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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.

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ABSTRACT

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

1. Introduction

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

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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 know 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, hystotype, 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

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