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Impact of Prophylactic Conversion to an Extended Infusion Schedule to Prevent Hypersensitivity Reactions in Ovarian Cancer Patients during Carboplatin Retreatment

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Abstract

Objective—Repeated exposure to carboplatin can lead to hypersensitivity reactions during retreatment with carboplatin. This may prevent its further use in platinum-sensitive ovarian cancer patients. At our institution, an increasing proportion of patients are prophylactically converted to an extended schedule of infusion after 8 cycles of carboplatin. We sought to determine whether an incrementally increasing, extended 3-hour infusion of carboplatin was associated with a lower rate of hypersensitivity reactions compared to the standard 30-minute schedule in sequentially treated patients.

Methods—We performed a retrospective electronic medical record review of patients with recurrent ovarian cancer retreated with carboplatin at our institution from 01/98–12/08.

Results—Seven hundred seventy-seven patients with relapsed ovarian, fallopian tube, or primary peritoneal cancer were retreated with carboplatin and met study inclusion criteria. Of these, 117 (17%) developed hypersensitivity reactions during second-line or greater carboplatin-based

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CONFLICT OF INTEREST STATEMENT

Roisin O'Cearbhaill: no conflicts of interest to declare

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treatment for recurrent disease. Only 6 (3.4%) of the 174 patients who received the extended schedule developed hypersensitivity reactions (0% grade 4; 1.7% grade 3) compared to 111 (21%) of 533 patients in the standard schedule group (12% grade 4; 77% grade 3). The first hypersensitivity episode occurred after a median of 16 platinum (carboplatin and cisplatin) treatments in the extended group compared to 9 in the standard group. Using the Fisher-exact test, there was an association with a reduced incidence of hypersensitivity reactions with the extended infusion schedule ($P<0.001$).

Conclusion—Our data suggest appropriate premedication and prophylactic conversion to an extended infusion during carboplatin retreatment may reduce hypersensitivity reactions.

Keywords

Carboplatin; anaphylaxis; hypersensitivity reaction; ovarian cancer; peritoneal cancer; adverse drug reactions

INTRODUCTION

Hypersensitivity reactions (HSRs) can occur in epithelial ovarian cancer patients during retreatment with carboplatin, preventing further use of carboplatin. The risk of HSRs rises with increased lifetime carboplatin exposure and with a longer platinum-free interval [1–3]. Patients with recurrent epithelial ovarian cancer are frequently retreated with carboplatin for platinum-sensitive recurrent disease. The risk of HSRs in this population is as high as 44% in one series [4].

The clinical symptoms of carboplatin HSR are heterogeneous. Treatment of acute reactions with anti-histamines and corticosteroids is often required. There is, however, the possibility of severe cardiopulmonary compromise, and even death, despite aggressive resuscitative efforts [3]. For this reason, in recurrent epithelial ovarian cancer, where treatment is non-curative and several alternative non-platinum-based options exist, one must weigh the risks and benefits of further carboplatin treatment.

The recently published 2009 National Comprehensive Cancer Network (NCCN) ovarian cancer guidelines recommend that patients are counseled regarding the risk of HSRs associated with repeat use of platinum drugs [5]. They emphasize the importance of educating patients about the symptoms of HSRs. Additionally, they recommend that carboplatin retreatment is administered in an appropriately equipped medical setting by staff familiar with the management of HSRs. In patients who experience severe, life-threatening carboplatin HSR, further exposure to platinum-agents should be avoided. In the case of less severe HSR, a desensitization protocol is recommended for any subsequent re-challenge with carboplatin.

Using a desensitization protocol, patients with a history of carboplatin HSR are sometimes able to receive additional platinum treatment. We hypothesized that by prophylactically changing patients to a prolonged infusion in advance of HSR occurrence, that the risk of developing HSR over the course of retreatment might be lessened. This became usual practice by several treating physicians at our center. We report the incidence of carboplatin

HSRs among a large, retrospective series of patients prophylactically converted to an extended schedule of carboplatin administration after approximately 8 cycles of treatment. The objective of this retrospective study was to determine whether the extended schedule of carboplatin administration was associated with a lower rate of HSRs compared to the standard schedule in sequentially treated patients at Memorial Sloan-Kettering Cancer Center (MSKCC).

METHODS

We performed a comprehensive retrospective electronic medical record review of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer who received retreatment with carboplatin for recurrent disease between January 1998 and December 2008. Approval from the MSKCC Institutional Review Board was obtained. In order to identify patients who received second-line or greater carboplatin treatment, the pharmacy database was examined for patients who had received at least one partial dose of carboplatin beyond 365 days of their initial diagnosis date.

Inclusion criteria included: (1) histologically documented epithelial ovarian, fallopian tube, or primary peritoneal cancer; (2) first-line treatment with carboplatin-based chemotherapy; and (3) retreatment in second line or greater with carboplatin-based chemotherapy. A diagnosis of carboplatin HSR required: (1) documented symptoms suggestive of carboplatin HSR; and (2) onset temporally related to administration of carboplatin (ranging from minutes to days post commencement of carboplatin treatment). Exclusion criteria included: (1) pre-existing history of platinum allergy; and (2) patients who had not received prior platinum treatment. Carboplatin skin allergy testing was not performed prior to HSR occurrence.

All hospital/medical records were reviewed. Data collection included patient demographics, tumor type and stage, documented allergies, comorbidities, and prior cancer treatment. The institutional allergy database was used to identify patients with a documented HSR to carboplatin. The electronic medical records were then reviewed to confirm signs and/or symptoms consistent with HSR and attributable to carboplatin treatment. Details of the carboplatin administration were obtained, including the duration of infusion, premedications, cycle on which the HSR occurred, and number of total prior platinum treatments. The National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 was used [6]. We noted the timing of symptoms/signs related to the infusion, the treatment initiated, and whether or not hospitalization was required.

In the subset of patients who were re-challenged with carboplatin following HSR, we collected data regarding the schedule of subsequent carboplatin infusion and success of re-challenge. The standard method of carboplatin administration was an intravenous infusion over 30 minutes. The protocol for the extended infusion, shown in Table 1, was based on previously published experiences of desensitization protocols [7].

Statistical Methods

Summary statistics were reported as percentages for categorical variables and as medians and ranges for continuous variables. A comparison based on these summary statistics was carried out between two cohorts--one who received the extended schedule of infusion and one who received the standard schedule. The Fisher-exact test was used to determine the association between the investigational extended schedule of infusion and the incidence of HSRs when compared to the standard schedule of carboplatin administration. All analyses were performed in SAS 9.1.

RESULTS

We identified 715 patients who received retreatment with second-line or greater carboplatin at our center between January 1998 and December 2008. Eight patients (1.1%) were excluded from the analysis--7 had a history of preexisting carboplatin allergy and 1 a prior history of cisplatin allergy.

Of the remaining 707 patients, 117 (16%) had a documented carboplatin HSR during second-line or greater carboplatin-based treatment. Characteristics of this cohort are listed in Table 2. The median age at initial diagnosis was 58 years (range, 16–88 years). All patients received cisplatin or carboplatin in combination with a taxane as first-line adjuvant therapy or neoadjuvant chemotherapy. Fifty-seven percent of patients had a documented history of at least one prior drug allergen, with similar rates in the HSR and non-HSR groups.

A total of 174 patients (25%) received the prophylactic extended schedule of infusion during carboplatin retreatment; the remaining 533 receiving the standard schedule. Only 6 patients (3.4%) who received the extended schedule versus 111 patients (21%) who received the standard schedule developed HSR. Using the Fisher-exact test, there was a significant relationship between the use of the extended carboplatin regimen and a reduced incidence of HSRs ($P<0.001$).

The characteristics of the patients who developed HSRs ($n=117$) are summarized in Table 3. Sixty percent of this cohort and 2 of the 6 patients (33%) in the extended infusion HSR group had a prior drug allergy history. The median number of total platinum (carboplatin and cisplatin) cycles delivered prior to HSR was 16 (range, 12–22 cycles) in the extended infusion group versus 9 (range, 7–35 cycles) in the standard infusion group. Thirty-three patients (28%) received at least one cycle of cisplatin (range, 1–8 cycles). HSR occurred during the second carboplatin-containing regimen in 91 patients (78%).

Characteristics of carboplatin HSR

The median interval between prior platinum-containing regimen and HSR was 20 months (range, 8–106 months). At the time of HSR, only 4 patients (3.4%) were receiving carboplatin dosed with an area under the curve (AUC) 6, while 63 patients (54%) received AUC 4. Fifty-one HSR patients (44%) received carboplatin with gemcitabine as the most frequently used second-line chemotherapy regimen.

No patient developed HSR during the first treatment in a carboplatin series. Fifty-nine HSR patients (50%) developed the reaction during the second treatment in a given series and a further 38 patients (32%) during the third treatment. HSR occurred in 30 patients (26%) when less than 20% of the carboplatin infusion had been administered. Twenty-five patients (21%) had delayed allergic reactions (i.e., HSRs occurred after completion of carboplatin infusion) with vast majority exhibiting HSR within 1 hour of completion of treatment. One patient, however, reported periorbital edema and a sensation of throat tightness 7 days post treatment with resolution, and their relationship to carboplatin infusion was uncertain.

All 117 HSR patients received corticosteroids, and 63 (54%) also received diphenhydramine immediately prior to the carboplatin infusion. Forty-seven patients (40%) received premedication with dexamethasone the night before and morning of chemotherapy. A substantially higher percentage (83%) of the extended infusion schedule cohort was premedicated with all the aforementioned. The details of carboplatin infusion in the HSR group are summarized in Table 4.

Clinical manifestations of HSR

The most common clinical features of the HSRs are listed in Table 5. Among HSR patients, there were 89 (76%) grade 3 and 14 (12%) grade 4 HSRs. This represented a 13% incidence of grade 3 and a 2% incidence of grade 4 HSRs, for the total population of 707 patients. There were no HSR-related deaths. Ninety-six HSR patients (82%) exhibited flushing and/or rash. In the standard infusion HSR group (n=111), 36 patients (32%) reported chest pain and 18 (16%) experienced severe cardiopulmonary compromise. Twelve patients (11%) required hospitalization; 2 to the intensive care unit. No patient in the extended infusion cohort developed significant cardiopulmonary compromise or required hospitalization; however, this group contained only 6 patients, so the numbers are too small to assume the risk for severe HSRs differs.

In general, reactions were treated by the immediate discontinuation of the infusion (if not already completed) and intravenous administration of 25–50 mg of diphenhydramine. A combination of 8–16 mg oral or intravenous dexamethasone (or 100 mg intravenous hydrocortisone), intravenous ranitidine (50 mg), nebulized albuterol, oxygen, and intravenous fluids were administered for the more severe reactions. Eight patients required epinephrine, and 1 patient necessitated a total of 3 doses of 0.3 ml (1 mg/ml) epinephrine.

Subsequent re-challenge with carboplatin post HSR

Twenty-three HSR patients (20%) were subsequently re-challenged with carboplatin. No patient in the original extended infusion cohort was re-challenged. The median interval between HSR and re-challenge was 1 year. The majority of these patients had experienced a grade 3 reaction at the time of the initial HSR. Carboplatin was successfully administered in 13 (57%) of the patients re-challenged. In 91% of cases the extended infusion schedule was used in the re-challenge (Table 6). Subsequent reactions among the 8 patients who were unsuccessfully re-challenged using the extended infusion schedule were less severe than the initial HSR.

DISCUSSION

To date, platinum compounds remain the most active agents for recurrent platinum-sensitive ovarian cancer [8]. Carboplatin HSR is rarely (<1% of patients) seen during the first course of carboplatin treatment [9]. This risk, however, rises considerably with increased platinum exposure [1, 10]. Clinical manifestations of carboplatin HSR, such as skin rash, flushing, itching, and abdominal cramping, usually resolve quickly following administration of antihistamines and steroids [11]. However, there is the risk of life-threatening systemic anaphylaxis [12].

Desensitization protocols are often used to treat patients who have already developed HSR during retreatment. These protocols involve the gradual re-introduction of small amounts of drug antigen in incremental steps, building up to full therapeutic doses [13]. However, even with the utilization of such protocols, HSR patients may still be unable to receive further carboplatin or cisplatin [14, 15]. Skin testing may help identify patients at risk for HSR but not accurately predict HSR severity [16, 17]. In cases of severe HSRs, the clinician or patient may feel that the potential risks outweigh the likely benefits, and permanently discontinue platinum-based therapy.

At MSKCC, in an attempt to diminish the risk of carboplatin HSR, a number of patients have been changed from a standard 30-minute infusion of carboplatin to an extended schedule after receiving 8 cycles. The extended schedule is administered as follows: 1% of total (first hour), 9% (second hour), and 90% (third hour). Patients were premedicated with dexamethasone 20 mg orally the night before and morning of carboplatin treatment. In addition, an antihistamine and H₂ receptor antagonist were administered (Table 1). In our study, 25% of patients who received retreatment with carboplatin were prophylactically switched to the extended infusion schedule. This prophylactic use of an extended schedule differs from current general practice in which patients are changed to a desensitization schedule only after experiencing HSR. In contrast to the complex and lengthy desensitization protocols often used in post-HSR platinum re-challenge, the 3-hour, extended infusion can be easily administered in the outpatient clinic setting.

In our series, 174 (25%) of 707 patients were retreated with carboplatin using the prophylactic, extended schedule. Baseline patient demographics were similar in the HSR and non-HSR groups. Due to the small number of patients in the extended infusion cohort who developed HSR (n=6) it was not possible to draw any meaningful conclusions regarding differences in baseline characteristics between the extended and standard infusion HSR cohorts. In the literature, a drug allergy history has been reported to predict for an increased risk of carboplatin HSRs [1, 3]. However, we did not observe this in our study as there were similar prior drug allergy histories in both groups.

No patient developed HSR during the first cycle of carboplatin retreatment. HSRs tended to occur during the second or third cycle of retreatment which is in contrast to paclitaxel allergy. These findings are consistent with the hypothesis that carboplatin HSRs are mediated through type 1, immunoglobulin E (IgE)-dependant mechanisms [18]. Sensitization occurs during the initial 6 (or 8) cycles of first-line carboplatin-based

chemotherapy. After disease recurrence, patients are re-exposed to the drug during the first cycle of platinum retreatment. The clinical signs and symptoms of carboplatin HSRs then manifest on subsequent cycles [3, 13, 19].

We demonstrated a significant reduction in the incidence of carboplatin HSRs associated with the use of the extended infusion protocol when compared to those treated on a standard 30-minute infusion schedule (3% vs. 21%, $P=0.001$) in a univariate analysis. This analysis did not control for number of prior carboplatin cycles, use of premedication, or any other patient characteristics. Interestingly, it was noted that the median total number of carboplatin cycles delivered prior to HSR occurrence was 16 in the extended infusion group in contrast to a median number of 9 cycles in the standard cohort. One might postulate that the prophylactic utilization of the extended infusion might permit a larger number of carboplatin cycles to be delivered to an individual patient over the course of many relapses. However, due to the small number of patients in the extended group who developed HSR it is not possible to definitively conclude this from our study.

In the recently reported Calypso trial, there was a significantly increased incidence of > grade 2 HSRs among women with relapsed platinum-sensitive ovarian cancer who received the carboplatin and paclitaxel doublet (18%) compared with carboplatin and liposomal doxorubicin (5%) [20]. It is theorized that the surfactant Cremophor EL, used as a solubilization vehicle for paclitaxel, heightens mast cell sensitivity, resulting in an augmented rate of HSRs during the ensuing carboplatin infusion [21]. None of our patients received a carboplatin and liposomal doxorubicin doublet. However, the results of the Calypso trial suggest that this combination might be an attractive alternative to carboplatin/paclitaxel in further diminishing the risk of carboplatin HSRs. Not surprisingly, in our study the majority of HSRs occurred during non-paclitaxel-containing regimens, i.e. carboplatin with gemcitabine (44%) and single-agent carboplatin (35%). This reflects the fact that these two regimens were the most commonly prescribed carboplatin-containing regimens for recurrent ovarian cancer at our center during the study period.

Carboplatin dose intensity has not been shown to improve overall survival in recurrent ovarian cancer [22, 23]. The majority of patients in our series received reduced doses with AUC ranging from 4–5 at retreatment. The risk of carboplatin HSR is directly related to total lifetime dose of carboplatin and number of prior platinum treatments [1, 10]. It is uncertain which factor is more important and not clear whether using lower doses in retreatment may also reduce the potential for HSRs.

One important observation in our series was that 86% of grade 4 HSRs occurred within 15 minutes of commencement of the carboplatin infusion. One patient had a severe delayed HSR 1 week following carboplatin treatment, but it is uncertain whether it was linked to the carboplatin or another unknown allergen. It is reassuring to note that all other grade 4 HSRs occurred during the carboplatin infusion. Hence, these patients were under medical supervision at the time of the HSRs, and appropriate treatment was initiated. In contrast, 23% of grade 3 HSRs were diagnosed following completion of the carboplatin treatment. There is a potential bias for underreporting in this patient group. Patients may have been unaware of the clinical manifestations of delayed carboplatin HSRs. Therefore, they may

have failed to mention potentially significant symptoms, such as rash, to the treating physician at the subsequent follow-up visit. In fact, the recently published 2009 NCCN ovarian cancer guidelines emphasize the importance of educating patients regarding signs and symptoms of HSRs for this very reason [5]. Overall, medical sequelae were less severe in patients who received the extended infusion compared to the standard infusion. No patient in the extended group required hospitalization or developed significant cardiovascular compromise. This may have clinical relevance when deciding on further platinum in patients with significant preexisting comorbidities.

In our study, the extended schedule cohort received more premedication compared to the standard group. However, for patients receiving a carboplatin and taxane doublet, rates of premedication were similar in both groups. Patients are routinely premedicated with steroids the night before and morning of taxane treatment to minimize the risk of paclitaxel allergy. It is unclear from the literature, and also from the results of this retrospective study, whether aggressive premedication alone with ranitidine, diphenhydramine, and corticosteroids administered intravenously immediately prior to chemotherapy combined with oral corticosteroids taken by the patient at home the night before and morning of treatment might be sufficient to reduce the incidence of carboplatin HSRs [24].

The contributions of premedication versus infusion length in reducing HSRs cannot be separated. In one review, premedication with H₁ and H₂ receptor antagonists alone was associated with a reduction of HSRs from 9.7% to 5.7%. Nevertheless, the majority of patients who received such premedication were being treated in the first-line setting. Therefore, it was not possible to determine if the lower incidence of HSRs noted in the premedicated group was a direct result of premedication or because these patients had less prior exposure to carboplatin [1]. Another retrospective study reported HSR incidence of 22% despite systematic prophylactic premedication with corticosteroids, antihistamines, and H₂ antagonists [3].

Only 23 (20%) of the 117 HSR patients were subsequently re-challenged with carboplatin (Table 6). Using the extended schedule of infusion and appropriate premedication, 12 (52%) of these patients were able to receive additional platinum-based chemotherapy. A further patient was successfully re-challenged using the standard 30-minute infusion and premedication. In the 9 patients (39%) who developed recurrent HSR despite use of the extended infusion protocol, the clinical sequelae were less severe compared to those of the initial HSR. This would support our findings that the extended infusion not only reduces the incidence of carboplatin HSRs but also potentially the severity.

Our study should be interpreted cautiously. This a retrospective review and prospective validation is required in order to definitively conclude that the extended infusion is associated with a reduction in HSRs. The results of our study do not apply to patients who developed HSR during initial carboplatin treatment as we excluded them from our review. Extreme caution must be exercised when re-challenging patients with prior carboplatin HSR. The true incidence of carboplatin HSRs may have been higher than our study suggests. It is possible that patients and healthcare professionals may have erroneously attributed subtle clinical manifestations of carboplatin HSRs to a concurrent illness or

medication. Failure to document the occurrence of carboplatin HSRs in our institutional allergy database would also have led to underreporting. Nonetheless, our experience suggests that the extended infusion does reduce the incidence of carboplatin HSRs and thus should be considered when retreating patients. Although not reviewed in this retrospective analysis, one could argue that there was physician bias to treat patients deemed to be at higher risk for the development of carboplatin HSR (i.e., those with a history of atopy or multiple prior drug allergens and those with a poorer performance status or significant comorbidities with the extended schedule), whereas the standard infusion schedule might have been employed in “healthier” patients.

Due to discrepancies in the extent of premedication between the extended and standard groups, it will be important to determine prospectively whether aggressive premedication with dexamethasone, H₁ and H₂ receptor antagonists alone could be sufficient to explain the observed reduction in the rate of HSRs. One could also consider expanding the aforementioned multi-drug premedication regimen to include an oral, cysteinyl leukotriene receptor antagonist (montelukast) and a 5-lipoxygenase inhibitor (zileuton) [25]. This may serve to block additional immunological pathways that potentially play a role in the development of HSR. Alternative strategies to further diminish the risk of HSRs may include skin testing [16, 17] and the use of a lower AUC during carboplatin retreatment. It now seems that choice of second chemotherapeutic agent in platinum doublets may also be important.

CONCLUSION

Retreatment with carboplatin for women with recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer was associated with a 17% incidence of grade 2 or worse carboplatin HSRs. Patients who received all carboplatin retreatment by 3-hour infusion after a lifetime total of 8 cycles of carboplatin appear to have had a lower risk of HSRs and received more total lifetime cycles of carboplatin before HSR developed. The contribution of the extended schedule versus the administration of premedications to the observed reduction in HSRs cannot be ascertained from this study. The results of this study warrant further prospective validation.

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REFERENCES

1. Navo M, Kunthur A, Badell ML, Coffey LW 2nd, Markman M, Brown J, et al. Evaluation of the incidence of carboplatin hypersensitivity reactions in cancer patients. *Gynecol Oncol.* 2006; 103:608–613. [PubMed: 16797060]
2. Schwartz JR, Bandera C, Bradley A, Brard L, Legare R, Granai CO, et al. Does the platinum-free interval predict the incidence or severity of hypersensitivity reactions to carboplatin? The experience from Women and Infants' Hospital. *Gynecol Oncol.* 2007; 105:81–83. [PubMed: 17157366]
3. Gadducci A, Tana R, Teti G, Zanca G, Fanucchi A, Genazzani AR. Analysis of the pattern of hypersensitivity reactions in patients receiving carboplatin retreatment for recurrent ovarian cancer. *Int J Gynecol Cancer.* 2008; 18:615–620. [PubMed: 18754135]

4. Morgan JS, Adams M, Mason MD. Hypersensitivity reactions to carboplatin given to patients with relapsed ovarian carcinoma. *Eur J Cancer*. 1994; 30A:1205–1206. [PubMed: 7654458]
5. [Cited 2009 March 24] The NCCN Clinical Practice Guidelines in Oncology™ Ovarian Cancer (Version 1.2009) © 2009 National Comprehensive Cancer Network, Inc. Available from: http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf.
6. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*. 2003; 13:176–181. [PubMed: 12903007]
7. Windom HH, McGuire WP 3rd, Hamilton RG, Adkinson NF Jr. Anaphylaxis to carboplatin—a new platinum chemotherapeutic agent. *J Allergy Clin Immunol*. 1992; 90(4 Pt 1):681–683. [PubMed: 1401647]
8. Markman M, Rothman R, Hakes T, Reichman B, Hoskins W, Rubin S, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol*. 1991; 9:389–393. [PubMed: 1999708]
9. Kook H, Kim KM, Choi SH, Choi BS, Kim HJ, Chung SY, et al. Life-threatening carboplatin hypersensitivity during conditioning for autologous PBSC transplantation: successful rechallenge after desensitization. *Bone Marrow Transplant*. 1998; 21:727–729. [PubMed: 9578315]
10. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol*. 1999; 17:1141. [PubMed: 10561172]
11. Polyzos A, Tsavaris N, Kosmas C, Arnaouti T, Kalahanis N, Tsigris C, et al. Hypersensitivity reactions to carboplatin administration are common but not always severe: a 10-year experience. *Oncology*. 2001; 61:129–133. [PubMed: 11528251]
12. Markman M. Hypersensitivity reactions to carboplatin. *Gynecol Oncol*. 2002; 84:353–354. [PubMed: 11812104]
13. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol*. 2008; 122:574–580. [PubMed: 18502492]
14. Shukunami K, Kurokawa T, Kubo M, Kaneshima M, Kamitani N, Kotsuji F. Hypersensitivity reaction to carboplatin during treatment for ovarian cancer: successful resolution by replacement with cisplatin. *Tumori*. 1999; 85:297–298. [PubMed: 10587037]
15. Dizon DS, Sabbatini PJ, Aghajanian C, Hensley ML, Spriggs DR. Analysis of patients with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after the development of a carboplatin allergy. *Gynecol Oncol*. 2002; 84:378–382. [PubMed: 11855873]
16. Zanotti KM, Rybicki LA, Kennedy AW, Belinson JL, Webster KD, Kulp B, et al. Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. *J Clin Oncol*. 2001; 19:3126–3129. [PubMed: 11408510]
17. Hesterberg PE, Banerji A, Oren E, Penson RT, Krasner CN, Seiden MV, et al. Risk stratification for desensitization of patients with carboplatin hypersensitivity: clinical presentation and management. *J Allergy Clin Immunol*. 2009; 123:1262.e1–1267.e1. [PubMed: 19501233]
18. Calvert AH, Harland SJ, Newell DR, Siddik ZH, Jones AC, McElwain TJ, et al. Early clinical studies with cis-diammine-1,1-cyclobutane dicarboxylate platinum II. *Cancer Chemother Pharmacol*. 1982; 9:140–147. [PubMed: 6761010]
19. Cleare MJ, Hughes EG, Jacoby B, Pepys J. Immediate (type I) allergic responses to platinum compounds. *Clin Allergy*. 1976; 6:183–195. [PubMed: 1277442]
20. Pujade-Lauraine E, Mahner S, Kaern J, GebSKI V, Heywood M, Vasey P, et al. A randomized, phase III study of carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in relapsed platinum-sensitive ovarian cancer (OC): CALYPSO study of the Gynecologic Cancer Intergroup (GCIg). *J Clin Oncol* (Meeting Abstracts). 2009; 27(15S) LBA5509-.
21. Gelderblom H, Verweij J, Nooter K, Sparreboom A. Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. *Eur J Cancer*. 2001; 37:1590–1598. [PubMed: 11527683]

22. Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN, et al. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. *J Clin Oncol.* 1992; 10:520–528. [PubMed: 1548516]
23. Markman M, Markman J, Webster K, Zanotti K, Kulp B, Peterson G, et al. Thrombocytopenia associated with second-line carboplatin-based chemotherapy for ovarian, fallopian tube, and primary peritoneal cavity cancers. *J Cancer Res Clin Oncol.* 2004; 130:741–744. [PubMed: 15338296]
24. Zorzou MP, Efstathiou E, Galani E, Bozas G, Kastritis E, Papadimitriou C, et al. Carboplatin hypersensitivity reactions: a single institution experience. *J Chemother.* 2005; 17:104–110. [PubMed: 15828452]
25. Markman M, Hsieh F, Zanotti K, Webster K, Peterson G, Kulp B, et al. Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: carboplatin-hypersensitivity reactions. *J Cancer Res Clin Oncol.* 2004; 130:25–28. [PubMed: 14564516]

Table 1

Protocol for Extended Infusion Schedule

Premedication	Drug
Night before and morning of carboplatin	Dexamethasone 20 mg orally
Immediately prior to carboplatin	Diphenhydramine 50 mg intravenously
	Ranitidine 50 mg intravenously
Infusion time	Amount of carboplatin infused
1 st hour	1%
2 nd hour	9%
3 rd hour	90%
Total: 3-hour infusion	100%

Table 2

Demographics of All Patients

Variable	All	HSR	No HSR
n	707	117	590
Diagnostic age, years			
Median (range)	58 (16–88)	56 (37–80)	58 (16–88)
Cancer type, n (%)			
Ovarian	598 (85)	107 (91)	491(83)
Fallopian Tube	38 (5)	5 (4.3)	33 (6)
Primary Peritoneal	71 (10)	5 (4.3)	66 (11)
Drug allergy, n (%)			
Negative	301 (43)	47 (40)	254 (43)
Positive 1 allergen	406 (57)	70 (60)	336 (57)
Infusion, n (%)			
Standard schedule	533 (75)	111 (95)	422 (72)
Extended schedule	174 (25)	6 (5)	168 (28)

HSR, hypersensitivity reaction

Table 3

Demographics and Platinum Treatment Histories of HSR Patients (n=117)

Variable	HSR group
HSR age, years	
Median (range)	60 (39–83)
Cancer stage, n (%)	
I–II	16 (14)
III	82 (70)
IV	19 (16)
Cancer grade, n (%)	
1	7 (6)
2	26 (22)
3	82 (70)
Not reported	2 (1.7)
Histology, n (%)	
Serous	87 (74)
Endometrioid	8 (7)
Mixed	9 (8)
Poorly/undifferentiated	9 (8)
Other	4 (3)
Number of comorbidities, n (%)	
0	19 (16)
1–3	82 (70)
4–6	16 (14)
History of asthma, n (%)	
Yes	11 (9)
Number of prior drug allergens, n (%)	
0	47 (40)
1–2	53 (45)
3–4	12 (10)
>4	5 (4)
Number of prior platinum cycles	
Median (Mean)	11 (12)
Range	7–35
Number of prior carboplatin cycles	
Median (Mean)	10 (11)
Range	7–35
Number of prior carboplatin regimens, n (%)	
1	91 (78)
2	22 (19)
3	4 (3.4)

HSR, hypersensitivity reaction

Table 4

Details of Carboplatin Infusion at HSR

Variable	HSR group
Interval between prior platinum regimen and HSR, months	
Median (range)	20 (8–106)
AUC, n (%)	
2	2 (1.7)
4	63 (54)
5	48 (41)
6	4 (3.4)
Regimen at HSR	
Carboplatin single agent	41 (35)
Carboplatin/gemcitabine	51 (44)
Carboplatin/paclitaxel	24 (21)
Carboplatin/docetaxel	1 (0.9)
Cycle no. of retreatment regimen on which HSR occurred, n (%)	
1	0 (0)
2	59 (50)
3	38 (32)
4	8 (7)
5	6 (5)
6	6 (5)
Amount infused when HSR occurred, n (%)	
1–20%	30 (26)
21–50%	39 (33)
51–99%	23 (20)
100%	25 (21)
Premedications prior to chemotherapy, n (%)	
Dexamethasone night before and morning of chemotherapy	47 (40)
Dexamethasone immediately prior	117 (100)
Diphenhydramine immediately prior	63 (54)

HSR, hypersensitivity reaction; AUC, area under the curve

Table 5**Clinical Manifestations of HSR and Summary of Management**

Variable	Extended Infusion Group n=6	Standard Infusion Group n=111
HSR grade, n (%)		
1	2 (33)	3 (2.7)
2	1 (17)	8 (7)
3	3 (50)	86 (77)
4	0 (0)	14 (13)
Hospitalized, n (%)		
Yes	0 (0)	12 (11)
ICU	0 (0)	2 (1.8)
Symptoms/signs, n (%)		
Flushing and/or rash	5 (83)	101 (91)
Pruritus	2 (33)	51 (46)
Dyspnea and/or wheeze	2 (33)	41 (37)
Palpitations and/or tachycardia	2 (33)	59 (53)
Throat tightness and/or tongue swelling	1 (17)	21 (19)
Hypotension	0 (0)	18 (16)
Chest pain	0 (0)	36 (32)
Unresponsiveness	0 (0)	7 (6)
Treatment administered, n (%)		
None	2 (33)	7 (6)
IV steroids	1 (17)	56 (50)
IV diphenhydramine	4 (67)	102 (92)
IV ranitidine	2 (33)	21 (19)
IV fluids	2 (33)	21 (19)
Epinephrine	0 (0)	8 (7)

HSR, hypersensitivity reaction; ICU, intensive care unit; IV, intravenous

Table 6

HSR Patients Subsequently Re-challenged with Carboplatin

Variable	
Re-challenged	n (% of HSR group)
Standard infusion group	23 (20)
Extended infusion group	0 (0)
Prior HSR grade	n (% of re-challenged)
2	2 (9)
3	20 (87)
4	1 (4)
Schedule used in re-challenge	n (% of re-challenged)
Extended infusion	21 (91)
Standard infusion	2 (9)
Successful	n (% of re-challenged)
Yes	13 (57)
Interval from HSR, months	
Median (range)	12(0.8–42)

HSR, hypersensitivity reaction