of the use of conventional premedication with glucocorticoid, and histamine H_1 and H_2 antagonists. The incidence of HSRs to paclitaxel in patients with ovarian cancer seemed to be considerably higher than those reported by other investigators in patients with other carcinomas such as non-small-cell lung cancer and breast cancer. Four risk factors were identified: (1) history of mild dermal reactions such as facial flushing and urticaria in previous courses, (2) presence of respiratory dysfunction, (3) obesity (body mass index >25), and (4) postmenopausal at the time of ovariectomy. The incidence of hypersensitivity increased linearly as the number of risk factors increased ($r=0.992$, $P=0.008$). It is likely that disappearance of the estrous cycle facilitates the occurrence of HSRs to paclitaxel.

Keywords Paclitaxel · Hypersensitivity reaction · Ovarian cancer · Risk factor

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Introduction

Paclitaxel (Taxol), a tubulin stabilizer, is one of the most extensively used chemotherapeutic agents for several malignancies, including ovarian, breast, non-small-cell lung cell and stomach cancers. However, its use is often limited because of the occurrence of severe adverse events. Hypersensitivity reactions (HSRs), which are characterized by erythematous rashes, respiratory distress, bronchospasm, hypotension and pulmonary edema, are one of the dose-limiting side effects of paclitaxel [41]. Although the etiology of paclitaxel hypersensitivity remains unknown, Cremophor EL, a histamine-releasing agent [7, 23] that is added to the paclitaxel injection as surfactant, has been considered to be the major cause of the HSRs [30, 35, 36, 40, 41]. Based on this assumption, histamine H_1 and H_2 antagonists in combination with glucocorticoid have been prescribed for the prophylaxis of HSRs to paclitaxel [1, 2, 21, 42].

The prophylactic regimen (long premedication) consists of dexamethasone 12 h and 6 h before, and intravenous ranitidine or famotidine and oral diphenhydramine 30 min before, paclitaxel injection. Although dexamethasone is usually given orally, the package insert of paclitaxel in Japan indicates that dexamethasone should be injected intravenously twice 6–7 h and 12–14 h before paclitaxel treatment. Bookman et al. [3] have reported that a brief premedication (short premedication), in which dexamethasone, antihistaminic agent and H_2 antagonist are administered simultaneously 30 min before paclitaxel injection, is as effective as the long premedication. Following this report, short premedication has been carried out in a number of medical institutions. However, patients sometimes encounter moderate to severe HSRs that lead to discontinuation of chemotherapy. In particular, the incidence is high (8–14%) in patients with ovarian cancer [6, 20, 24, 41]. Recently, Kwon et al. [21] have reported that the incidence of HSRs is significantly higher (17.3%) in

patients who received short premedication than those who received long premedication (7.5%). Therefore, care should be taken to avoid HSRs during paclitaxel injection, particularly in patients with a high risk of HSRs, although there have been few epidemiologic studies on the risk factors for HSRs to paclitaxel.

In the present study, we investigated the incidence of HSRs and the risk factors in patients with ovarian cancer receiving paclitaxel and carboplatin combination therapy as postoperative chemotherapy.

Methods

Subjects

The subjects were 105 inpatients with ovarian cancer who received paclitaxel–carboplatin combination chemotherapy between May 1998 and June 2002 in the Department of Obstetrics and Gynecology at Kyushu University Hospital. All the patients had been subjected to surgical ovariectomy before the chemotherapy. An extensive retrospective review of all patients was conducted from the medical records and database in the University computer system.

Adjuvant chemotherapy

The postoperative combination chemotherapy with paclitaxel and carboplatin was performed every 4 weeks for up to six courses. In the chemotherapy regimen, paclitaxel at 180 mg/m^2 was infused intravenously over 3 h, followed by intravenous carboplatin infusion over 1 h at an AUC of 5 mg/ml min, according to the Calvert equation [4]. The dose of paclitaxel was adjusted depending on the severity of myelosuppression or peripheral neuropathy. A total of 105 patients received a total of 553 courses of the chemotherapy.

Premedication for prophylaxis of HSRs

All the patients received premedication for the prophylaxis of paclitaxel HSRs. The premedication consisted of long premedication and short premedication. In the former, dexamethasone (20 mg) was injected twice 12–14 h and 6–7 h before, and oral diphenhydramine (50 mg) and intravenous ranitidine (50 mg) were administered 30 min before, paclitaxel infusion, while in the latter, these medicines were administered once 30 min before paclitaxel infusion.

Data analysis

Moderate to severe HSRs that led to the discontinuation of chemotherapy such as dyspnea and hypotension were obtained from medical records. Data were analyzed using the Statistics Program for Social Science ($SPSS_X$, version 10) for Windows (SPSS, Chicago, Ill.). A multivariate stepwise logistic regression analysis was carried out to determine the factors and odds ratio for severe HSRs. The following independent variables were analyzed: number of pregnancies; history of drinking, smoking and allergy; postmenopausal at the time of therapy; stage of ovarian cancer; body mass index (BMI >25 kg/m^2); occurrence of mild dermal reactions such as facial flushing and urticaria during the first course of chemotherapy; and the presence of respiratory dysfunction. The patients were divided into two groups according to ovarian cancer stage (stage I/II and stage III/IV). A variable was considered prognostically significant when the P value was less than 0.05.

Results

Patient characteristics

The incidence of independent variables, including history of allergy, non-smoking, non-drinking, family

Table 1 Comparison of profiles of patients who showed no or moderate to severe HSRs to paclitaxel

	HSR group ($n=14$)	Non-HSR group ($n=91$)	P value
Performance status			
0	85.7% (12/14)	79.1% (72/91)	0.731
1	14.3% (2/14)	20.9% (19/91)	0.731
Stage			
I/II	42.9% (6/14)	40.7% (37/91)	1.00
III/IV	57.1% (8/14)	59.3% (54/91)	1.00
History of mild dermal responses in previous courses	42.9% (6/14)	33.0% (30/91)	0.549
Respiratory dysfunction	28.6% (4/14)	15.4% (14/91)	0.254
Non-smoking	57.1% (8/14)	75.8% (69/91)	0.192
Family history of cancer	42.9% (6/14)	51.6% (47/91)	0.579
Postmenopausal at the time of ovariectomy	57.1% (8/14)*	26.4% (24/91)	0.029
Age (mean ± SD, years)	52.1 ± 11.2	57.1 ± 11.3	
Number of pregnancies (mean ± SD)	2.1 ± 1.4	2.6 ± 2.0	
Number of chemotherapy courses (mean ± SD)	4.6 ± 2.2	5.4 ± 1.4	

*$P<0.05$ versus non-HSR group, Fisher's exact test.

Table 2 Individual cases for HSRs to paclitaxel in patients with ovarian cancer

Patient no.	Course of chemotherapy	Premedication regimen	Onset of HSR	Symptoms
1	1	Long	2 h	Facial flushing, dyspnea
2	2	Short	Within a few minutes	Facial flushing, chest discomfort
3	2	Long	Within a few minutes	Facial flushing, hypotension, diaphoresis
4	2	Short	20 min	Dyspnea
5	1	Short	Within a few minutes	Facial flushing, dyspnea, hypotension
6	2	Short	15 min	Hypertension, dyspnea, chest pain
7	3	Short	Within a few minutes	Dyspnea, facial flushing
8	1	Short	Within a few minutes	Dyspnea
9	2	Short	Within a few minutes	Chest discomfort, facial flushing
	3	Long	Within a few minutes	Cough, facial flushing
10	3	Long	Within a few minutes	Facial flushing, pruritus
11	1	Short	Within a few minutes	Facial flushing
12	2	Short	35 min	Facial flushing, chest discomfort
	3	Long	Within a few minutes	Facial flushing
13	2	Short	Within a few minutes	Dyspnea, chest pain, vomiting
14	2	Long	Within a few minutes	Facial flushing, dyspnea

history of cancer, postmenopausal at the time of ovariectomy, average age, number of pregnancies, and number of chemotherapy courses, were compared between patients who showed HSRs and those without HSRs. Moderate HSRs occurred in 14 of 105 patients (13.3%) and 16 of 553 courses (2.9%), despite the use of premedication for prophylaxis of HSRs. Among the variables, only postmenopausal at the time of ovariectomy was significantly different ($P = 0.03$ by Fisher's exact test) between the two groups (Table 1). Among the 105 patients, 32 were postmenopausal when they were subjected to surgery. Therefore, the incidence of HSR was 25% (8 of 32) in patients who were postmenopausal at the time of ovariectomy, and 8.2% (6 of 73) in patients who had menstrual cycles before ovariectomy.

Time of onset and symptoms of HSRs to paclitaxel

As shown in Table 2, HSRs appeared in most patients within a few minutes of the start of paclitaxel infusion. The major symptoms consisted of facial flushing (12 out of 16 courses), followed by respiratory dysfunction (8 of 16), and chest discomfort (4 of 16). The HSRs occurred in every patient during the initial three courses of chemotherapy. Short premedication was used in 10 of 16 HSR-positive courses.

Risk factors determined by multivariate stepwise logistic regression analysis

Multivariate stepwise logistic regression analysis showed that five factors significantly affected the incidence of HSRs to paclitaxel (Table 3): (1) history of mild dermal reactions such as facial flushing and urticaria in previous courses (odds ratio 29.3, 95% CI 4.0–214.9, $P = 0.001$), (2) presence of respiratory dysfunction (odds ratio 10.92, CI 1.58–75.24, $P = 0.015$), (3) obesity (BMI > 25 kg/m^2) (odds ratio 8.47, CI 1.48–48.57, $P = 0.017$), and (4) postmenopausal at the time of ovariectomy (odds ratio 5.78, CI 1.21–27.65, $P = 0.028$).

Relationship between number of risk factors and incidence of HSRs

Subsequently, we examined the relationship between the number of risk factors and the incidence of moderate to severe HSRs to paclitaxel. As shown in Fig. 1, there was a linear relationship between the number of risk factors and the incidence rate of HSRs to paclitaxel ($r = 0.992$, $P = 0.008$), although no HSRs occurred in patients who had only one of these risk factors.

Discussion

The combination chemotherapy of paclitaxel and carboplatin is the standard regimen for ovarian cancer, but its use is often limited due to the occurrence of HSRs associated with paclitaxel infusion. It is unlikely that carboplatin contributes to the HSRs evaluated in the

Table 3 Risk factors for HSRs to paclitaxel in patients with ovarian cancer assessed by multivariate stepwise logistic regression analysis

Independent variables	Odds ratio	95% CI	*P* value
Postmenopausal at the time of ovariectomy	5.78	1.21–27.65	0.028
History of mild hypersensitivity during the first course	29.29	3.99–214.94	0.001
Respiratory dysfunction	10.92	1.58–75.24	0.015
Obesity (BMI > 25 kg/m^2)	8.47	1.48–48.57	0.017

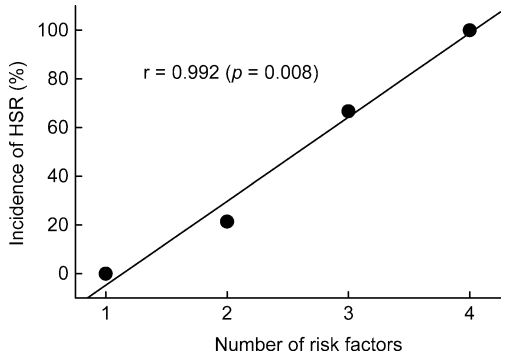

Fig. 1 Relationship between the number of risk factors and the incidence of HSRs to paclitaxel in patients with ovarian cancer. Patients all received premedication including dexamethasone, diphenhydramine and ranitidine before paclitaxel infusion. The four risk factors for HSRs to paclitaxel were (1) history of mild dermal reactions such as facial flushing and urticaria during the first course, (2) respiratory dysfunction, (3) BMI >25 kg/m^2, and (4) postmenopausal at the time of surgery

present study, since this agent is infused after the end of a 3-h infusion of paclitaxel. Several premedication regimens for the prophylaxis of HSRs to paclitaxel have been reported by a number of investigators [3, 9, 19, 21, 32, 34], but these regimens cannot fully reduce the incidence of HSRs [10, 38]. In the present study, the frequency of severe HSRs was 13.3%, which was comparable to those reported by several other investigators (Table 4). Moreover, the incidence of HSRs to paclitaxel is higher in patients with ovarian cancer than in patients with non-small-cell lung carcinoma (0–6%) or breast cancer (0–2%) (Table 4).

It has been reported that the HSRs to paclitaxel generally occur during the initial few courses of the chemotherapy [15, 35], and indeed, in the present study, all moderate to severe HSRs were observed during the first three courses: four, eight and four patients showed HSRs during the first, second and third course, respectively.

Paclitaxel injection contains Cremophor EL and ethanol. Since Cremophor EL is known to release histamine from mast cells, anaphylactoid reactions are considered attributable to the action of Cremophor EL [30, 36, 40, 41]. Ethanol may also be involved in the development or modulation of HSRs [8].

The present multivariate stepwise logistic regression analysis showed that there were five risk factors that affect the incidence of HSRs to paclitaxel: (1) history of mild dermal allergic reactions such as facial flushing and urticaria in previous courses, (2) respiratory dysfunction, (3) obesity, (4) postmenopausal at the time of ovariectomy, and (5) non-drinker. In our study, 18 of 105 patients had respiratory dysfunction, in which the forced expiratory volume in 1 s (FEV1.0) and the forced vital capacity (FVC) were less than 70% and 80%, respectively. Among these patients, 4 (28.6%) showed HSR. Robert et al. [34] have reported that paclitaxel-based regimens have a higher risk of pulmonary toxicity than other chemotherapeutic regimens. Therefore, patients with respiratory dysfunction may be more prone to HSRs to paclitaxel than those who have no respiratory dysfunction.

On the other hand, patients who were postmenopausal at the time of ovariectomy had a 5.8-fold higher risk of developing HSRs to paclitaxel. It has been demonstrated that postmenopausal women have a higher risk of cardiovascular disease [11]. This may be due to the reduction in estrogen synthesis and the resultant decrease in endothelial activity in synthesizing prostacyclin and

Table 4 Comparison of the incidence of HSRs to paclitaxel among patients with ovarian, breast, and non-small-cell lung cancer (*PTX* paclitaxel, *PTX+* PTX with and without other agents, *CBDCA* carboplatin, *CDDP* cisplatin, *GEM* gemcitabine, *5-FU* 5-fluorouracil, *EPI* epirubicin, *CYP* cyclophosphamide, *IFO* ifosfamide)

Dose (mg/m^2)	Regimen	Incidence	Reference
Ovarian cancer			
180	PTX + CBDCA	13.3% (14/105 patients)	This study
175	PTX	16% (8/50 patients)	5
175–210	PTX	14% (12/86 patients)	6
175	PTX + CBDCA	13% (12/92 patients)	25
	PTX	11% (32/301 patients)	41
135	PTX+	8% (9/112 patients)	20
	PTX+	7.5% (8/107 patients)	21
175	PTX+	4.6% (13/283 patients)	3
175	PTX	4% (3/70 patients)	42
175	PTX+	2% (4/183 patients)	26
Non-small-cell lung cancer			
175	PTX + CBDCA	6% (6/102 patients)	14
200	PTX + CBDCA + GEM	4% (3/77 patients)	16
100–250	PTX + CBDCA	3% (1/35 patients)	28
210	PTX	2% (1/60 patients)	12
200	PTX + CBDCA	0% (0/52 patients)	31
175	PTX	0% (0/51 patients)	27
Breast cancer			
175	PTX + CDDP	2% (1/46 patients)	17
175 or 225	PTX	2% (1/51 patients)	13
210	PTX	2% (1/62 patients)	18
	PTX + 5-FU + EPI + CYP	1% (1/69 patients)	33
175	PTX + IFO	0% (0/24 patients)	29

nitric oxide [11]. We have also found that postmenopausal female patients are more prone to HSRs to radiographic contrast medium, including urticaria, rash and itch [37]. Also, in experiments in rats, we have found that allergic reactions to iodinated radiographic contrast medium, such as dyspnea and vascular hyperpermeability, are exaggerated by ovariectomy and that the enhanced reactions are reversed by estradiol treatment [39]. Moreover, the allergic reactions to the contrast medium are augmented by inhibiting nitric oxide synthase but suppressed by a nitric oxide donor. Serum levels of estradiol are reduced in postmenopausal women. Moreover, the levels are further reduced after surgical ovariectomy in postmenopausal patients. Therefore, the severe depletion of estrogen may be related to a change in sensitivity to paclitaxel. Thus, ovariectomy in postmenopausal patients may cause severe depletion of estrogen, which affects vascular endothelial function by reducing the synthesis of prostacyclin and nitric oxide, and leads to the enhancement of HSR to paclitaxel. In this respect, ovariectomy may be the fundamentally important factor that induces HSR to paclitaxel.

It was notable that the incidence of HSRs was increased linearly as the number of risk factors increased, thereby suggesting that the incidence of HSRs can be predicted by determining the number of risk factors. Therefore, care should be taken to prevent HSRs in patients who have multiple risk factors by conducting a long premedication instead of a short premedication, by prolonging the infusion period (6–24 h) or by adopting an alternative chemotherapeutic agent such as docetaxel [22].

In conclusion, logistic regression analysis was carried out to explore the risk factors for HSRs to paclitaxel in 105 patients (553 courses) with ovarian cancer. Of these 553 courses, 16 (2.9%) in 14 patients (13.3%) revealed HSRs such as respiratory distress and hypotension. Four risk factors for HSRs, including history of mild dermal allergic reactions such as facial flushing and urticaria in previous courses, respiratory dysfunction, obesity, and postmenopausal state, were found. The HSRs seemed to occur with a higher frequency in patients with ovarian cancer than in those with other carcinoma. Therefore, the disappearance of the estrous cycle may enhance the incidence of HSRs to paclitaxel.

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