



Cisplatin can be safely administered to ovarian cancer patients with hypersensitivity to carboplatin[☆]

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HIGHLIGHTS

- HSR are a common adverse event in patients rechallenged with carboplatin for ROC
- Carboplatin-PLD is associated with a lower risk of developing HSR compared to other doublets
- Several strategies have been developed to continue platinum-based therapy in these patients.
- Cisplatin rechallenge in patients with carboplatin HSR is a safe and feasible approach.
- In patients treated with cisplatin without a carboplatin-related HSR, a low rate of cisplatin-related HSR has been detected.

ARTICLE INFO

Article history:

Received 22 August 2016

Received in revised form 10 October 2016

Accepted 17 October 2016

Available online 27 October 2016

Keywords:

Ovarian cancer

Chemotherapy

Carboplatin

Cisplatin

Hypersensitivity reaction

Adverse drug reaction

ABSTRACT

Objective. Hypersensitivity reactions (HSR) are frequently reported in patients rechallenged with carboplatin for recurrent ovarian cancer (ROC) and represent a critical issue, since discontinuation of the platinum-based therapy could affect prognosis. Several strategies to allow platinum rechallenge have been described, with controversial outcomes. The aim of this study is to illustrate a 10-year experience with cisplatin in patients with a previous HSR to carboplatin or at risk for allergy.

Methods. A retrospective review of all patients with platinum sensitive ROC retreated with carboplatin was performed between January 2007 and May 2016 at the Istituto Nazionale Tumori, Fondazione “G. Pascale”, Naples.

Results. Among 183 patients, 49 (26.8%) presented HSR to carboplatin, mainly during second line therapy. Mean number of cycles before HSR was 8 (range 3–17). G2, G3 and G4 reaction were detected in 83%, 15% and 2% of patients, respectively. In a multivariate analysis including age, histotype, BRCA status, previous known HSR, and combination drug administered, only the type of carboplatin-based doublet used as 2nd line therapy was found to significantly affect HSR development, with a protective effect of PLD (pegylated liposomal doxorubicin) ($p = 0.014$, OR = 0.027). Thirty seven patients (77%) with a previous HSR to carboplatin were rechallenged with cisplatin. Treatment was generally well tolerated. 5 patients (13.1%) experienced mild HSR to cisplatin, successfully managed in all cases. 14 patients were treated with cisplatin even without a carboplatin-related HSR due to other allergies. Among these, only one developed HSR (7.1%).

Conclusions. Cisplatin rechallenge is a feasible approach in patients experiencing HSR to carboplatin to maintain the beneficial effect of platinum while reducing hypersensitivity-related risks.

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1. Introduction

Carboplatin based doublets are standard treatment for ovarian cancer both in front-line and platinum sensitive recurrences [1,2]. Despite

[☆] Source support: Dr. Sandro Pignata is recipient of a grant from AIRC (Associazione Italiana Ricerca sul Cancro) (13114).

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surgery and chemotherapy, advanced ovarian cancer recurs in approximately 75% of patients; up to 70% of recurrent patients receive a carboplatin based therapy for their platinum sensitive relapse [3,4].

Extensive use of platinum compounds in chemotherapy for ovarian cancer during the last decade has led to a significant increase in the incidence of hypersensitivity reactions (HSR). Markman et al. were the first to report a 12% rate of HSR in 205 patients treated with carboplatin for gynecologic malignancies [5].

Hypersensitivity to carboplatin is rarely observed during first line therapy. In fact, differently from allergy to non-platinum agents, most

allergic reactions are reported after the patient has received a significant number of infusions [5–7].

Platinum hypersensitivity symptoms more frequently develop early during infusion, more rarely after hours, or days after the infusion [8]. A skin rash may be the first sign of hypersensitivity, and it will be followed by more severe reactions in most patients. Symptoms of mild hypersensitivity include skin rash, urticaria, flushing, palmar itching, burning, edema of the face and hands, abdominal cramping and diarrhea, back pain, and pruritus. More severe reactions manifest with bronchospasm, tachycardia, hypotension or hypertension, seizures, and chest pain; life-threatening systemic anaphylaxis has been described [8–11].

Risk factors for carboplatin allergy have been described: particularly relevant are the number of prior platinum treatments, total lifetime exposure, the interval between the last infusion of first-line chemotherapy and retreatment. High rate of drug infusion also seems to be important [8–16]. Recently Moon et al. [17] observed that carboplatin hypersensitivity is more frequent in patients with BRCA mutated ovarian cancer, and this is likely related to the high probability of these patients to be repeatedly retreated with platinum during their life. Moreover, it has been reported that also exposure to DNA-platinum adducts, increased as a consequence of dysfunctional BRCA, might be immunogenic, potentially leading to HSR [17]. This is even more interesting when considering that a particular hyperactivity of the immune system has been detected in BRCA mutated patients [18]. The incidence of carboplatin hypersensitivity seems to be also associated with the type of carboplatin based doublets prescribed as second or third line. Data from the CALYPSO trial showed that HSR are significantly more frequent in patients receiving carboplatin-paclitaxel, as compared to carboplatin with pegylated liposomal doxorubicin (PLD) (18.8% versus 5.6%), although the reason for this difference is not clear [19].

Since the discontinuation of the platinum based therapy can significantly affect the prognosis of these patients several strategies to allow rechallenge and therapy continuation have been published and adopted in clinical practice especially in cases where patients are going to benefit from the drug.

Desensitization protocols have been implemented in order to re-administer the same platinum agent. However, successful desensitization protocols are usually time-consuming, success rates are not always satisfactory and severe reactions may still occur [20–29]. Few studies have suggested the replacement of carboplatin with different platinum salts, but the true incidence of cross-reactivity is not yet known [30–35]. It has been proposed that skin testing can prove helpful in an effort to rule out cross-reactions when one platinum salt is substituted by another [36–40]. More specifically, patients testing negative for cross-reaction in skin tests seem to be able to safely continue chemotherapy with a different platinum compound.

In 2003 we reported 10 cases successfully treated with cisplatin after carboplatin hypersensitivity [41] and after that, this practice has been adopted in our Department. In this study we describe our 10 years experience with cisplatin in patients with previous moderate/severe HSR to carboplatin and in a small group of patients considered at high risk of allergy directly treated with cisplatin due to previous carboplatin-unrelated HSR.

2. Patients and methods

All medical records of patients with platinum sensitive relapsed ovarian cancer retreated with carboplatin between January 2007 and May 2016 at the Division of Medical Oncology, Department of Urology and Gynecology of the National Cancer Institute of Naples, Italy were retrospectively reviewed. Data including patient demographics, tumor histotype, stage, grade, previous history of drug hypersensitivity, BRCA status as long as all details related to platinum based treatment were collected.

During the 10 years period platinum-sensitive recurrent ovarian carcinoma presenting a moderate to severe HSR, after an appropriate

patient counselling, underwent rechallenge with cisplatin when continuation of therapy was considered useful for the patient outcome. All patients received chemotherapy with cisplatin in the intensive care unit from 2005 to 2010, while later on the therapy was given in the chemotherapy unit.

The protocol adopted during this period consisted on cisplatin 60 mg/m² i.v. on day 1, either alone or in combination with paclitaxel or gemcitabine. Cisplatin in combination with PLD was administered every 28 days. Cisplatin-based chemotherapy was given at least 21 days after the allergic reaction with standard intravenous (i.v.) hydration, every 21 days, with infusion lasting 90 min. Antiemetics (5-hydroxytryptamine-3 antagonists) were routinely administered during chemotherapy. Premedication was administered 3 days before the therapy with ranitidine 150 bid, betamethasone 1 mg bid, promethazine 25 mg and 30 min prior to the infusion with dexamethasone 20 mg i.v., ranitidine 50 mg i.v. and promethazine 50 mg as intramuscular injection. Adequate renal, hepatic and hematological functions were required.

Occurrence of HSR to cisplatin, its management, course, outcome and subsequent therapy schedule were registered.

2.1. Statistical analysis

All the above mentioned demographic, pathologic and clinical variables were described and statistically compared between patients according to the development of carboplatin-related HSR. Median and ranges were reported for continuous variables, percentages for categorical variables. The Pearson chi square test for categorical variables or the Student's *t*-test for continuous ones were used to assess the significance of difference between the two groups. In all analysis, a *p* value of <0.05 was considered statistically significant.

Multivariable logistic regression analysis was performed in order to adjust for potential confounders.

For all statistical analyses SPSS version 17.0 (SPSS Inc., Chicago, IL, United States) was used.

3. Results

A total of 183 patients with platinum sensitive relapsed ovarian cancer were retreated with platinum-based chemotherapy at our Institution.

One hundred fifty eight patients were rechallenged with carboplatin as second line, 10 with cisplatin due to hypersensitivity to carboplatin in first line, 14 with cisplatin even without hypersensitivity to carboplatin, due to a previous HSR to other drugs used as concomitant medications. A total of 2140 cycles of carboplatin chemotherapy were administered. The median number of carboplatin cycles received was 12 (range 3–18).

Forty-nine patients (26.7%) presented an HSR to carboplatin: of these, 10 (20.4%), 34 (69.4%) and 5 (10.2%) during the first, second and the third line of rechallenge with carboplatin, respectively. The median number of carboplatin cycles administered before the occurrence of HSR was 8 (range 3–17).

Patients and chemotherapy characteristics stratified according to the occurrence of HSR are summarized in Table 1. No significant difference in age, previous known drug hypersensitivity, BRCA status, histotype, platinum free interval (PFI) was detected between the two groups. Carboplatin-doublet distribution in second line chemotherapy was different in the two groups, with a significantly lower PLD rate as combination treatment in the hypersensitivity group (Table 1). Interestingly, no significant correlation was detected between the time interval from carboplatin treatment and HSR at rechallenge. In a multivariate analysis including age, histotype, BRCA status, previous known drug hypersensitivity and combination drug administered, only the type of carboplatin-based doublet in 2nd line therapy was found to significantly affect the development of HSR, with a protective effect of PLD in patients

Table 1
Patients and chemotherapy details of patients according to the development of HSR.

	Hypersensitivity (N, %)	No hypersensitivity (N, %)	P
Age (median)			0.09
Mean $\pm$ SD	53.76 $\pm$ 8.37	56.53 $\pm$ 9.04	
Known drug hypersensitivity			0.39
Yes	6 (12.2)	42 (31.3)	
No	43 (87.8)	92 (68.7)	
Histotype			0.30
High grade serous	34(69.4)	97(72.4)	
Low grade serous	4(8.2)	13(9.7)	
Endometrioid	4(8.2)	3(2.2)	
Clear cell	1(2.0)	6(4.5)	
Undifferentiated	2(4.0)	6(4.5)	
Others	4(8.2)	9(6.7)	
PFI			0.70
6–12 months	8(16.3)	34(25.3)	
>12 months	41(83.7)	100(74.6)	
Combined treatment second line			0.04
Paclitaxel	14(41.2)	48(39.3)	
PLD	1(2.9)	28(23.0)	
Gemcitabine	17(50)	42(34.4)	
None	2(5.9)	4(3.3)	
Combined treatment third line			0.20
Paclitaxel	1(20)	4(16.7)	
PLD	1(20)	4(16.7)	
Gemcitabine	0	11(45.8)	
None	3(60)	5(20.8)	

rechallenged with carboplatin ($p = 0.014$, OR = 0.027, 95% CI 0.01–1.14).

Respiratory distress (chest tightness, wheezing, dyspnea), urticaria/erythema, facial swelling, tachycardia, hypertension or hypotension were the most frequent symptoms. Most patients presented a G2 HSR (83%), 15% G3. Only one patient had a G4 reaction. All reactions were successfully managed with infusion interruption, promethazine and dexamethasone administration.

Among all patients presenting hypersensitivity to carboplatin, 38 (77%) were rechallenged with cisplatin. Chemotherapy regimen characteristics are summarized in Table 2. The total number of cisplatin cycles administered was 211.

No reductions of chemotherapy doses were needed. The treatment with cisplatin was generally well tolerated. However 5 patients (13.1%) developed hypersensitivity, 3 after two cycles and 2 after six cycles. HSR occurred in all cases during or at the end of cisplatin infusion and consisted in mild or moderate reactions with facial flushing, sometimes extending to the chest; urticaria occurred only in one patient, while in two cases respiratory symptoms (cough and shortness of

breath) were registered. In all patients HSR were successfully controlled; in most cases only with cisplatin discontinuation and intravenous administration of 500 cm³ saline; in case of persistence, patients were further treated with ranitidine and 500 mg of hydrocortisone intravenously.

In one case, after 1 h from hypersensitivity remission, cisplatin infusion was successfully reattempted in the same cycle and later on, provided a slow infusion (3 h). One patient was rechallenged with oxaliplatin, with no hypersensitivity cross-reaction. In all other cases cisplatin infusion was discontinued either for completion of treatment or for disease progression. We have observed a single case of HSR to weekly carboplatin, appeared after the 7th administration, and successfully rechallenged in intensive care unit with carboplatin on a three-weekly schedule, performed in three escalation doses and after a three days prophylaxis with antihistaminics and corticosteroids.

Among the 14 patients treated with cisplatin without a previous HSR to carboplatin, only one patient (7.1%) developed a mild HSR to cisplatin administered in combination with gemcitabine during the third cycle. HSR was successfully managed and treatment was continued with only gemcitabine. Due to the subsequent platinum-resistant relapse, this patient was not considered eligible for platinum rechallenge.

4. Discussion

About 70% of patients with a platinum sensitive recurrence are rechallenged with a carboplatin-based regimen and a considerable amount of patients receiving carboplatin will eventually experience an HSR [2–4]. Several studies have tried to determine typical HSR patterns of presentation and related risk factors [6–17]; however, mechanisms underlying such reactions are still poorly understood, even if both an immediate type IgE mediated hypersensitivity reaction and a direct action of platinum on mast cells, leading to the release of vasoactive substances, are thought to play a relevant role. The risk of developing HSR has been reported to increase with the number of carboplatin lines and is estimated to be <1% during first line, and as high as 27% in patients treated with more than seven cycles of therapy. The overall incidence of carboplatin hypersensitivity further increases in the third-line setting [6,8,11]. Our findings, with an overall 26.7% rate of HSR are in line with data reported in literature, as well as the median number of cycles at which HSR presented. A possible role of the combination drug in affecting the risk of developing an HSR has been suggested. Data from the CALYPSO trial showed that HSR are significantly lower in patients treated with carboplatin + PLD as compared to carboplatin + paclitaxel [19]. We found a similar protective effect of PLD when combined to carboplatin in patients retreated with carboplatin.

Several efforts have been made aiming to identify possible strategies to avoid platinum discontinuation in these patients, as changing the treatment strategy could significantly worsen the prognosis. However, outcomes are not always reassuring and the best approach to follow still has to be determined. Prolonging the carboplatin infusion time has been described as a useful approach to reduce the risk of developing HSR. O’Cearbhaill et al. reported in their retrospective study that a preventive 3 h infusion schedule as compared to the standard 30-min significantly helps in reducing the incidence of HSR [28]. However, this approach is time consuming and would be rarely applied in patients with a previous HSR to carboplatin.

Carboplatin desensitization protocols have been implemented throughout the years in order to reduce HSR rates. The rationale is the gradual, prolonged reinfusion of the antigen to reach the full dose. Several desensitization protocols have been described in literature, with an overall success rate of 68–100% in 221 reported patients [20–27]. The one supported by the best evidence is a 12-step protocol developed by the Dana Farber Cancer Institute and Brigham and Women’s Hospital, applied to 60 patients and with a high success rate [21]. Even if a recently published review assessing safety, cost and efficacy of rapid drug

Table 2
Baseline characteristics of patients treated with cisplatin after hypersensitivity to carboplatin ($n = 38$ out of 183 recurrent platinum sensitive ovarian cancer patients).

Age (years)	
Median	54
Range	37–74
PFI (months)	N (%)
6–12	7 (18.4)
>12	31 (81.6)
Lines of cisplatin (number)	N (%)
Second	23 (60.5)
Third	6 (15.8)
Second and third	9 (23.7)
Combination drug in each line	N (%)
Paclitaxel	5 (10.7)
Cisplatin alone	16 (34.0)
Gemcitabine	26 (55.3)

desensitization to chemotherapy considers it safe and cost-effective [42], clear limitations are the time requested to undertake such a treatment, given that it should be administered at every cycle, and the recurrence of unpredictable HSR. Markman reported two deaths following anaphylaxis in patients rechallenged with carboplatin and following a desensitization protocol [43]. Moreover, both the risk assessment to select patients for a desensitization protocol and its successful application rely on the team's experience; therefore, this procedure can be hardly standardized. In this setting, skin testing has been suggested as a useful way to predict HSR to carboplatin and some Authors even recommend all patients to be tested after the 6th cycle [39]. This could help clinicians to select which patients to candidate for a desensitization protocol, as suggested by Markman, or to rule out a potential cross-reaction with another platinum drug. More specifically, patients testing negative for cross-reaction in skin tests could be able to safely continue chemotherapy with a different platinum compound. However, it cannot be safely performed in all patients (e.g. cardiovascular disease or elderly patient) and its results could be affected by certain medications. Another limitation is the time interval from HSR that should be observed before performing this test: to avoid false negative results 2–6 weeks should elapse before testing [40].

In 2003 Jones et al. described a cisplatin desensitization protocol for 5 patients experiencing a previous HSR to carboplatin, requiring a premedication and a 4-escalating dose cisplatin schedule, provided a previous negative skin test. The results of this study, however limited, suggest that in these patients a full desensitization protocol should be used, since the administration of a shorter protocol led to a new HSR. This approach is however described from the Author themselves as time consuming and labor intensive [44].

Cisplatin rechallenge without previous desensitization appears to be a reasonable approach, given that cisplatin has been for years a cornerstone in ovarian cancer treatment, with a comparable efficacy despite a worse toxicity profile [1–4]. This approach could positively combine the clinical efficacy of cisplatin, its low risk hypersensitivity profile and an easier administration schedule as compared to desensitization protocols. Nevertheless, experience with cisplatin rechallenge after a carboplatin-related HSR without prior desensitization is limited, as literature mainly consists of small case series and case reports, with a total of 59 reported patients [30–34,40]. Among these, in 2003 our group had reported an early experience of cisplatin rechallenge experimentally adopted in 10 patients [41]. Given the positive results, for the next 13 years this approach has become systematic in our Department. To the best of our knowledge, results from this experience represent the largest series currently available in literature.

Our data showed that out of 37 patients treated with cisplatin after a carboplatin-related HSR, 5 (13.1%) developed HSR after cisplatin rechallenge, a lower rate when considering outcomes reported by Calhoun et al., documenting a HSR rate of 25% (6/24 patients) with a similar cisplatin infusion schedule (90 min) but a different premedication (20 mg dexamethasone vs 8 mg in our series + 10 mg chlorpheniramine); however, this rate is in line with the overall rate of HSR (15%) when considering all 59 cases reported in the literature including two deaths from anaphylaxis; it is therefore extremely important to perform cisplatin rechallenge only after patient counselling, under safe conditions and with a proper antiallergic premedication. In our series all HSR were mild and successfully managed with drug discontinuation, hydration therapy and, in some cases, ranitidine and hydrocortisone intravenous administration. The success rate of the strategy reported here is similar and even higher as compared to that achieved with desensitization protocols, and surely less time consuming. Moreover, 14 patients considered at high risk for HSR due to other previous allergies were treated with cisplatin, with a low rate of HSR (7.1%). Therefore, we suggest cisplatin rechallenge as a possible successful strategy for patients with ROC considered at risk for HSR. All reactions to cisplatin rechallenge, either in patients with carboplatin-related and unrelated HSR group, were mild and successfully managed until complete remission.

5. Conclusions

Cisplatin rechallenge is a feasible, safe and practical approach to those patients experiencing HSR to carboplatin in order to positively balance the beneficial effect of platinum rechallenge with hypersensitivity-related risks. It may also represents an alternative in patients without previous carboplatin-related HSR, but considered at risk due to a history of previous HSR to other drugs.

Conflict of interest statement

Dr. Sandro Pignata is recipient of a grant from AIRC (Associazione Italiana Ricerca sul Cancro).

All Authors declare no potential conflicts of interest.

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