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ORIGINAL ARTICLE

# Cisplatin administration following carboplatin desensitization failure in primary peritoneal cancer: a brief report

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**Abstract**
*Purpose* Platinum-based therapy is the cornerstone of ovarian cancer treatment. Development of platinum hypersensitivity can limit therapeutic options. In this brief report, we present case of successful cisplatin administration following two unsuccessful carboplatin desensitization attempts, and without the need for pre-treatment steroids.
*Methods* Retrospective chart review was performed.
*Results* One case of recurrent primary peritoneal carcinoma previously treated with a carboplatin-based regimen, developed a platinum hypersensitivity. Two attempts at carboplatin desensitization were unsuccessful. Cisplatin was substituted and the patient achieved a complete response to therapy without further hypersensitivity.
*Conclusions* Platinum-based therapies are vital to the treatment of primary peritoneal and ovarian carcinoma. Protocols that successfully incorporate platinum agents, despite a platinum hypersensitivity, are clinically relevant.

**Keywords** Platinum hypersensitivity · Peritoneal carcinoma · Platinum desensitization failure · Cisplatin

## Introduction

Platinum-based drugs have shown activity against a variety of solid tumors, and their activity is mediated through formation of DNA adducts that lead to arrest of replication and ultimately apoptosis [1]. Platinum agents are an important component of chemotherapy regimens used for the treatment of ovarian and primary peritoneal cancers in adjuvant, neoadjuvant and recurrent settings [2, 3]. Although cisplatin and carboplatin demonstrate equal efficacy in the treatment of advanced-stage cancers of the ovary and peritoneum, carboplatin is the preferred platinum-based agent due to its more favorable toxicity profile [4]. Hypersensitivity reactions, thought to be mediated by immunoglobulin-E related histamine release, can result from platinum-based treatments, especially with prolonged exposure. The cumulative risk of a hypersensitivity reaction is 0.92% during the first five cycles, rises sharply to 6.5% with the sixth cycle, and peaks at 19.2% after eighth cycles of therapy [5]. Hypersensitivity reactions typically range from mild facial flushing, itching, and rash to severe chest pain, seizures and anaphylaxis.

Patients with platinum-sensitive tumors have improved survival when treated with platinum-based therapy [6]. Given the survival advantage for platinum-sensitive patients, protocols continuing platinum-based treatment despite a hypersensitivity reaction are clinically relevant, but are not to be undertaken lightly as rare deaths have been reported [7]. In this report, we present a patient who experienced a carboplatin hypersensitivity reaction, failed two attempts at carboplatin desensitization, and successfully completed a cisplatin based protocol.

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## Case

The patient is a 65-year-old Caucasian female with a past medical history significant for hypertension, asthma and glucose intolerance. Allergies include diphenhydramine and promethazine. The patient was referred to our institution in September 2006, following an exploratory laparotomy, omental biopsy and right salpingo-oophorectomy at an outside facility. As per the operative report, no visible tumor remained at the completion of her surgery. The uterus and contralateral ovary were left in situ. After review by a gynecologic pathologist, final pathology was consistent with stage IIIB primary peritoneal carcinoma. Adjuvant chemotherapy was begun in October 2006 with intravenous (IV) paclitaxel (175 mg/m$^2$) and carboplatin (AUC 6). During treatment, the patient experienced grade 2 fatigue and peripheral neuropathy, and grade 3 neutropenia which required a treatment delay. In March 2007, after six cycles of therapy, a complete clinical and tumor marker response was noted. The treating physician offered a completion laparotomy with hysterectomy, left oophorectomy and omentectomy. This was completed in May 2007, and all pathology was negative for any residual carcinoma.

Twelve months later, the patient's CA-125 was noted to be elevated. Imaging revealed peritoneal nodularity along the left abdominal wall and right hepatic edge suspicious for recurrent disease. Image-guided biopsy followed by pathologic review confirmed recurrent serous peritoneal carcinoma. The patient was offered enrollment in a clinical trial for recurrent, platinum-sensitive carcinoma (Gynecologic Oncology Group protocol 213), and was randomized to receive paclitaxel (175 mg/m$^2$), carboplatin (AUC 5), and bevacizumab (15 mg/m$^2$) per protocol. During the second cycle, the patient experienced shortness of breath, generalized pruritus, chest pain, and erythema on her face, arms, legs, back and palms within minutes of receiving carboplatin. Symptoms were consistent with a carboplatin hypersensitivity reaction, and were treated with loratadine 10 mg PO, dexamethasone 10 mg IV twice, albuterol inhaler and hydroxyzine 25 mg intramuscular (IM) with complete resolution. Subsequently, this patient underwent two attempts at carboplatin desensitization using the scheme set forth in the clinical trial protocol: day 1 paclitaxel (175 mg/m$^2$) plus bevacizumab (15 mg/m$^2$), followed by day 2 famotidine 20 mg IV, dexamethasone 20 mg IV, ondansetron 24 mg per os (PO), hydroxyzine 25 mg PO, hydrocortisone 100 mg IV, and carboplatin (AUC 5) through increasing concentrations (1:1,000, 1:100, 1:10, 1:1). Despite the use of this desensitization regimen, the patient experienced widespread pruritus, erythema, and chest tightness with each attempt once the highest concentration was reached. Successful treatment of hypersensitivity symptoms with antihistamines (loratadine 10 mg PO, famotidine 20 mg IV, hydroxyzine 25 mg IM) and steroids (dexamethasone 20 mg IV) was achieved. Given the lack of desensitization success, after a discussion of the potential risks of further hypersensitivity reactions, the patient was switched to an off-protocol regimen of paclitaxel (175 mg/m$^2$), bevacizumab (15 mg/m$^2$) and cisplatin (50 mg/m$^2$) with standard antiemetic pre-medications (ondansetron 24 mg PO, dexamethasone 20 mg IV). On this regimen, the patient completed an additional four cycles of therapy (total of 6), with complete resolution of all peritoneal disease by imaging and normalization of her tumor marker (CA-125). During this treatment, the patient did not experience further hypersensitivity events. At last follow-up, the patient's performance status was normal, and was noted to have persistent grade 2 peripheral neuropathy in her fingers.

## Discussion

Platinum agents are highly active in the treatment of ovarian and primary peritoneal carcinomas. Thus, protocols that allow the continuation of platinum-based therapy in the setting of a platinum hypersensitivity are useful. One strategy utilizes desensitization of mast cells to platinum-based agents, most often carboplatin. Patients are exposed to dilute preparations of carboplatin, and desensitization occurs with escalating doses [5]. Desensitization is commonly effective as demonstrated by one study in which 29 of 33 (88%) patients with clinically documented carboplatin sensitivity were successfully re-challenged [8]. Another approach to desensitization involves the suppression of the immune reaction by using corticosteroid starting 24 h before the planned use of the inciting agent. Using this strategy, investigators at MD Anderson reported a 94% success rate for re-treating patients. This included successful re-treatment of all ten patients with hypersensitivity to platinum agents [9].

Patients refractory to the above desensitization schemes are often changed to a non-platinum regimen; however, response rates to these agents can be significantly lower [10]. An alternative approach for treatment of patients with carboplatin hypersensitivity is to substitute cisplatin without any specific desensitization. Using this strategy, Callahan et al. reported 24 patients with carboplatin allergy without prior desensitization attempts. Eighteen (75%) patients were treated with cisplatin without hypersensitivity reactions. Five patients eventually developed a hypersensitivity to cisplatin after a median of three cycles. In their series, patients did not receive extended pre-treatment corticosteroids beyond the standard dexamethasone (20 mg IV) used as part of the antiemetic regimen [11]. The patient presented here successfully received cisplatin treatment after unsuccessful carboplatin desensitization attempts with corticosteroid suppression.

Mechanisms of hypersensitivity to platinum agents remain poorly understood, but clearly must be related to more than just the platinum component of these molecules. While both cisplatin and carboplatin contain the element platinum in association with two ammonium groups, potentially important differences exist in both structure and biological targets. Molecular analysis has shown that cisplatin and carboplatin, along with oxaliplatin and tetraplatin, exhibit disparate effects on the expression of a wide range of genes, including many involved in the cell cycle and signal transduction [12].

For patients with epithelial ovarian or primary peritoneal cancer who have failed carboplatin desensitization, the strategy described in this report may offer an option for those who desire to continue platinum-based therapy. However, the possibility of developing a hypersensitivity reaction to the substituted platinum agent does exist, with reported incidence as high as 25% [11]. Furthermore, two cases of fatal cisplatin reactions following carboplatin hypersensitivity have been reported in the literature [7, 13]. This underscores the importance of informed consent and adequate facilities to deal with potential anaphylaxis.

Some authors have advocated the use of skin testing for carboplatin sensitivity. A negative test is highly predictive of future success with carboplatin, though the clinical utility of a positive result is less certain [14]. In one prospective study of 38 patients with a prior carboplatin reaction, 25 (66%) tested positive. Despite this, 37 (99%) successfully completed a carboplatin desensitization protocol. Patients with a positive skin test were more likely to experience subsequent reactions during desensitization compared to patients with a negative test [15].

Whether or not the use of newer platinum derivatives, such as oxaliplatin or nedaplatin has a role in the setting of a prior carboplatin or cisplatin reaction is unclear. Additional studies are necessary to determine optimal practice guidelines when treating a platinum-sensitive patient who develops a significant platinum hypersensitivity.

**Conflict of interest statement** All authors indicate there are no conflicts of interest to disclose.

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