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## Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: carboplatin-hypersensitivity reactions

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**Abstract** *Purpose:* Carboplatin hypersensitivity is an increasingly recognized toxicity in individuals receiving > 6 cumulative courses of this important antineoplastic agent. We wished to determine if a novel multi-pronged approach to re-treating patients with a high risk for this potentially serious side effect could permit the safe delivery of this class of cytotoxic drugs. *Methods:* Five patients with gynecologic malignancies who had either experienced a documented carboplatin hypersensitivity reaction ( $n = 4$ ) or had a “positive” carboplatin skin test ( $n = 1$ ), received a multi-drug oral regimen administered over several days which was designed to block known mediators of anaphylaxis. Four of these individuals subsequently underwent treatment with either cisplatin or carboplatin employing a “dose escalation” desensitization schema. *Results:* Four patients underwent successful treatment with either cisplatin or carboplatin (3, 4, 5, 6+ total additional courses) without any further evidence of hypersensitivity. *Conclusion:* In this preliminary report of a limited patient population, we have demonstrated the ability to safely deliver a platinum agent to individuals with either documented carboplatin hypersensitivity, or a high risk for this potentially serious toxicity of carboplatin. Further exploration of this novel management strategy in a larger group of patients is indicated.

**Keywords** Carboplatin · Hypersensitivity reactions · Ovarian cancer

### Introduction

Considerable retrospective data have documented the clinical utility of platinum agents when employed as second-line treatment of recurrent ovarian cancer (Markman and Bookman 2000; Gershenson et al. 1989; Hoskins et al. 1991; Gore et al. 1990; Markman et al. 1991). Objective response rates ranging from 20–70% have been reported in this clinical setting, based on the length of the “treatment-free interval” from the completion of primary chemotherapy (Hoskins et al. 1991; Gore et al. 1990; Markman et al. 1991). Due to its more favorable toxicity profile, carboplatin is generally the preferred platinum drug in this clinical setting (Markman and Bookman 2000; Markman et al. 1997).

Unfortunately, it is now well-recognized that patients receiving carboplatin as second-line treatment of ovarian cancer have at least a modest risk for experiencing *hypersensitivity reactions* (Markman et al. 1999; Dizon et al. 2002; Robinson et al. 2001; Rose et al. 1998; Chang et al. 1995; Weidmann et al. 1994; Hendrick et al. 1992; Morgan et al. 1994). The symptoms associated with this process range from a minor rash to diffuse erythroderma, severe anxiety, dyspnea, tachycardia, hypotension, and (in very rare cases) death. (Markman et al. 1999; Dizon et al. 2002; Robinson et al. 2001; Rose et al. 1998; Chang et al. 1995; Weidmann et al. 1994; Hendrick et al. 1992; Morgan et al. 1994; Zweizig et al. 1994).

Several management approaches have been proposed to deal with this relatively uncommon, but potentially serious, complication of carboplatin treatment. These include avoidance of further administration of the drug following documentation of hypersensitivity, delivery of the agent by an extended infusion schedule, and use of a variety of “desensitization schema” (Markman et al. 1999; Dizon et al. 2002; Robinson et al. 2001; Rose et al. 1998; Chang et al. 1995; Weidmann et al. 1994; Hendrick et al. 1992; Goldberg et al. 1996; Broome et al. 1996).

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Development of an effective strategy to prevent future platinum-associated hypersensitivity reactions in individuals experiencing such an event requires consideration of the substantial *clinical heterogeneity* of the symptom-complex, both in presentation and severity (Markman et al. 1999). In some patients the signs of hypersensitivity develop *immediately* upon initiation of the drug infusion, similar to the almost universal pattern observed with paclitaxel anaphylaxis (Markman et al. 2000). However, in others, the reaction begins when one-half or more of the treatment volume has been instilled. Finally, in a subset of patients, minor rashes may be noted several days after therapy (Markman et al. 1999). Further, while reactions can be quite mild in severity, events of far greater consequence can occur.

This unpredictable pattern suggests multiple immunological and non-immunological mechanisms may be involved in different patients experiencing carboplatin-associated hypersensitivity reactions (Cromwell et al. 1979; Orbaek 1982; Freedman and Krupey 1968; Zanotti and Markman 2001). As a result, it is not surprising that prevention of this process has met with variable reported success (Markman et al. 1999; Dizon et al. 2002; Robinson et al. 2001; Rose et al. 1998; Chang et al. 1995; Weidmann et al. 1994; Hendrick et al. 1992; Morgan et al. 1994; Zweizig et al. 1994; Goldberg et al. 1996; Broome et al. 1996).

We have recently developed a novel “desensitization strategy” which attempts to block multiple biological pathways potentially involved in the evolution of the clinical symptoms associated with drug-induced hypersensitivity. In this report we describe the outcome of five patients who either had previously experienced a carboplatin-associated hypersensitivity reaction, or developed a “strongly positive” carboplatin skin test

(Zanotti et al. 2001), where an attempt was made to deliver further platinum treatment employing this technique.

## Methods and materials

### Desensitization procedure

The “desensitization” protocol consisted of a number of elements designed to reduce the risk for the subsequent development of a serious hypersensitivity reaction, including:

1. Substitution of cisplatin for carboplatin: previous anecdotal reports have suggested that patients documented to have experienced hypersensitivity to carboplatin may be successfully treated with cisplatin (Dizon et al. 2002; Weidmann et al. 1994; Hendrick et al. 1992). [It was planned that if a patient was able to be treated with cisplatin without developing a reaction, but systemic side effects were found to be unacceptable (e.g., emesis), subsequent treatment with carboplatin, employing an identical protocol as described below, would be considered.]
2. Delivery of cisplatin (or carboplatin) at escalating concentrations: a standard management strategy designed to prevent serious immediate-type hypersensitivity reactions in patients known to be highly allergic to a medication includes drug administration at progressively higher concentrations, beginning with extremely dilute solutions (Table 1). [Our group, and others, had previously shown this strategy to be potentially useful in a subset of individuals experiencing severe paclitaxel-associated anaphylaxis (Markman et al. 2000; Essayan et al. 1996)].
3. Administration of several pharmaceutical agents prior to each platinum treatment, each designed to block different immunological pathways potentially involved in the clinical symptoms of hypersensitivity: these included: (a) corticosteroids (prednisone); (b) H-2 receptor [famotidine (Pepcid)] and H-1 (diphenhydramine) blockade; (c) 5-lipoxygenase inhibition [zileuton (Zyflo)]; (d) cysteinyl leukotriene receptor-1 antagonism [montelukast sodium (Singulair)]; (e) COX 1 and COX 2 inhibition (indomethacin); and (f) an oral beta-agonist [albuterol sulfate (Volmax)]. The drug administration schedule and doses employed are outlined in Table 2.
4. Cisplatin/carboplatin skin testing: immediately prior to infusing the first dilution of cisplatin/carboplatin an intradermal skin test was performed [0.02 ml cisplatin or carboplatin removed from the solution (“undiluted”) which had been prepared for treatment]. If a “positive test” (at least 5 mm wheel with a surrounding flare) was observed, the planned platinum treatment would not be given (Zanotti et al. 2001).

All patients being considered for treatment with this program who had previously experienced a carboplatin hypersensitivity reaction, or who had developed a “positive” carboplatin skin test, were extensively counseled regarding the potential for the development of a serious anaphylactic reaction resulting from additional platinum, despite the precautions to be employed to prevent such an event. Further, alternative non-platinum-based management options were discussed in detail.

**Table 1** Cisplatin/carboplatin administration schedule during “desensitization procedure”. Each solution was administered in 50 ml of normal saline (1st 30 min; 2nd 15 min; 3rd 15 min; final 30 min) with the next higher concentration delivered immediately following successful completion of the preceding infusion. The “dilutions” were made from the solution prepared for drug administration. (With cisplatin, the final concentration of drug was administered with 25 grams of mannitol)

1	1/1,000 dilution	Example: 0.09 mg cisplatin
2	1/100 dilution	0.9 mg cisplatin
3	1/10 dilution	8.1 mg cisplatin
4	Remainder of “undiluted” drug solution	81 mg cisplatin

**Table 2** Multi-drug regimen employed to prevent generation of mediators of anaphylaxis

Prednisone 50 mg PO q	6 h×3 doses beginning the day (10 a.m.; 4 p.m.; 10 p.m.) prior to chemotherapy
Famotidine (Pepcid) 20 mg IV	30 minutes prior to treatment
Dexamethasone 20 mg IV	30 minutes prior to treatment
Diphenhydramine 50 mg IV	30 minutes prior to chemotherapy
Zileuton (Zyflo) 600 mg PO QID	For 5 days prior to chemotherapy
Montelukast sodium (Singulair) 10 mg PO QD HS	For 5 days prior to chemotherapy
Indomethacin 50 mg PO TID	For 1 day (10 a.m.; 4 p.m.; 10 p.m.) prior to chemotherapy
Albuterol sulfate (Volmax) 8 mg PO BID	For 1 day (10 a.m.; 10 p.m.) prior to chemotherapy

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## Results

To date, a total of five patients (median age 58 years) with ovarian cancer cared for in the Gynecologic Cancer program of the Cleveland Clinic have undergone an attempt to be re-treated with platinum therapy employing this “desensitization procedure”.

All five women had previously been treated with carboplatin during primary therapy without experiencing hypersensitivity. In three patients there was evidence of a both a biological and clinical response to second-line treatment with carboplatin when the allergic reaction occurred.

Four of these women had documented carboplatin-associated anaphylaxis, while one had a markedly “positive” carboplatin skin-test prior to employing the “desensitization program” (Zanotti et al. 2001). In two patients evidence of carboplatin-hypersensitivity initially led to therapy with other cytotoxic agents before attempting re-treatment with a platinum drug.

All patients were informed of the potential serious risk associated with re-treatment with a platinum agent, prior to proceeding with the “desensitization regimen”.

Two patients had the dose of oral prednisone reduced from 150 mg (50 mg TID), the day immediately prior to chemotherapy, to 50 mg, due to excessive anxiety, agitation, and insomnia.

Four of the five patients were able to successfully receive treatment with platinum-based chemotherapy (two patients continued with cisplatin, two switched to carboplatin) employing the “desensitization program” outlined in Table 2 (total additional platinum-cycles delivered: 3, 4, 5, 6+). One patient developed a “positive” skin test immediately prior to the first test dose of platinum, despite the extensive pre-treatment regimen, and further attempts to employ a platinum agent were abandoned.

The clinical course of one of the five patients included in this report is particularly noteworthy. The patient initially experienced a carboplatin hypersensitivity reaction in the fall of 1999 (erythematous pruritic rash on the legs, arms, face, neck). At that time an *unsuccessful attempt* was made to treat her with a similar, but not identical “desensitization program” to that described in this report (4 days of oral prednisone, followed by regimen of escalating concentrations of carboplatin). The patient developed a diffuse rash when the final solution was being infused, and she was subsequently treated with several non-platinum based cytotoxic regimens. With recent disease progression, the patient elected to try this modified “desensitization program”. To date, she has received a total of six cycles of *cisplatin* employing this procedure, and has achieved major symptomatic benefit from the agent. In addition to the use of cisplatin, rather than carboplatin, with this more recent attempt at “desensitization” the regimen employs multiple pharmacologic agents (rather than

only a corticosteroid) designed to prevent an immunological response.

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## Discussion

In this preliminary report of a small group of women with documented carboplatin-associated hypersensitivity, or a high risk for development of such an event based on a “strongly positive” carboplatin-skin test, we have shown that use of a novel multi-pronged management approach has permitted the safe administration of a platinum agent.

While it is unknown if alternative, and perhaps less complex, strategies might have produced similar favorable results, it is the belief of our group that the potential severity of carboplatin hypersensitivity in this setting warrants *major efforts to prevent reactions* if this class of agents is ever to be administered again. In this regard it is important to recognize that several deaths have been documented in individuals with known platinum-hypersensitivity who were retreated with platinum agents (Zweizig et al. 1994; Dizon et al. 2002). Further, of eight patients with either documented carboplatin hypersensitivity reactions or a “positive” skin test our group has attempted to re-treat over the last several years with a less rigorous “desensitization protocol” (e.g., several days of high dose steroids followed by a “dose escalation” desensitization schema), five subsequently experienced an anaphylactic reaction (Markman et al. 1999; Zanotti et al. 2001).

It remains unknown which biological pathway is most likely to be implicated in the signs and symptoms of carboplatin-associated anaphylaxis. As previously noted, the heterogeneity of the observed reactions argues for the conclusion that the pathophysiology of hypersensitivity to platinum agents is quite complex. Thus, in this clinical setting, attempting to interfere with as many known immunological and non-immunological pathways of anaphylaxis as possible would appear to be the most rational management strategy.

The regimen employed in this patient population included modification of the platinum species (substitution of cisplatin or carboplatin), general immunosuppression and interference with both basophil and eosinophil activation (prednisone); attempts to prevent mast cell degranulation (escalating concentrations of cisplatin/carboplatin; oral beta-agonist therapy), interference with H-1 (famotidine) and H-2 (diphenhydramine) receptors, prevention of the formation, and inhibition of the activity of cysteinyl leukotrienes (montelukast sodium, zileuton) and prevention of the formation of proinflammatory prostaglandins (indomethacin).

While the outcome of treatment for the individuals included in this preliminary report appears promising, the number of patients managed in this manner is quite limited and the overall success of this novel strategy remains to be defined. As a result, we have initiated a formal study to more critically evaluate the role of this

program in those patients with either documented carboplatin hypersensitivity or a “positive” carboplatin skin test.

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