RESEARCH ARTICLE

Comparison of Hypersensitivity Reactions to Carboplatin Retreatment in Gynecologic Cancer Patients between One and Two Hour Infusions: a Randomized Trial Study

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Abstract

Objective: To compare the incidence rate of carboplatin hypersensitivity reactions (HSRs) in gynecologic cancer patients receiving one-hour or two-hour carboplatin retreatment infusions. **Setting:** A Prospective Randomized Controlled Trial. **Methods:** Recurrent gynecologic cancer patients 25 to 80-years of age who were scheduled to receive carboplatin retreatment after previously receiving at least six cycles of carboplatin without a history of platinum allergy were invited to enroll. They were randomized to receive either a one-hour or two-hour carboplatin infusion in each cycle. The nurses recorded any occurrence of HSR. Patients who developed carboplatin HSR were discontinued from the study. **Results:** Forty-five patients were enrolled and randomized to receive either a one-hour carboplatin infusion arm in 69 cycles or a two-hour infusion arm in 67 cycles. Both groups were well balanced regarding median age, body mass index, type of cancer, history of drug allergy, median platinum free interval time, median total number of previous carboplatin cycles, premedication type, regimen and median total dose of carboplatin. Five (3.67%) of the 136 cycles resulted in carboplatin HSR, all of which were Grade 1. Of these, four cycles developed HSR during the one-hour infusion and only one cycle with a two-hour infusion (P=0.37). The onset of carboplatin HSR occurred within 30-105 minutes after infusion start. **Conclusion:** Extending the carboplatin infusion time to two hours from one hour did not significantly decrease carboplatin HSR.

Keywords: Carboplatin- hypersensitivity reaction- gynecologic cancer- extended infusion time

Asian Pac J Cancer Prev, **18 (2)**, 425-430

Introduction

Carboplatin is a widely used platinum based chemotherapy for gynecologic cancer treatment especially ovarian cancer and peritoneal cancer. It is usually administered with paclitaxel as a PT regimen both in primary and in platinum sensitive recurrent settings (ICON2,1998; ICON3,2002; Trimbos et al.,2003). The previous studies reported 12-19 percent of hypersensitivity reaction (HSR) rates occurred in those patients who received a PT regimen and the incidence rate increased when more cycles of carboplatin were administered. Zanotti et al. found that the patients who were treated by more than seven cycles of carboplatin had an increased incidence of HSR as high as 27 percent, compared with only one percent in patients who received six or fewer cycles (Zanotti et al., 2001).

The mechanism of carboplatin HSR remains unclear. O'Cearbhaill et al. believed that the carboplatin HSR was mediated through a Type I immunoglobulin E (IgE) dependent mechanism. In addition, the clinical manifestations of HSR varied in a range from asymptomatic or transient flushing to anaphylaxis or death (O'Cearbhaill et al., 2010). Thus, numerous immunological and non-immunological mechanisms might be associated with HSR.

To prevent HSR of carboplatin, one simplified method was the extended carboplatin infusion time. O'Cearbhaill et al. conducted a retrospective study and found that the extended infusion time of carboplatin could decrease the HSR events. They compared the 30-minute to three-hour carboplatin infusion time and reported the incidence of HSR decreased from 21 percent in the patients who received a 30-minute infusion to only nine percent in the patients with a three-hour infusion time (O'Cearbhaill et al., 2010). In our center, carboplatin containing regimens were given in an out-patient setting with one-hour infusions as standard schedule (Koshiba et al., 2009) and occasionally carboplatin HSR was noted especially in patients who had previously received numerous cycles of carboplatin. To determine if the extended carboplatin infusion time could decrease HSR, we conducted this randomized controlled trial in gynecologic cancer patients who were historically treated by at least six carboplatin-included regimens cycles and required retreatment by a carboplatin-included regimen. The aim

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was to compare the incidence of carboplatin HSR in the cycle with one-hour carboplatin infusion to a two-hour infusion. We selected a two-hour infusion instead of a three-hour infusion as mentioned in the previous report because it was more convenient in our outpatient setting.

Materials and Methods

This study was a prospective randomized controlled trial conducted at the One Day Chemotherapy Unit of the Chiang Mai University Hospital between June 1, 2015 and June 30, 2016. After approval from the Research Ethics Committee of Faculty of Medicine, Chiang Mai University and registry as a Thai Clinical Trial. (TCTR20151123001), the patients with recurrent gynecologic cancer who met the inclusion criteria were selected. Carboplatin retreatment patients who had historically received carboplatin included regimen of at least six cycles and revealed normal bone marrow, renal and liver function were included. The patients with a preexisting history of carboplatin or another platinum allergy were excluded.

After enrollment, the patients were randomly allocated to receive either a one-hour or two-hour carboplatin infusion in each cycle. A randomization list was computer-generated. The investigator prepared sealed, opaque and sequentially numbered envelopes with the respective allocation codes. The nurse in the One Day Chemotherapy Unit opened an envelope and started premedication and infused carboplatin included-chemotherapy in one or two hours following the identification code. Data of HSR symptoms were collected by the attending nurses. The patients were administered the premedication 30 minutes prior to the initiation of the carboplatin-included chemotherapy. The two types of premedication that were given included: lorazepam (0.5 mg) 1 tablet orally, intravenous solution of dexamethasone 20 mg plus ondansetron 8 mg in 100 ml of 5% dextrose water at 50 drops/minute, ranitidine 50 mg intravenous slowly pushed over two minutes and chlorpheniramine 10 mg slow intravenous push. The difference between the two premedication regimens was intravenous hydrocortisone 100 mg slowly push either added or not added to the regimen. The premedication regimens were selected by the physicians' preference. In the combination regimen, carboplatin was given lastly. After started the chemotherapy infusion, the attending nurses recorded vital signs and any HSR symptoms referenced by the Common Terminology Criteria for Adverse Events Volume 3.0 (CTCAE v3.0) consisting of Grades 1 to 5 categorized from minimal to severe symptoms of HSR in each chemotherapy (Trotti et al., 2003). If HSR occurred, the attending nurse immediately stopped the chemotherapy infusion and notified the doctor for HSR standard treatment. Those patients who developed any grade of carboplatin HSR were discontinued in this study. The basic clinical data and the type of HSR were recorded.

The sample size was calculated based on the prevalence of carboplatin HSR in a former study (O'Cearbhaill et al., 2010). The result was 63 cycles of carboplatin infusion per arm to obtain 80% power with alpha error less than 0.05 and a difference of 20% in the outcome measurement. Data were analyzed using IBM SPSS statistic version 22.0 for Windows. The summary statistics were reported as percentages for categorical number. The Mann-Whitney U test and the Chi-square test were used to determine the variable and the incidence of carboplatin HSRs between the controls and the study groups as appropriate. A p-value of less than 0.05 was set up as statistically significant.

Results

Forty-five patients met the inclusion criteria and were enrolled in the present study with 163 cycles of carboplatin included regimens administered. Twenty-four cycles were excluded from this study due to the patients refusal to participate in the study. Thus, 139 cycles of carboplatin included regimens were randomized to administer carboplatin in one-hour (69 cycles) and two-hour infusions (70 cycles). However, 3 cycles of 2-hour infusion were excluded due to the erroneous of enrollment process that recruited the patient who developed carboplatin HSR in the former cycle. Therefore, the final analysis was done in 69 cycles of 1-hour carboplatin infusion arm and 67 cycles od 12 -hour infusion arm as shown in Figure 1.

Both groups were well balanced in age, body mass index, body surface area, type of cancer, history of drug allergy, underlying disease presented, initial stage, mean interval time of the latest given carboplatin, the line and regimen of previous chemotherapy, the median total of the former cycles of carboplatin and the median dosage of carboplatin as listed in Table 1. The details of chemotherapy for both infusion times were presented in Table 2. The most frequent regimen in both groups was carboplatin plus paclitaxel. There were no statistically significant differences in the type of premedication, mean total of carboplatin in each cycle, the type of calculation for the dosage of carboplatin and the mean total number of carboplatin dosages and cycles in both arms. Three patients developed Grade 1 HSR to paclitaxel in seven cycles. Of these cycles, three cycles were one-hour

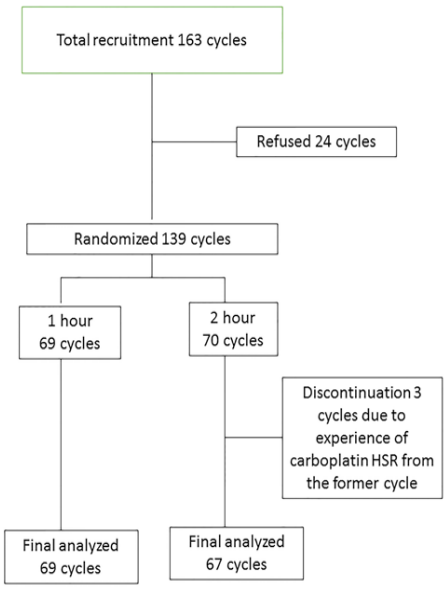

Figure 1. Flow of the CyclesThrough the Study

Table 1: Demographic and Clinical Characteristics of Patients Enrolling to Compare Carboplatin Hypersensitivity Reaction, By Randomized 1 Hour versus 2 Hours Carboplatin Infusion Time. (N = 45 , 136 Cycles)

Characteristic	1 hour (69 cycles) (%)	2 hours (67 cycles) (%)	P value
Median age (range:years)	56.0 (37-71)	56.0 (37-71)	0.96*
Median BMI (range:kg/m^2	23.3 (1113.5-36.7)	23.5 (16.5-33.9)	0.73*
Median BSA (range:m2	1.5 (1.1-1.9)	1.51 (1.2-1.8)	0.66*
Type of Cancer			0.35**
Ovary	34 (49.3)	35 (50.7)	
Uterine	11 (15.9)	6 (9.0)	
Cervix	13 (18.8)	9 (13.4)	
Other	11 (15.9)	17 (25.4)	
History of Drug Allergy	6 (8.7%)	7 (10.4)	0.78**
Underlying Disease	19 (27.5)	20 (29.9)	0.56**
Initial Stage			0.31**
Early	25 (39.1)	30 (50.0)	
Advanced	44 (63.8)	37 (55.2)	
Median Interval Time from Last Carboplatin (months, range)	12.0 (1-44)	12.0 (1-56)	072*
Line of Chemotherapy			0.36**
Second Line	36 (52.2)	43 (64.2)	
Beyond Second Line	33 (47.8)	24 (35.8)	
Previous Chemotherapy			0.40**
Carboplatin and Paclitaxel	33 (47.8)	40 (59.7)	
Carboplatin	3 (4.3)	3 (4.5)	
Median total Previous Cycles of Carboplatin (range)	9.0 (6-23)	9.0 (6-21)	0.83*

BMI, Body Mass Index; BSA, Body Surface Area; **, Chi-square test; *, Mann-Whitney U test

carboplatin infusions while the remaining four cycles were in the two-hour carboplatin infusion arm. All paclitaxel allergy patients did not develop carboplatin HSR.

Only five cycles (3.7%) of the 136 cycles or 5 patients of the 45 patients (11%) developed carboplatin HSR and all were Grade 1. Of these cycles, four cycles developed in the one-hour infusion arm and only one cycle developed during a two-hour infusion arm. However, this difference did not reach statistical significance (P value =0.37). The details of the five patients who developed carboplatin HSR were presented in Table 3. All of them received carboplatin plus paclitaxel and had received carboplatin previously for more than ten cycles. The dosage was in a range of 440-620 mg. Three patients developed HSR symptoms

Table 2. Chemotherapy Detailed in Each Carboplatin Infusion Time

	1 hour (69 cycles) (%)	2 hours (67 cycles) (%)	P value
Present regimen			0.63*
PT	61(88.4)	62 (92.5)	
Carboplatin	5(7.2)	2 (3.0)	
Carboplatin and PLD	3(4.3)	3 (4.5)	
Premedication			0.62**
Without Hydrocortisone	48(72.7)	49 (76.6)	
With Hydrocortisone	18(26.1)	15 (22.4)	
Median Total Dose of Carboplatin in Each Cycle (range)	500.02(310-670)	500.0 (300-700)	0.90***
Dosage of Carboplatin			0.743*
AUC 5	52(75.4)	56 (83.6)	
AUC 5 with 25% Dose Reduction	2(2.9)	1 (1.5)	
AUC 6	3(4.3)	2 (3.0)	
400 mg/m^2	11(15.9)	8 (11.9)	
400 mg/m^2 with 25% Dose Reduction	1(1.4)	-	
Median Total of all Cycles of Carboplatin (included this research) (range)	10.07-24)	10.0(7-22)	0.90***

PT, carboplatin + paclitaxel; PLD, Pegylated liposomal doxorubicin; AUC, Area under the curve; *, Fisher's exact test; **, Chi-square test; ,***, Mann-Whitney U test

Table 3. Clinical Data of 5 Patients with Carboplatin Hypersensitivity Reaction (HSR)

Patient code	Age	Platinum free interval (months)	Cycle	Cycle of carboplatin	Dosage of carboplatin (mg)	Premedication	Interval of carboplatin infusion (hour)	Onset of HSR (min)	Stop† (min)	Symptoms‡
37	53	20	6	16	620	A	1	70	-	Flushing/transient rash
										Rx: CPM
0 57	58	17	6	12	500	B	1	30	30	Transient rash/ nausea & vomiting
										Rx: ondansetron
71	57	15	6	12	440	B	1	35	30	Transient rash
										Rx: CPM
69	69	27	3	12	560	A	1	60	-	Flushing, transient rash
										Rx:CPM
			4	13	500	A	2§	75	30	Flushing
										Rx: CPM
			5	14	500	A	2§	105	45	Flushing, transient rash
										Rx:CPM
			6	15	530	A	2	-		none
16	69	11	3	13	500	A	2	35	35	Transient rash
										Rx: CPM
			4	14	500	B	1	-		none
			5	15	460	B	1	-		none
			6	16	580	B	1	-		none

All of them received carboplatin plus paclitaxel; Premedication: A, routine drugs + hydrocortisone 100 mg intravenously; B, routine drugs only; HSR, Hypersensitivity reaction; Rx, treatment; CPM, Chlorpheniramine; min, minutes; †,The time of discontinued carboplatin infusion; ‡, All hypersensitivity reaction was grade 1according to Common Terminology Criteria for Adverse Events Volume 3.0 (CTCAE v3.0) (7); §, This patient was developed carboplatin HSR at cycle 3 and was discontinued from the study; However, with the erroneous of recruitment process, she still received carboplatin with 2-hour infusion time at cycle 4-6 and developed carboplatin HSR at cycle 4 and 5.

in the last cycle while two patients developed HSR in the third cycle and one of them still developed Grade 1 HSR in the fourth and fifth cycles but did not develop it in the sixth cycle. This patient was discontinued from the study due to the experience of carboplatin HSR in cycle 3 that infused carboplatin in 1-hour but with the erroneous of the enrollment process, she was randomized to 2-hour infusion group in the rest 3 cycles and still developed carboplatin HSR in cycle four and five. The remaining patients received cycles four through six without HSR even though receiving carboplatin over one-hour. All carboplatin HSR in the present study were in Grade 1 with only transient flushing or a rash that improved after administration of chlorpheniramine and were able to complete their carboplatin infusion after discontinued the carboplatin for 30 -45 minutes while the onset of carboplatin HSR were 30-105 minutes.

Discussion

The incidence of carboplatin induced HSR in the literature was varied from 1 to 35% (Pandey et al., 2014). However, it occurred more frequently in the patients who received carboplatin beyond the first line setting with the peak incidence at median number of seven cycles of carboplatin (Robinson et al., 2001). Variable clinical manifestations of carboplatin HSR have been reported such as itching, rash, chest tightness, emesis, blood pressure changes and facial swelling that could occur after just starting or completing an infusion (Fotopoulou , 2014). In the present study, we found the incidence of carboplatin HSR only 3.7% of cycles or 10% of patients even in the recurrence setting and all of these events were Grade 1 HSR that revealed only transient flushing or rash. This different incidence rate might be from the variation in premedication type, the race, the dosage of carboplatin and the criteria of HSR. We used Common Terminology Criteria for Adverse Events volume 3.0 (Trotti et al., 2003) for collecting data of HSR. These criteria did not include some events such as emesis while other studies included this event (Fotopoulou , 2014).

Caiado J and Castells M, (2015) recently reviewed platinum HSR and summarized that the most important predictive factor for carboplatin HSR was the multiple and repeated exposure to carboplatin. They reported the incidence rate of carboplatin HSR before the sixth infusion was 0.92 and was increased to 19%-23% during the retreatment setting. Robinson et al., (2001) retrospectively reviewed 32 patients with HSR from chemotherapy. Of those patients, 16 of them occurred from carboplatin exposure with the median prior course of seven. Other predictive factors were recently reported by a Japanese study. They found that a previous history of drug allergy, a prolonged platinum-free interval more than 13 months and a high dosage more than 650 mg increased the risk of carboplatin HSR (Sugimoto et al., 2011) In the present study, all five patients who developed carboplatin HSR revealed the median cycle of carboplatin exposure as 13 cycles, the median dosage of carboplatin administered was 500 mg and the median interval of platinum-free interval was 17 months. These findings were relevant to the previous reports except the dosage of carboplatin. Our patients did not receive carboplatin in as high a dose as in previous studies. Thus, we did not have such experience.

The exact mechanism of carboplatin induced HSR remains unclear. With the repeated exposure to free platinum metal which was contaminated in the carboplatin composition, this substance may produce allergic manifestations developed through a type 1 IgE mediated HSR mechanism via the releasing of vasoactive cytokines and histamine from basophils and mast cells (Pandey et al., 2014).

One interesting method that was mentioned to prevent carboplatin HSR was the extension of the carboplatin infusion time. Two previous studies reported the comparative study and found significantly reduced carboplatin HSR incidence by increasing the infusion carboplatin time from 30 minutes to three hours (O'Cearbhaill et al., 2010; Pasternak et al., 2016). The first study was published in 2010 by review of the electronic medical records of the patients with recurrent ovarian cancer, fallopian tube cancer and primary peritoneal cancer who were retreated with carboplatin with the study period over ten years. The authors reviewed 777 patients and found 117 patients developed carboplatin HSR. Of these, only 3.4% of 174 patients received three-hour carboplatin infusions compared to 21% of 533 patients who received a 30 minutes infusion (O'Cearbhaill et al., 2010). Various premedication types were used and included the patients who experienced chemotherapy allergy in this study. Another study was published this year with a retrospective chart review design. The authors included 326 patients who were diagnosed with ovarian, fallopian tube and primary peritoneal cancer and were treated with at least eight cumulative cycles of carboplatin between January, 2007 and September, 2014. Of these, 161 patients received 30-60-minute infusions and 165 patients received three-hour extended infusions of carboplatin. The patients who received the three-hour extended infusions significantly received triple premedication therapy. They found 40% of the patients with the 30-60 minute infusions developed carboplatin HSR while only 24.2% of the three-hour extended infusions developed such events ($P = 0.0027$) (Pasternak et al., 2016). However, both of them were retrospective studies with a longer period of studied time of seven to ten years than our present study. Recently, a small prospective trial that recruited 15 patients with 3 -hour infusion carboplatin retreatment found carboplatin HSR in 6 patients (40%). This incidence rate was close to their own experience of carboplatin HSR that occurred in 35% of patients who received carboplatin without extended infusion time (Lax et al., 2016). The authors concluded that the extended carboplatin infusion time did not benefit to decrease HSR.

One interesting point that observed from our study was the onset of carboplatin HSR. Of seven cycles that developed such event, the onset was in a range of 30-105 minutes. O'Cearbhaill et al. found that only 20% of carboplatin HSR occurred within initial 1/5 of the total infusion time while the rest occurred after that and about 20% developed carboplatin HSR within one hour after completion of carboplatin administer (O'Cearbhaill et

al., 2010).

Regarding the present study that was conducted in randomized controlled trial, we still did not find the significant differences of carboplatin HSR in the one-hour infusion group versus the two-hour infusions. In five cycles of carboplatin exposure, four cycles developed carboplatin HSR during one-hour infusions while one cycle developed in a two-hour infusion time. However, the non-significant difference might be from the low incidence rate of carboplatin HSR in our patients so that the further study should recruit more participants. This was the limitation of the present study.

In conclusion, the extended carboplatin infusion time did not decrease the rate of carboplatin HSR, significantly.

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgements

We wish to thank The National Research University Project under Thailand's Office of Higher Education Commission and Chiang Mai University for their financial support in this project.

References

Caiado J, Castells M (2015). Presentation and diagnosis of hypersensitivity to platinum drugs. *Curr Allergy Asthma Rep*, **15**, 15.

Fotopoulou C (2014). Limitations to the use of carboplatin-based therapy in advanced ovarian cancer. *EJC Suppl*, **12**, 13-6.

Koshiba H, Hosokawa K, Kubo A, et al (2009). Incidence of Carboplatin-related hypersensitivity reactions in Japanese patients with gynecologic malignancies. *Int J Gynecol Cancer*, **19**, 460-5.

International Collaborative Ovarian Neoplasm Group (2002). Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet*, **360**, 505-15.

International Collaborative Ovarian Neoplasm Study (1998). ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. ICON Collaborators. *Lancet*, **352**, 571-6.

Lax T, Dizon DS, Birrer M, et al (2016). Extended carboplatin infusion does not reduce frequency of hypersensitivity reaction at initiation of retreatment in patients with recurrent platinum-sensitive ovarian cancer. *J Allergy Clin Immunol Pract*, **25**, 2213-98.

O'Cearbhaill R, Zhou Q, Iasonos A, et al (2010). The prophylactic conversion to an extended infusion schedule and use of premedication to prevent hypersensitivity reactions in ovarian cancer patients during carboplatin retreatment. *Gynecol Oncol*, **116**, 326-31.

Pasternak AL, Link NA, Richardson CM, Rose PG (2016). Effect of prophylactic extended-infusion carboplatin on incidence of hypersensitivity. *Pharmacotherapy*, **36**, 723-30.

Pandey A, Bhosale B, Pandita V, et al (2014). Carboplatin hypersensitivity in relapsed ovarian carcinoma: A therapeutic challenge. *Indian J Med Paediatr Oncol*, **35**, 17-20.

Robinson JB, Singh D, Bodurka-Bevers DC, et al (2001). Hypersensitivity reactions and the utility of oral and intravenous desensitization in patients with gynecologic malignancies. *Gynecol Oncol*, **82**, 550-8.

Sugimoto H, Iwamoto T, Murashima Y, et al (2011). Risk factors contributing to the development of carboplatin-related delayed hypersensitivity reactions in Japanese patients with gynecologic cancers. *Cancer Chemother Pharmacol* **67**, 415-9.

Trimbos JB, Parmar M, Vergote I, et al (2003). International collaborative ovarian neoplasm trial 1 and adjuvant chemoTherapy in ovarian neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst*, **95**, 105-12.

Trotti A, Colevas AD, Setser A, et al (2003). CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* **13**, 176-81.

Zanotti KM, Rybicki LA, Kennedy AW, et al (2001). Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. *J Clin Oncol*, **19**, 3126-9.