

Platinum desensitization in patients with carboplatin hypersensitivity: A single-institution retrospective study

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HIGHLIGHTS

- Highlights an effective, safe and short desensitization protocol
- Allows hypersensitive patients to continue with carboplatin therapy
- Employs a straightforward home and inpatient premedication regimen
- Identifies factors that help to risk stratify patients undergoing desensitization
- Decreases the burden on health care by reducing admissions to the hospital and ICU

ARTICLE INFO

Article history:

Received 7 May 2016

Received in revised form 27 September 2016

Accepted 30 September 2016

Available online 24 October 2016

Keywords:

Carboplatin desensitization

Gynecologic malignancy

Allergy to carboplatin

Hypersensitivity reactions

ABSTRACT

Objectives. The carboplatin desensitization (CD) protocol presented here allows patients with either a positive skin test or a prior hypersensitivity reaction (HSR) to safely, rapidly and effectively continue with carboplatin infusions. Newly described factors can identify patients at risk for developing adverse events during CD.

Methods. A retrospective review was performed on patients with gynecologic cancer who underwent CD between 2005 and 2014. The CD protocol uses a four-step dilution process over 3.5 h.

Results. 129 patients underwent CD and completed a total of 788 cycles. The desensitization protocol prevented HSRs in 96% (753 out of 788) of these cycles. Patients achieved an average of 6.1 cycles ($SD \pm 4.55$, range 0–23) with CD. The CD protocol allowed 73% (94 of 129) of the patients to undergo carboplatin infusion without reaction. Patients with moderate to life-threatening HSRs (grade 2 through 4) were 10.5 years younger at initial CD than patients with grades 0 or 1 HSRs (52.3 vs. 63, $P = 0.0307$). One patient death occurred during her thirteenth desensitization cycle. The HSR in this case was complicated by pre-existing pulmonary hypertension.

Conclusions. This is the largest study of its kind showing a safe, effective and rapid (3.5 h) CD protocol. The majority of patients with a history of either carboplatin hypersensitivity reaction or a positive skin test completed the CD protocol without HSRs. Age was identified as a risk factor for HSR severity during CD. Age can be employed along with pre-load dependent cardiac conditions as a way to help risk stratify patients undergoing CD.

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1. Introduction

Platinum-taxane combination regimens are used as neoadjuvant and adjuvant therapy for ovarian, uterine and cervical cancers [1]. In addition, platinum drugs have proven efficacy in the relapse setting of

gynecologic cancers. Carboplatin [*cis*-diammine (cyclobutane-1,1-dicarboxylate-O,O')platinum(II)] was approved in 1989 for the treatment of ovarian carcinoma. This platinum agent has been found to have therapeutic equivalency to cisplatin but with less emetogenesis, audio toxicity, and nephrotoxicity [2,3]. Hypersensitivity reactions to platinum compounds were first described in refinery workers inhaling complex platinum salts. These refinery workers developed respiratory (wheezing, dyspnea), gastrointestinal (cramping, diarrhea) and dermatologic (pruritus, urticaria and angioedema) reactions [4]. Patients who receive multiple doses of carboplatin chemotherapy have also been

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observed to experience these hypersensitivity reactions (HSR). The rates of HSRs in carboplatin-treated patients has shown to range between 5% and 34% [3]. Along with variable rates, carboplatin HSRs also present in a heterogeneous fashion. Some reactions develop minutes after the initiation of an infusion whereas other reactions can occur immediately following completion or days later [5]. The etiology of carboplatin HSR is currently unknown, but it is speculated that carboplatin can act as a hapten and promote a type I, IgE-mediated, histaminergic reaction. This type I response, with activation through IgE, causes a release of inflammatory molecules from basophils and mast cells (prostaglandin D2, leukotriene C4, IL-6, and tumor necrosis factor alpha) [6,7]. An alternative to the IgE-centric mechanism of carboplatin hypersensitivity is the T cell-mediated hypothesis. This type IV hypersensitivity, mediated by T cells, is a delayed reaction occurring after sensitization from multiple exposures of a noxious stimuli. A patient rarely has hypersensitivity until a critical number of cycles has been administered [5,7,8]. Additionally, patients with a history of allergy to medications or environmental stimuli have a greater potential of developing platinum HSRs, further supporting a type IV response [6–8]. With this evidence in mind, it is likely that the etiology of carboplatin HSR is multifactorial, involving more than one pathway [9]. Although the mechanisms underlying HSRs are not fully elucidated, many desensitization protocols have been implemented in an attempt to mitigate these reactions. The prevention of HSRs has been attempted using many premedication regimens [4,5,9,10]. These premedication regimens block the inflammatory pathways involved in HSR. Oral steroids, such as prednisone or dexamethasone have been used to reduce inflammation by achieving capillary membrane stability and suppression of the immune response. Escalating concentrations of antihistamines, like diphenhydramine (H-1 blockers) and famotidine (H-2 blockers), are utilized to help prevent mast cell degranulation [5,10]. Notably, some premedication regimens require an extended 5 days of therapy. These prolonged regimens, in addition to the administration of corticosteroids and antihistamines, have included application of selective leukotriene receptor antagonist (montelukast) and non-steroidal anti-inflammatory inhibitors (indomethacin) [5,10]. These premedication regimens are implemented, along with a slow infusion of increasing carboplatin concentration, to prevent both a type I and type IV hypersensitivity response to carboplatin.

Carboplatin administration in a patient with hypersensitivity can be severe and potentially life-threatening. Therefore, some authors argue to discontinue platinum treatment at the initial sign of a HSR. These same authors suggest exhausting all other options before utilizing a desensitization protocol [2,11,4]. Due to the severity of a carboplatin hypersensitivity, patients must be selected properly to ensure safety during standard carboplatin administration. To determine patient eligibility for a desensitization protocol clinicians use either, 1) clinical evidence of HSRs during carboplatin infusions, or 2) a carboplatin skin test method. In the first group, clinical evidence of hypersensitivity reactions are graded 0 through 5 (grade 5 being death) by using the NCI Common Terminology Criteria for Adverse Events (CTCAE v. 4.03, Table 1). For the second group, there is no clinical evidence of HSRs, therefore, utilizing the skin test method helps to determine patients at risk for developing carboplatin hypersensitivity [12]. Since Zannotti et

Table 1
Grading system for carboplatin hypersensitivity reactions with the NCI Common Terminology Criteria for Adverse Events (CTCAE v. 4.03).

Grade	Clinical manifestations
0	No reaction
1	Mild: transient flushing/rash, drug fever <38 °C
2	Moderate: rash, flushing, mild bronchospasm
3	Severe: symptomatic bronchospasm ± urticaria, edema/angioedema, hypotension
4	Life-threatening: anaphylaxis
5	Death

al.'s index study of carboplatin skin tests, various other authors have reported false-negative rates as high as 8.5% [10,13–16]. To prevent HSR in patients with a positive skin test or history of HSRs, a carboplatin desensitization (CD) protocol can be employed. Desensitization protocols utilize hypersensitivity-mitigating pre-medications like antihistamines and corticosteroids. Following the pre-medication's temporary state of reduced immune reactivity, carboplatin infusion is initiated at increasing concentrations. Windom et al. first successfully described this technique in 1992 [10]. Since then, multiple investigators have reported successful platinum desensitization regimens [9,17–19].

Many previously published carboplatin desensitization protocols are heterogeneous and vary in terms of their safety, speed, location, effectiveness, and validation. The current existing protocols have time intervals that can range from 2 to 16 h, initially take place in an intensive care unit (ICU), require multiple steps, lack effectiveness (60% of patients with reacts during desensitization), apply <6 cycles per patient, and relate only to a restricted number of patients (4 to 57 patients) with mild grade reactions [20–25]. Given this heterogeneity, large retrospective studies or randomized controlled trials exploring carboplatin desensitization are necessary to elucidate the optimal regimen. The purpose of this study is to describe, with the largest retrospective data in the literature, our carboplatin desensitization protocol. This protocol can be used as a means of continuing therapy for patients harboring HSRs and positive skin tests. Additionally, we aim to identify risk factors in patients with adverse events during CD.

2. Materials and methods

An institutional-review board approval was obtained from the Yale Human Investigations Committee (HIC# 1308012505). A retrospective review of the Yale-New Haven Hospital Tumor Registry was conducted. All gynecologic cancer patients who received chemotherapy between 2005 and 2014 were identified. Patients with a history of either a positive carboplatin skin test (administered after 6 cycles of a carboplatin-based chemotherapy regimen), or a history of prior HSRs to carboplatin were selected. Of the patients identified, those who underwent carboplatin desensitization were selected for inclusion. The CD utilized in this study was based on our institutional protocol (Table 2).

Baseline demographic data including age, race, cancer diagnosis, and cancer stage were documented. Details about their desensitization regimens were also collected. Information included, indications for desensitization, location of desensitization, and number of platinum doses received prior to desensitization. Patients with a history of HSRs prior to desensitization had their grade and symptoms recorded. The location, symptoms and grade of HSR during desensitization were documented and reported for all patients undergoing desensitization. Reaction symptoms were graded on a scale from 0 to 5 using the Common Terminology Criteria for Adverse Events (CTCAE v. 4.03, Table 1) [26].

Table 2
Yale-New Haven Hospital carboplatin desensitization protocol.

Home Premedications (2 drug regimen):
1. Fexofenadine - 60 mg BID 24 h prior to protocol, 120 mg 3 h prior to protocol
2. Dexamethasone - 20 mg 12 h prior to protocol, 20 mg 3 h prior to protocol
Premedications prior to desensitization protocol (3 drug regimen):
1. Dexamethasone 20 mg IV 30 min prior to protocol
2. Famotidine 20 mg IV 30 min prior to protocol
3. Diphenhydramine 50 mg IV 30 min prior to protocol, 25 mg every 4 h × 3 doses
Carboplatin desensitization protocol
Determine total dose using Calvert equation, estimated or measured CrCl
Bag 1 - 1/1000 dilution in 30 cm ³ NS. Infuse over 30 min
Bag 2 - 1/100 dilution in 50 cm ³ NS. Infuse over 30 min
Bag 3 - 1/10 dilution in 100 cm ³ NS. Infuse over 60 min
Bag 4 - remainder of total dose mixed in 250 cm ³ NS and infused over at least 90 min

Yale-New Haven Hospital carboplatin desensitization protocol. NS (normal saline), min (minutes), CrCl (creatinine clearance).

Following the CTCAE v. 4.03 we categorized grades 1 and 2 HSRs as mild/moderate and grades 3 and 4 as severe/life-threatening (Table 1). Finally, the number of successfully completed platinum cycles performed with carboplatin desensitization were recorded.

Statistical analysis was completed using GraphPad Prism v.7.01. Two sided Fischer's exact test and student's *t*-test were used to calculate statistical significance where indicated.

3. Results

One hundred and twenty-nine patients who underwent carboplatin desensitization between 2005 and 2014 were identified. Collectively, a total of 788 desensitization infusions were administered, and 753 out of 788 cycles were completed without reactions (96%). Baseline demographic data were collected (Table 3). Eighty-five percent of the patients were Caucasian women (110 of 129), 55.6% had stage III disease (or higher), the majority of patients had ovarian cancer, and the mean age at desensitization was 62.1 years old (SD $\pm$ 9.1 years, range 43–89 years). Patients completed an average 9.5 cycles (SD $\pm$ 4.5, range 0–23) of carboplatin before experiencing a HSR or a positive skin test.

Two groups of patients underwent carboplatin desensitization (CD): 1) patients with a history of HSR during their standard carboplatin infusion, and 2) patients with a positive carboplatin skin test (Table 3). The first group, undergoing carboplatin desensitization due to their history of HSR, was composed of 56 out of the 129 total patients (43.4%). During the initial HSR, prior to desensitization, patients most commonly presented with pruritus at 42.8% (24 of 56) (Table 4), 3 patients (2.3%) experienced grade 3 reactions or higher, 2 patients (1.5%) experienced anaphylaxis and none died (Fig. 1A). During the carboplatin desensitization protocol, 42 of the 56 patients (75%) had no reaction and 14 (25%) patients reacted (Fig. 1A). Of the 42 patients who did not react, 19 (45%) had grade 2–4 (moderate to life-threatening) reactions during their initial standard infusion prior to CD. Of the remaining 14 patients that had reactions, 5 (35.7%) were able to complete their desensitization protocol after the reaction was reversed. Of the 14 patients that reacted during desensitization, none had received neoadjuvant chemotherapy. Comparatively, 26% (11 of 42) of the patients without HSRs during desensitization previously had received neoadjuvant chemotherapy (OR 0.094, CI: 0.0052–1.7). Additionally, these 14 patients were more likely to have a lower grade reaction (grade 1) during standard infusion when

Table 4
Symptoms of carboplatin hypersensitivity during carboplatin infusion.

Outcomes	Before desensitization	During desensitization
Shortness of breath/cough/bronchospasm	11 (19.6%)	5 (15.2%)
Itching	24 (42.8%)	17 (51.5%)
Rash	15 (26.8%)	16 (48.5%)
Facial flushing	13 (23.2%)	5 (15.2%)
Palmar erythema	12 (21.4%)	10 (30.3%)
Angioedema	1 (1.8%)	4 (12.1%)
Fever	1 (1.8%)	1 (3.0%)
Anaphylaxis	2 (3.5%)	1 (3.0%)
Death	0	1 (3.0%)

compared to patients who did not react during CD (OR 11.0, CI 1.6–120, Fisher's exact). Ninety-three percent (13 of 14) of the patients with CD reactions had a history of grade 1 HSRs during standard carboplatin infusion, while 45% (19 of 42) of the patients without CD reactions possessed a history of grade 2 reactions during standard infusion. The patients who did not react during desensitization were found to have more advanced stage disease (stages III to IV) when compared to the patients with reactions during CD (81% vs. 78%, *P* = 0.2522).

The second group of patients undergoing carboplatin desensitization, due to a positive skin test, were composed of 73 patients (56.5%). There were no HSRs seen in 52 patients (71.2%) during the CD (Fig. 1B). Of the 21 patients that reacted, 7 (33.3%) were able to complete their infusion after the reaction was identified. The most common reaction during desensitization for both the HSR and skin test groups combined was pruritus at 51.5% (17 of 33) (Table 4).

Patients who underwent desensitization were able to complete an average of 6.1 additional carboplatin cycles (SD $\pm$ 4.55, range 0–23). Most patients (125 of 129) completed their first CD cycle as an inpatient in a non-intensive care unit (ICU) setting; more than a third (49 of 129) were transitioned to an outpatient infusion clinic. Fifty-eight percent (75 of 129) of the patients completed their entire desensitization as inpatients. Two patients (1.5%) completed their entire desensitization in an outpatient infusion clinic. Two patients (1.5%) started desensitization in the ICU and completed their desensitizations in the outpatient infusion clinic. One patient was transferred to the ICU to complete the CD protocol. Only 5 out of the total 788 CD infusion cycles were administered in the ICU (0.6%). Moderate to life-threatening reactions (grade 2 through 4) were only seen in 9% of the patients (12 out of 129) during CD. The patients with moderate to life-threatening reactions (grades 2–4) during CD were found to be 10.5 years younger than the patients with grade 0 and grade 1 reactions (median age of 52.3 vs. 63, *P* value 0.0307). The mean number of carboplatin cycles, prior to desensitization, showed no difference between grades 0–1 and grades 2–5 (*P* = 0.4542, grades 0–1 vs. grades 2–5). The mean number of desensitization cycles for grades 0–1 vs. grades 2–5 were 6.184 (SD $\pm$ 0.424) and 5.33 (SD $\pm$ 1.405), respectively (*P* = 0.540). The patients with grade 2 through 5 reactions had a higher percentage of patients with earlier stage disease when compared to patients with either grade 0 or grade 1 reactions, 33% (4 of 12, grade 2–5) vs. 17% (4 of 24, grade 0) and 18% (17 of 93, grade 1), respectively (*P* = 0.2522 for grade 0 vs. grade 2–5 and *P* = 0.397 for grade 1 vs. grade 2–5). Nine patients (6.9%) had their CD cancelled due to grade 3 or 4 reactions, minor reactions at first dilution, and/or death. Three patients (2.3%) had severe systemic reactions (grade 3 or 4) requiring rapid response intervention and ICU treatment, 5 patients had minor reactions at first dilution of carboplatin and one patient died from anaphylaxis during her treatment (Table 4).

The patient who died during CD was known to have long standing type I diabetes, peritoneal dialysis for chronic kidney disease and new onset pulmonary hypertension. The patient was undergoing carboplatin therapy for a history of stage III serous ovarian carcinoma. The patient's

Table 3
Baseline demographic data of patients undergoing carboplatin desensitization protocol.

	Number of patients
Diagnosis	
Cervical cancer	3 (2.3%)
Ovarian cancer	109 (84.5%)
Endometrial cancer	14 (10.9%)
Fallopian tube cancer	3 (2.3%)
Mean age at desensitization in years	62.1 $\pm$ 9.1 (43–89)
Race	
White	110 (85.3%)
Asian	6 (4.7%)
Hispanic	4 (3.1%)
Black	9 (6.9%)
Cancer stage	
I	7 (5.4%)
II	18 (14.0%)
III	49 (38.0%)
IV	23 (17.8%)
X	32 (24.8%)
Indication for desensitization	
Positive carboplatin skin test	73 (56.5%)
History of prior reaction	56 (43.5%)

X = unexplored patients who received neoadjuvant chemotherapy.

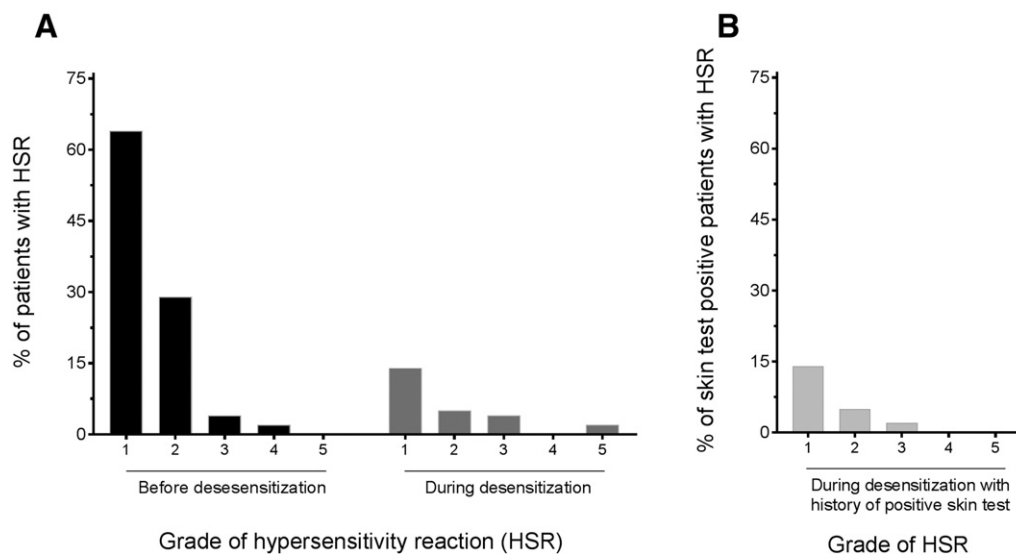


Fig. 1. Carboplatin desensitization (CD) prevents hypersensitivity reactions (HSR) in patients with prior carboplatin HSRs. The protocol also prevents HSRs, at comparable rates, in patients with prior positive skin tests. (A) Percentage of patients with HSRs during standard carboplatin infusions (black bars), compared with HSRs in the same patients at the time of carboplatin desensitization (CD) (dark grey bars). (B) The percentage of skin test positive patients with HSRs during CD protocol (light grey bars). One hundred and twenty-nine (129) patients undergoing carboplatin desensitization were analyzed from 2005 to 2014 at Yale-New Haven Hospital.

first desensitization was at age 46. At the time she was initiated on carboplatin desensitization for a grade 1 HSR during her eighth standard cycle. The patient was able to complete 12 CD cycles thereafter without issue. She passed away in the midst of her 13th CD cycle due to cardiopulmonary arrest. The cardiopulmonary arrest occurred during an anaphylactic reaction in the setting of newly diagnosed pulmonary hypertension.

4. Discussion

The carboplatin desensitization protocol proposed here is optimal given its rapid infusion schedule, safety and effectiveness. This is the first large (129 patients, 788 infusions) report of a short (3.5-hour) CD protocol. In terms of effectiveness, our protocol allowed 73% (94 of 129) of the patients to undergo carboplatin infusion without reactions. Of the patients that did react, the grade of reaction was low and included itching, rash, and palmar erythema. Emphasizing safety, the majority (96%, 125 of 129) of patients underwent CD in a non-ICU setting. Furthermore, many of these patients (38%) were able to complete their protocols in an outpatient infusion clinic, thereby reducing hospital costs.

According to our institutional criteria, a patient can be transitioned to an outpatient infusion clinic if HSRs do not occur during CD. If a patient has a HSR in the outpatient infusion clinic, the next CD cycle is scheduled inpatient with minor modifications to the pre-medications and infusion schedule. Patients with grade 4 (life-threatening) reactions and airway compromise result in permanent cessation of any further CD attempts. Likewise, any grade HSR that occur during the first two dilutional steps also trigger immediate cessation and failure. This CD protocol allowed 84% (108 of 129) of the patients to continue with carboplatin therapy. Thirty-four percent (12 of 35) of the patients who did have systemic reactions during protocol were able to complete their carboplatin infusions. This protocol has been shown to be safe in a large number of patients thereby permitting the majority of individuals with HSRs to continue carboplatin infusions.

For a patient to require a CD protocol, they must prove to be hypersensitive. A clinical history of HSRs during standard carboplatin infusion reveals a true carboplatin hypersensitivity reaction. Therefore, a CD protocol is presumed effective if further systemic reactions are prevented in patients with prior clinical HSRs. The CD protocol established in our

institution was able to prevent reactions in 75% (42 of 56, Fig. 1A) of patients with a history of HSRs (mild, moderate, severe and life threatening reactions) to standard carboplatin infusions. This suggests that the majority of patients with true clinical hypersensitivity were able to benefit from the CD protocol. In terms of safety, only one of the 56 patients (2%) required transfer to the ICU for continuation. This CD protocol is effective and safe, as evidenced by the low rate of HSRs in patients with clinically proven mild to life threatening grade reactions.

The second approach of identifying a patient at risk for HSRs to carboplatin, is the skin test method. The carboplatin skin test is the only known screening method for recognizing patients who could be at risk of developing carboplatin HSRs. Skin testing is able to detect both a type I and a type IV response. Theoretically, an immediate positive skin test (reaction after 1 h) is indicative of an IgE-mediated type I response. Conversely, a delayed positive skin test may signify a type IV delayed hypersensitivity. Patients with carboplatin hypersensitivity may present with both types of responses. These mixed responses to carboplatin skin tests suggest multiple etiologies, and high susceptibility for developing angioedema/anaphylaxis [27]. Due to the risk of angioedema/anaphylaxis and death, patients with a positive skin test will typically be discontinued from further carboplatin therapy despite continued anti-tumor response. We show that the majority (71%, 52 of 73, Fig. 1B) of these patients with positive skin tests are able to complete carboplatin desensitization. None of the 73 patients required an ICU admission during their CD. Therefore, our institutional CD protocol allowed these patients, who otherwise would be restricted from platinum therapy, to continue with rapid carboplatin infusion.

A number of CD protocols have been described in the literature. Many of these studies have cohorts ranging from 4 to 57 patients, are completed initially in the ICU, have 60% HSR rates during CD, have medians of 2–4 CD cycles per patient, and only include patients with a history of low grade HSRs (mild grade) [16,24,28]. More recently, two new studies have nicely highlighted an abbreviated 4-step CD protocol. One of these studies, by Takase et al., achieved desensitization in 4 h. Takase et al. included 20 patients with mullerian cancer undergoing a total of 83 CD cycles. Sixty percent of these patients in the study had HSRs during carboplatin desensitization. Of the patients who reacted, 67% had grade 2 reactions or higher [24]. Although Takase et al. was able to limit the desensitization protocol to 4 h or less, there was still a significant amount of reactions during the small number of CD cycles infused.

In our protocol 129 patients underwent a total of 788 CD cycles. Ninety-six percent of the 788 cycles were without HSRs, achieving an average of 6 reactionless cycles per patient. Of the 129 patients, only 28% (36 of 129) of the patients had CD reactions. Thirty-three percent of those who did react (12 out of 36) had grade 2 reactions and above, which is 30% lower than was seen by Takase et al. Our protocol is comparable in duration to Takase et al., but with larger numbers of CD cycles and lower rates of HSRs.

The recent study by Li et al. detailed an even shorter, 1.5 h 4-step, carboplatin desensitization protocol [25]. The group reported 18 patients who underwent carboplatin and cisplatin desensitization for a total of 95 desensitization cycles. Of the 18 patients, 13 underwent carboplatin desensitizations and the remainder received cisplatin desensitizations. Nine of these 18 patients previously had mild reactions during standard platinum infusion. The remaining 9 patients initially had “low-risk moderate” reactions during standard infusion. Li et al. reported that 32% of the CD cycles were complicated with HSRs, a clinically significant number of reactions (30 out of 95 CD cycles). In total, the group was able to administer a median of 2 cycles per person. In our study, we utilized the NCI Common Terminology Criteria for Adverse Events (CTCAE v. 4.03, Table 1) to categorize reactions. In doing so, we found that 34% (19 of the 56) of our patients underwent CD due to a history of moderate, severe and life threatening grade HSRs. One-hundred percent of these patients had no HSRs during their CDs. This finding is in contrast to Q. Li et al. where a 32% HSR rate ensued in patients with only a history of mild or “low-risk moderate” reactions. In total, with our protocol, we reviewed 129 patients with 753 reactionless CD cycles, this translates to an average of 6 cycles per patient. Unfortunately, during the 788 CD cycles one patient mortality occurred.

The patient death took place in the setting of her 13th CD cycle. The patient, prior to CD, had a complicated medical history with long standing type I diabetes, peritoneal dialysis, and a new diagnosis of pulmonary hypertension. Tragically, during the patient's final CD cycle, a HSR resulted in an episode of hypotension. The hypotension, in the presence of preexisting pulmonary hypertension, led to rapid cardiovascular collapse and death. Paradoxically, the CD treatment had been preventing progression of this young patient's cancer, as seen by a stable CA-125 and unchanged imaging. This incident, along with the results from the remaining 128 patients, aids in identifying patients at risk for high grade reactions and adverse events during CD. In our study, we found that individuals with high grade HSRs underwent initial CD at a younger age than those with low grade HSR. This difference was not dependent on the number of carboplatin cycles prior to CD, nor on the number of CD cycles. The risk factors identified here include a young age at initial CD and patients with multiple medical co-morbidities, particularly pre-load dependent cardiac conditions. Further analysis of our data suggests that patients who receive neoadjuvant chemotherapy may have a lower rate of HSRs during carboplatin desensitization. Although this finding was not statistically significant, the possibility that neoadjuvant carboplatin could have a role in tolerance to carboplatin remains an important area to explore.

Limitations of this study include our inability to determine the predictive value of the skin test. The true and false positives of a skin test can only be distinguished if carboplatin infusions are given after a positive skin test. There are obvious ethical issues with applying a standard dose of carboplatin to a patient in this scenario. High numbers of false positive skin tests can undermine the gynecologic oncologist's ability to treat carboplatin-sensitive tumors. Physicians may choose to omit carboplatin therapy when encountering a positive skin test in these patients. In our study, the likely false positive group of patients reside, assuming they exist, in the seventy-three patients who had positive skin testing. Fifty-two patients (71.2%) with positive skin tests (possible false positives included) were able to complete carboplatin desensitization administration without any reactions. In this way, even the unknown number of patients with false positive skin tests were still able to continue successfully with carboplatin infusion therapy.

The CD protocol established at our institution is fast, safe, effective, and validated in a large number of patients. The protocol's effectiveness is exemplified by a 96% completion rate of CD cycles, averaging six additional cycles per patient. The identification of medical co-morbidities and age as predictive risk factors will help stratify patients at high risk for reactions or adverse events during CD. Risk factor identification in combination with our protocol allows properly selected individuals to safely continue with the cornerstone of management in gynecologic malignancies. Further studies are needed to determine both the positive predictive value of a skin test and the mechanisms underlying carboplatin hypersensitivity.

Conflict of interest

Authors declare no conflict of interests.

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