

Analysis of the pattern of hypersensitivity reactions in patients receiving carboplatin retreatment for recurrent ovarian cancer

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Abstract. Gadducci A, Tana R, Teti G, Zanca G, Fanucchi A, Genazzani AR. Analysis of the pattern of hypersensitivity reactions in patients receiving carboplatin retreatment for recurrent ovarian cancer. *Int J Gynecol Cancer* 2008;18:615–620.

The aim of this paper was to assess hypersensitivity reactions in 69 patients who received carboplatin (CBDCA) retreatment for recurrent ovarian cancer. Hypersensitivity reactions developed in 15 (21.7%) patients and occurred during the second cycle of retreatment in 13 (86.7%) of them. Reactions consisted of skin rash, flushing, itching, or abdominal cramping in eight (53.3%) and severe respiratory or cardiovascular events in seven patients (46.7%). One patient had a chest pain, without any other symptoms suggestive of hypersensitivity, followed by cardiac arrest unresponsive to standard resuscitative measures. All the other cases promptly recovered from symptoms. Logistic regression analysis showed that allergy history and CBDCA retreatment interval (interval time between the last cycle of first-line chemotherapy and CBDCA retreatment) were independent predictive variables for the risk of hypersensitivity, whereas patient age, first-line chemotherapy, total CBDCA dose given during first-line treatment, recurrence treated with CBDCA (first versus other), and CBDCA regimen at recurrence had no predictive value. Hypersensitivity reaction rate was higher in patients with CBDCA retreatment interval longer than 23.4 months compared to those with a shorter interval (36.3% versus 8.3%, $P = 0.0132$). Nine patients were subsequently treated with cisplatin, and two (22.2%) still developed allergic reactions. In conclusion, hypersensitivity reactions to CBDCA retreatment can occur in approximately one fifth of the cases, and a CBDCA retreatment interval longer than 2 years appears to be the strongest predictive variable for the development of allergic reactions.

KEYWORDS: carboplatin, chemotherapy, hypersensitivity, ovarian cancer, recurrence.

Many chemotherapeutic agents, such as epipodophylotoxins, L-asparaginase, methotrexate, nitrogen mustard analogs, taxanes, and carboplatin (CBDCA), can induce hypersensitivity reactions^(1–9). CBDCA plays a major role in the treatment of ovarian cancer. Paclitaxel/CBDCA-based chemotherapy is the currently accepted standard first-line regimen for advanced disease, able to achieve a clinical complete response rate of approximately 50%, a pathologic complete response rate of 25–30%, a median progression-free survival of

15.5–22 months, and a median overall survival of 31–44 months^(10–14). CBDCA alone or in combination with other agents, such as paclitaxel or gemcitabine, is the treatment of choice for patients with recurrent platinum-sensitive ovarian cancer^(15–17). A substantial risk for hypersensitivity reactions is associated with prolonged CBDCA use. A recent review of the literature data showed that the incidence of these reactions is related to the number of cycles of CBDCA administered, being less than 1%, 6.5%, 7%, and 19.5%, respectively, for patients who had received less than or equal to five, six, seven, and eight cycles^(1,2,5,8). Therefore, most of the allergic reactions occur during retreatment for relapsed disease. These reactions range from mild symptoms and signs, such as flushing, itching, skin rash, abdominal cramping, diarrhea, and tongue

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edema, to life-threatening respiratory and cardiovascular compromise, including bronchospasm, dyspnea, chest pain, angina pectoris, tachycardia, hypotension, or hypertension^(5,8,18). The main mechanism of hypersensitivity is represented by type I, immunoglobulin E-mediated reactions, as suggested by the clinical presentation characterized by symptoms consistent with the release of mast cell mediators^(8,18–21). CBDCA appears to act as a hapten, binding to serum proteins⁽¹⁹⁾.

The aim of this paper was to assess the pattern of hypersensitivity reactions in patients receiving CBDCA retreatment for recurrent ovarian cancer in a single department experience.

Materials and methods

This retrospective study assessed 69 patients who received salvage CBDCA-based treatment for recurrent ovarian cancer between July 1999 and January 2007 at our department. All these patients had undergone primary cytoreductive surgery followed by first-line CBDCA-based chemotherapy.

The median age of patients at diagnosis was 58 (range, 35–78) years. According to the FIGO classification, tumor stage was IC in 3 patients, IIC in 1 patient, III in 62 patients, and IV in 3 patients. Histologically, 62 carcinomas were serous, 5 endometrioid, and 1 was mucinous. Tumor grade was well differentiated in 2 cases, moderately differentiated in 19, and poorly differentiated in 48. After initial surgery, 20 patients had residual disease that was less than or equal to 1 cm and 49 had a larger residual tumor. First-line chemotherapy consisted of paclitaxel 175 mg/m² (3-h infusion) + CBDCA area under the curve (AUC) 5–6 every 3 weeks for six cycles in 53 patients, epidoxorubicin 75 mg/m² + paclitaxel 175 mg/m² (3-h infusion) + CBDCA AUC 6 every 4 weeks for six cycles in 7 patients, and single-agent CBDCA AUC 5–6 every 3 weeks for six cycles in 9 patients. In 1999, our department started to enroll patients in a multicenter Italian trial (termed "After six") including different protocols aimed to assess the potential role of maintenance chemotherapy with paclitaxel in advanced ovarian cancer patients who achieved a complete or partial response after six cycles of paclitaxel/platinum-based chemotherapy⁽²²⁾. Therefore, some of the patients included in the present analysis continued to receive paclitaxel after the completion of first-line treatment.

All patients were periodically followed by physical and gynecological examination, abdominal–pelvic ultrasound, chest X-ray, and serum CA125 assay, whereas further investigations, such as computed tomography or positron emission tomography, were performed

when indicated. No patients received chemotherapy for rising CA125 levels without clinical or radiologic detection of recurrent disease.

Time to first recurrence was calculated from the date of the last cycle of first-line chemotherapy to the date of the clinical or radiologic diagnosis of relapse.

Some patients received CBDCA-based salvage chemotherapy at the time of first recurrence, whereas others were initially treated with other agents and received CBDCA at the time of a further recurrence.

CBDCA hypersensitivity reaction rate was related to i) patient age at CBDCA retreatment, ii) previous allergy history, iii) first-line chemotherapy regimen (single-agent CBDCA versus CBDCA in combination), iv) total CBDCA dose given during first-line treatment, v) CBDCA retreatment interval (interval time between the last cycle of first-line chemotherapy and CBDCA retreatment), vi) time of the clinical course of disease during which CBDCA retreatment was given (first recurrence versus further recurrence), and vii) CBDCA regimen at recurrence (single agent versus combination).

The statistical package SAS, release 6.7, was used for computations. Multiple logistic regression was carried out to investigate the relationship among the probability of developing an allergic reaction and the explanatory variables.

Results

Table 1 shows the characteristics of the 69 patients who received CBDCA retreatment for recurrent ovarian cancer. Median time to first recurrence was 18

Table 1. The characteristics of the patients who received CBDCA retreatment

Patient age at CBDCA retreatment	Median: 60 (range, 36–81) years
Previous allergy history	
Yes	9 patients
No	60 patients
First-line chemotherapy	
CBDCA in combination	60 patients
Single-agent CBDCA	9 patients
Total CBDCA dose in first-line chemotherapy	Median: 3270 (range, 1674–4656) mg
CBDCA retreatment interval	Median: 23.4 (range, 10.9–105) months
Recurrence treated with CBDCA	
First recurrence	60 patients
Second recurrence	5 patients
Third recurrence	2 patients
Fourth recurrence	2 patients
CBDCA regimen at recurrence	
CBDCA in combination	40 patients
Single-agent CBDCA	29 patients

months. Sixty patients were given CBDCA at the time of first recurrence. As for the type of regimen, single-agent CBDCA AUC 5–6 every 3 weeks was administered to 24 patients, paclitaxel 175 mg/m² + CBDCA AUC 5 every 3 weeks to 18 patients, doxil 30 mg/m² + CBDCA AUC 5 every 3 weeks to 13 patients, and gemcitabine 1000 mg/m² days 1 and 8 + CBDCA AUC 4 day 1 every 3 weeks to 5 patients.

Nine patients received CBDCA after one or more salvage chemotherapies (Table 2). As for the type of regimen, five patients received single-agent CBDCA AUC 5–6 every 3 weeks, three patients gemcitabine 1000 mg/m² days 1 and 8 + CBDCA AUC 4 day 1 every 3 weeks, and one patient paclitaxel 175 mg/m² + CBDCA AUC 5 every 3 weeks.

All the patients receiving CBDCA retreatment were systematically prophylaxed with corticosteroids, antihistamines, and H2 antagonists.

Hypersensitivity reactions occurred in 15 (21.7%) of the 69 patients (Table 3). All reactions developed within 40 min from the start of infusion, and no patients had delayed reactions. Hypersensitivity reactions occurred during the second cycle of CBDCA retreatment in 13 (86.7%) of the 15 patients and consisted of skin rash, flushing, itching, or abdominal cramping without respiratory or cardiovascular symptoms in 8 (53.3%) patients and severe respiratory or cardiovascular events in 7 (46.7%). One patient developed a sudden and lancinating chest pain, without any other signs or symptoms suggestive of hypersensitivity, immediately followed by cardiac arrest refractory to standard resuscitative measures. The death was attributed to an acute coronary syndrome, but autopsy was not performed because of relatives' refusal. All the other cases promptly recovered from symptoms after CBDCA infusion withdrawal. Patients with mild reactions received low-dose corticosteroids and antihistamines, whereas those with severe events

Table 2. Patients who received CBDCA retreatment after the first recurrence: prior salvage chemotherapies and CBDCA retreatment interval

Patient	Prior salvage chemotherapy	CBDCA retreatment interval (months)
LB	Doxil	20.6
MC	Topotecan, doxil, gemcitabine	64.8
MC	Doxil	26.4
MGD	Doxil, topotecan	25.2
IG	Doxil	22.5
LM	Topotecan, doxil	18.9
FM	Doxil	29.2
OM	Doxil	22.8
GT	Doxil, paclitaxel (weekly)	45.3

Table 3. Characteristics of hypersensitivity reactions at CBDCA retreatment

Patient	Age	Allergy history	First-line chemotherapy	Total CBDCA (mg)	CBDCA retreatment interval (months)	Recurrence treated with CBDCA	CBDCA regimen at relapse	CBDCA cycle with HR	Time from infusion start to HR (min)	Symptoms of HR
AS	74	No	TAX + CBDCA	2865	19.3	First	CBDCA	Second	20	Facial flushing, anxiety
BA	71	No	TAX + CBDCA	3270	35.9	First	TAX + CBDCA	Second	20	Skin rash
BL	74	No	TAX + CBDCA	3700	20.6	Second	CBDCA	Third	50	Skin rash
BV	51	Yes	CBDCA	4176	29.5	First	TAX + CBDCA	Second	15	Facial flushing, dyspnea
BAM	56	No	TAX + CBDCA	2418	44.7	First	TAX + CBDCA	Second	20	Facial flushing, dyspnea, chest pain
BR	51	Yes	TAX + CBDCA	2670	16.9	First	CBDCA	Second	10	Hypotension, chest pain, dyspnea, bronchospasm, skin rash
CM	73	No	TAX + CBDCA	1674	64.8	Fourth	CBDCA	Second	10	Dyspnea, chest pain, facial flushing, anxiety
DM	69	No	TAX + CBDCA	2010	27	First	CBDCA	Second	10	Skin rash
FI	81	No	CBDCA	1700	34.4	First	CBDCA	Second	5	Chest pain, cardiac arrest, death
GK	57	No	CBDCA	2952	52.8	First	TAX + CBDCA	Second	40	Anxiety, facial flushing
GL	70	Yes	TAX + CBDCA	3000	24.1	First	CBDCA	Second	15	Itching
MF	69	No	TAX + CBDCA	3300	29.2	Second	TAX + CBDCA	Second	40	Hypertension, dyspnea, facial flushing
PMA	57	No	TAX + CBDCA	3996	47.3	First	TAX + CBDCA	Fourth	20	Diarrhea, abdominal cramping
PA	56	No	TAX + CBDCA	4086	28.9	First	TAX + CBDCA	Second	10	Anxiety, abdominal cramping
TG	44	No	TAX + CBDCA	3552	45.3	Third	CBDCA + GEM	Second	20	Dyspnea, chest pain, facial flushing, palmar erythema

HR, hypersensitivity reaction; TAX, paclitaxel; GEM, gemcitabine.

were treated with high-dose corticosteroids, antihistamines, and individualized procedures (salbutamol, adrenalin, respiratory assistance, and colloid solutions).

Logistic regression analysis showed that previous allergy history and CBDCA retreatment interval were independent predictive variables for the risk of hypersensitivity (Table 4).

CBDCA reinfusion was never attempted, also after mild hypersensitivity reaction. Nine patients were subsequently treated with cisplatin, which caused a skin rash in one patient and a severe, not fatal dyspnea in another one. These two patients stopped further treatment with cisplatin.

Discussion

CBDCA-associated hypersensitivity reactions occur in less than 1% of the patients during primary treatment but in 8–44% of patients during second- or third-line retreatment^(1,2,5,8,23,24). The incidence of these reactions has been mainly related to the number of cycles of CBDCA administered. Patients are likely sensitized during the six cycles of first-line chemotherapy; after recurrence, they are reexposed to CBDCA during the seventh cycle and more frequently develop reactions during the eighth cycle. Hypersensitivity risk has been also related to a drug allergy history⁽²¹⁾ and to the total dose of previously administered platinum agents⁽²⁵⁾. Watanabe *et al.*⁽²⁵⁾ reported five cases of CBDCA

hypersensitivity after weekly low-dose paclitaxel (60 mg/m²)/CBDCA AUC 2 therapy in 23 platinum-pretreated patients with recurrent ovarian cancer. The range of the previously administered total dose of CBDCA before hypersensitivity occurred was 2582–9589 mg, and the mean CBDCA AUC of the first treatment exhibited appropriate intensity (1.92 ± 0.10 ; range, 1.76–2.10) in all patients.

Symptoms of hypersensitivity reactions vary from mild skin reactions to severe respiratory and cardiovascular events^(5,8,18).

In our department, the patients receiving CBDCA retreatment were systematically prophylaxed with corticosteroids, antihistamines, and H2 antagonists, but despite this premedication, the incidence of hypersensitivity reactions was above 20%. The administration of these drugs appears to have a limited effectiveness in the prophylaxis of severe reactions^(1,5,8). The clinical characteristics of hypersensitivity reactions were similar to those commonly reported in the literature. One patient developed a sudden chest pain, without any other signs or symptoms suggestive of hypersensitivity, immediately followed by fatal cardiac arrest. Two cases of CBDCA hypersensitivity presenting as coronary vasospasm have been described in the literature^(26,27). For instance, Chasen and Ebrahim⁽²⁷⁾ reported the case of a 68-year-old woman with advanced ovarian cancer who collapsed while receiving CBDCA infusion. The patient had a transient, significant ST

Table 4. Variables predictive of hypersensitivity reactions in patients who received CBDCA retreatment

Variable	Patients	HR (%)	P value	OR	95% CI
Patient age (years)					
≤60	35	7 (20.0)	0.8784	1.133	0.229–5.618
>60	34	8 (23.5)			
Previous allergy history					
Yes	9	4 (44.4)	0.0422	7.734	1.075–55.565
No	60	11 (18.3)			
First-line chemotherapy					
CBDCA in combination	60	12 (20.0)	0.4420	0.471	0.069–3.211
Single-agent CBDCA	9	3 (33.3)			
Total CBDCA dose (mg)					
≤3270	35	10 (28.5)	0.1282	1.351	0.059–1.430
>3270	34	5 (14.7)			
CBDCA retreatment interval (months)					
≤23.4	36	3 (8.3)	0.0132	7.084	1.506–33.329
>23.4	33	12 (36.3)			
Recurrence treated with CBDCA					
First recurrence	60	11 (18.3)	0.1224	4.185	0.680–25.736
Further recurrence	9	4 (44.4)			
CBDCA regimen at recurrence					
CBDCA in combination	40	8 (20.0)	0.1266	0.7219	0.257–7.096
Single-agent CBDCA	29	7 (24.1)			

HR, hypersensitivity reaction; OR, odds ratio; 95% CI, 95% confidence interval.

elevation and a right pleural effusion, without any other signs or symptoms suggestive of hypersensitivity. A coronary angiogram performed after patient referral to the intensive care unit showed normal coronary arteries.

In our series, previous allergy history and CBDCA retreatment interval were independent predictive variables for the risk of hypersensitivity, whereas patient age, first-line chemotherapy regimen, total CBDCA dose given during first-line treatment, recurrence treated with CBDCA, and CBDCA regimen at recurrence had no predictive value. It is worth noting that hypersensitivity reaction rate was significantly higher in patients with CBDCA retreatment interval longer than 23.4 months compared to those with a shorter interval (36.3% versus 8.3%, OR (Odd Ratio) = 7.084, 95% CI (Confidence Interval) = 1.506–33.329, $P = 0.0132$). Similarly in the study of Schwartz *et al.*⁽²⁸⁾ on 126 gynecological cancer patients who had multiple CBDCA regimens, the overall incidence of hypersensitivity reactions was 25.8% and 56.5% ($P = 0.0023$) for patients retreated within and after 12 months of their last CBDCA-based chemotherapy, respectively. Moreover, the incidence of a severe allergic reaction significantly increased with time, being 6.5%, 23.9%, and 47% ($P < 0.0091$) for a platinum-free interval shorter than 12 months, between 12 and 24 months, and longer than 24 months, respectively.

Replacement of CBDCA by cisplatin has often allowed to continue salvage treatment with platinum analogs, but in the literature, there are some reports of severe reactions, with such substitutions^(29–35). For instance in the experience of Memorial Sloan-Kettering Cancer Center, five out of seven ovarian cancer patients with CBDCA allergy were successfully treated with cisplatin without further reactions⁽³³⁾. However, one patient had facial swelling and dyspnea at the first cycle and diffuse erythema and chest tightness at the second cycle, and another one developed a severe anaphylactic reaction during the second cycle which progressed to fatal cardiac arrest despite standard resuscitative measures. In our series, cisplatin caused further allergic reactions in two (22.2%) of the nine patients who were treated with this drug. Substitution of CBDCA with oxaliplatin has been also suggested, but a cross-reactivity to CBDCA is still possible^(36,37).

Desensitization protocols, using increasing dilutions and prolonged infusion times, have been tested for patients with CBDCA hypersensitivity, but their use in clinical practice should be taken into consideration with a great caution as severe outcomes can occur despite desensitization^(6,8,38–40). Intradermal skin test with CBDCA, which appears to have a negative pre-

dictive value of 98% approximately, could decrease the risk of serious allergic reactions, but this method is not widely used because of the time, effort, and training involved^(8,28,41–43).

In conclusion, hypersensitivity to CBDCA retreatment can occur in approximately one fifth of recurrent ovarian cancer patients who have previously received six cycles of first-line CBDCA-based chemotherapy. A CBDCA retreatment interval longer than 2 years is the strongest predictive variable for the development of allergic reactions. Replacement of CBDCA by cisplatin can be associated with further hypersensitivity reactions. Based on the present results as well as literature data, patients candidate for CBDCA retreatment, and especially those with a long platinum-free interval, should undergo a skin test to predict the risk of drug hypersensitivity.

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