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Outpatient desensitization of patients with moderate (high-risk) to severe platinum hypersensitivity reactions

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HIGHLIGHTS

- We discuss a single-institution experience with desensitization of patients with moderate to severe platinum reactions.
- A 16-step desensitization protocol is associated with less severe breakthrough reactions compared to a 4-step protocol.
- Outpatient desensitization of patients with moderate (high-risk) to severe reactions is highly successful and feasible.

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ABSTRACT

Objectives. Platinum hypersensitivity reactions (HSR) affect approximately 5% of the general oncologic population. Here we report the efficacy and safety of outpatient platinum desensitization protocol (PD) in gynecologic oncology patients with moderate (high-risk) to severe platinum HSR.

Methods. This is a retrospective report of patients with gynecologic malignancies undergoing an outpatient PD for moderate (high-risk) to severe platinum HSR from 2011 to 2017. Patient demographics, chemotherapy histories, and PD outcomes were collected. Descriptive statistics were performed given the exploratory nature of the study.

Results. Forty-eight patients meeting inclusion criteria were identified. Most patients were being treated for ovarian cancer (56.3%) and were receiving carboplatin during their initial platinum HSR (75.0%). Patients received a mean of 10.3 platinum doses prior to their initial HSR. Transient hypertension was the most common sign of moderate (high-risk) HSR while persistent tachycardia was the most common sign of severe HSR. A total of 295 PD cycles were attempted with a successful completion rate of 96.6%. The mean number of PD cycles received by patients was 5.1. Almost 65% of patients experienced breakthrough reactions but over 58% of these breakthrough reactions were isolated to the first PD cycle. Only 8.3% of patients had severe breakthrough reactions, all of whom initially underwent shortened desensitization. Of these 4 patients, 2 successfully underwent desensitization with a prolonged protocol.

Conclusion. Outpatient PD is safe and effective in patients with gynecologic malignancies. This may present a feasible option for institutions with multi-disciplinary teams experienced with the management of platinum HSR.

1. Introduction

Platinum hypersensitivity reactions (HSR) affect an estimated 5% of the general oncologic population and occur at a rate of approximately 1% of all platinum administrations [1]. Risk factors for platinum HSR include six or more cycles of platinum, cumulative platinum dose, increased interval from prior platinum exposure, platinum doublet with paclitaxel, BRCA mutations and a history of prior systemic allergic reactions [2–6]. As survival in gynecologic cancer patients has increased, this has led to patients receiving multiple platinum-based regimens especially in the setting of recurrence. There has been a reported incidence of HSR in up to 27% of patients receiving seven or more cycles of carboplatin for treatment of ovarian cancer [7].

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Symptoms of platinum HSR can range from mild to severe in presentation and are typically graded using the Common Toxicity Criteria for Adverse Events (CTCAE) [8]. In this classification system, mild reactions (grade 1) are defined as transient flushing/rash or drug fever <38 °C while moderate reactions (grade 2) manifest with rash, flushing and mild bronchospasm. Severe reactions (grade 3) include symptomatic bronchospasm, urticaria, edema/angioedema and hypotension. Grades 4 and 5 reactions are anaphylaxis and death respectively. The incidence of grade 3 or greater HSR ranges between 33 and 50% [9]. Given the potential for catastrophic platinum HSR reactions, the National Comprehensive Cancer Network recommends that both clinicians and patients be prepared for the possibility of a drug reaction [10]. Treatment of acute reactions includes administration of antihistamines, H2-blockers, glucocorticoids, and epinephrine. Efforts to prevent HSR having included pretreatment with antihistamines and steroids as well as extended infusion times [11].

Recent research has looked at the possibility of desensitizing patients with prior platinum HSR to allow for further administration of platinum-based regimens. This was first described by Windom et al. in 1992 where pre-medication was followed by administration of increasing concentrations of carboplatin [12]. Since this time, there have been a number of studies describing platinum desensitization protocols (PD), and these protocols vary in terms of safety, speed, patient location (outpatient, inpatient, or ICU), and validation [13]. We have previously shown the feasibility and efficacy of an outpatient, rapid 4-step desensitization in patients with mild to moderate-low-risk HSR to carboplatin/cisplatin [14]. However, there is little research exploring desensitization protocols in patients with a history of moderate high-risk to severe HSR.

The gynecologic oncology group in our institution initiated a multidisciplinary working group to establish an outpatient protocol for patients undergoing desensitization for platinum HSR. For patients with mild to moderate (low-risk) reactions, the team often used a quick (4-step titration) desensitization protocol in the outpatient clinic as described by Li et al. [14]. During this time we also addressed the practice management of moderate (high-risk) and severe HSR using a protocol which had previously been developed as part of the standard practice. The multidisciplinary working group readdressed the previous usual practice and modified to ensure the consistent highest quality of patient care across the entire cancer programs at the James Cancer Hospital/Clinics of The Ohio State University.

Here we report on our retrospective experience in the efficacy and safety of outpatient PD in the treatment of gynecologic oncology patients with moderate (high-risk) to severe HSRs to cisplatin or carboplatin. We also assessed the incidence and severity of breakthrough reactions with each infusion protocol.

2. Methods

2.1. Patients

A retrospective review of the electronic medical record was conducted. Patients 18 years of age or older and diagnosed with a gynecologic cancer between January 2011 and June 2017 were identified. Patients with a history of moderate (high-risk) to severe acute HSR due chemotherapy infusion of cisplatin or carboplatin were selected. Reaction symptoms were classified based on the clinical classification system utilized at our institution as previously described (Table 1) [15]. This "Modified OSU" criterion for classification of platinum HSR incorporates specific objective criteria with patient-reported symptoms. For example, signs of moderate (high-risk) HSR include transient changes in blood pressure, heart rate or oxygen saturation lasting <10 min and angioedema in addition to symptoms such as chest pain, vision changes, ringing ears. Criteria of severe HSR include prolonged vital sign changes last longer than 10 min, anaphylaxis, and central nervous system disturbances such as mental status changes, hallucinations, and disorientation. While we refer to a category of "moderate-standard" HSR at our institution as these reflect the most "standard" or usual reactions encountered and the standard protocol which had been previously utilized at our center. We will refer to these patients as moderate (high-risk) in this paper to better reflect the population of patients studied.

Table 1
Clinical classification for platinum hypersensitivity reactions used at The Ohio State University.

Category	Clinical manifestations
Mild	Pruritus, facial flushing, localized rash, drug fever <100.4 °F
Moderate (low-risk)	Diffuse erythema or urticaria, nausea/vomiting, abdominal pain, nasal congestion, dyspnea without hypoxia, coughing/wheezing, drug fever ≥100.4 °F
Moderate (high risk)	Transient (<10 min) signs/symptoms including hypo/hypertension, tachy/bradycardia, chest pain, hypoxia, visual disturbance, tinnitus, angioedema without anaphylaxis
Severe	Sustained (≥10 min) signs/symptoms including hypo/hypertension, tachy/bradycardia, hypoxia despite oxygen supplementation, altered mental status, syncope, anaphylaxis

Of the patients identified, those who underwent platinum desensitization were selected for inclusion. An institutional-review board approval was obtained from the Ohio State Office of Research (Study ID 2014C0136).

2.2. Data collection

Baseline demographic data including age, race, cancer type, and history of prior drug allergy were documented. Details regarding patients' prior chemotherapy history was recorded and included line of chemotherapy when HSR occurred, current regimen, number of prior platinum exposures and length of platinum-free intervals from prior therapy. In those patients with platinum HSRs, we recorded reaction data, timing of presentation, signs/symptoms, severity and whether they were rechallenged with the drug on the same day as their HSR occurred. Information regarding PD outcomes were collected including the indication for PD, total courses of PD and outcome of desensitization. Patients with breakthrough reactions during their PD had the severity and symptoms of the reaction recorded. Additionally, the number of successfully completed platinum cycles performed with the PD protocol was recorded.

2.3. Desensitization protocols

All desensitization cycles were conducted either in an infusion center (OP-IC) or an outpatient acute care observation bed (OP-AC) under the supervision of a multidisciplinary team including a gynecologic oncologist, clinical pharmacists, nurse practitioner, and clinical nurse. Risks and benefits of desensitization were explained to all patients prior to treatment and consent was obtained. All patients were premedicated with intravenous (IV) H1 antagonists (diphenhydramine 50 mg), H2 antagonists (famotidine 20 mg), and glucocorticoids (dexamethasone 20 mg) 30 min prior to the desensitization. Oral or IV benzodiazepines were administered to patients as needed. Epinephrine was immediately available. Carboplatin doses were calculated using the Calvert formula and prepared in the standard 500-mL normal saline piggy bag while cisplatin was prepared in a 1000-mL normal saline bag per institution guidelines. All IV tubing was primed with active chemotherapy in patients undergoing PD unlike tubing priming with normal saline for patients without history of HSR to ensure accurate and consistent delivery of active drug during the infusion cycle.

During the initial development of desensitization protocols, most patients were desensitized with the shortened protocol. However, in an attempt to decrease the number and severity of breakthrough reactions, all patients with moderate (high-risk) HSR subsequently underwent desensitization with a 16-step, 1-solution PD. If patients

continued to have moderate (high-risk) or severe breakthrough reactions, they then underwent a more intensive PD using the prolonged protocol or were switched to a non-platinum containing regimen.

2.4. Shortened (4-step, 1-solution) protocol

This is a 4-step, 1-solution PD. Infusion was initiated at approximately 10% of goal rate for 15 min. The rate was then increased to 25% of goal, followed by 50% of goal, ultimately ending at the infusion goal rate for the remained of the infusion. Infusion rates were increased every 15 min. Goal rate for carboplatin infusions was based on an infusion time of 60 min using drug prepared in a standard 500 mL infusion, while the goal rate for cisplatin was based on an infusion time of 90 min for cisplatin in 1000 mL. Total time required for desensitization was 1.5 h for carboplatin and 2.25 h for cisplatin.

2.5. Standard desensitization (16 step, 1-solution) protocol

Following the standardized premedication and preparation, platinum infusion was started at a rate of 2 mL/h. The infusion rate is increased in 15 min intervals until a goal rate of 600 mL/h is reached. The full details of the infusion rates and dosing are listed in Table 2. Total infusion time was 4.25 h for carboplatin and 5.25 for cisplatin.

2.6. Prolonged desensitization (16-step, 3-solution) protocol

The prolonged PD used at our institution requires 3 solutions. The first bag contains 1/100 of the drug based on the final target concentration while bag 2 contains 1/10 of the target concertation of drug. The final bag contains the platinum at final target concentration. Infusion of bag 1 is started at 2 mL/h and increased every 15 min to a goal rate of 20 mL/h for 15 min. Bag 2 is then hung infused at 5 mL/h with the rate increased every 15 min until a rate of 40 mL/h for 15 min is reached. Finally bag 3 is started at a rate of 10 mL/h and increased every 15 min until an infusion rate of 75 mL/h is reached. This rate is continued for the remainder of the infusion resulting in a total infusion time of 9 h for carboplatin and 14 h for cisplatin administration. Premedication and priming for the prolonged PD protocol is identical to the aforementioned standard protocol. The length of the HD requires an acute care bed observation/admission.

Table 2
The Ohio State University standard platinum desensitization protocol infusion rates (for carboplatin).

Step	Rate (mL/h)	Time (min)	Time accumulated (h)	Volume infused per step (mL)	Admin dose (mg)	Accumulated dose (mg)
1	2.0	0	0.25	0.50	0.54	2.14
2	4.0	15	0.50	1.00	1.07	3.21
3	6.0	15	0.75	1.50	1.61	4.82
4	8.0	15	1.00	2.00	2.14	6.96
5	10.0	15	1.25	2.50	2.68	9.63
6	15.0	15	1.50	3.75	4.01	13.64
7	30.0	15	1.75	7.50	8.03	21.67
8	60.0	15	2.00	15.00	16.05	37.72
9	80.0	15	2.25	20.00	21.40	59.12
10	100.0	15	2.50	25.00	26.75	85.87
11	120.0	15	2.75	30.00	32.10	117.97
12	140.0	15	3.00	35.00	37.45	155.42
13	160.0	15	3.25	40.00	42.80	198.22
14	180.0	15	3.50	45.00	48.15	246.37
15	200.0	15	3.75	50.00	53.50	299.87
16	400.0	15	4.00	100.00	107.00	406.87
17	600.0	Completed target	4.25	257.10	192.60	600.00

2.7. Management of breakthrough reactions

Breakthrough reactions were defined as HSR reoccurring during desensitization cycles. Symptoms of these reactions were classified using the same system as the initial HSR. Frequency, presentation, and severity of these reactions could vary during desensitization cycles and may or may not be similar to the initial HSR. If a breakthrough reaction occurred, the infusion was suspended and IV diphenhydramine 25–50 mg and/or hydrocortisone 50–100 mg were given. Patients experiencing gastrointestinal symptoms were given IV famotidine 20 mg while those with respiratory symptoms received 2–4 puffs of inhaled albuterol. Per protocol, epinephrine was administered only in the case of anaphylaxis, compromised airway due to bronchospasm, angioedema or sustained hypotension that is unresponsive to previously administered medications. Pending resolution of symptoms and upon agreement of attending physicians and the patient, the infusion was resumed at the prior tolerated rate before the HSR breakthrough reaction occurred. Further titration was performed according to defined protocol. Typically, patients undergoing subsequent desensitization cycles would then be redosed with IV diphenhydramine 25–50 mg and/or hydrocortisone 50–100 mg at the step prior to when the breakthrough reaction occurred.

2.8. Subsequent desensitizations following breakthrough reactions

If a patient experienced a mild or moderate (low-risk) breakthrough reaction during desensitization, the previously utilized protocol could be continued for subsequent treatments pending discretion of the attending physician. Per institutional protocol, patients experiencing an HSR during desensitization that represented a progression in severity from prior HSRs were escalated to a subsequent desensitization treatment protocol by at least one level. A prolonged PD could also be considered. Alternative therapy was considered for patients experiencing persistent moderate (high-risk) or severe breakthrough reactions despite longer PD.

2.9. Statistical analysis

Statistical analysis was completed using SPSS v24.0 (IBM, Armonk, New York). Descriptive statistics were utilized to analyze demographics, primary and secondary end points. Fisher's exact test was used to compare incidences of breakthrough reactions between the different desensitization PD.

3. Results

Forty-eight patients with history of moderate (high-risk) and severe platinum HSR who underwent subsequent PD between 2011 and 2017 were identified. Baseline demographic data were collected (Table 3). The cohort had a mean age of 63.0 years with a majority of the patients being white (91.7%). Ovarian/fallopian tube/primary peritoneal cancer was the most common cancer type in the cohort (56.3%) followed by endometrial (27.0%) and cervical cancer (16.7%). Carboplatin was the agent most commonly responsible for initial platinum HSR (75.0%). A majority of patients were on at least their second line chemotherapy when their initial HSR occur, and the average number of prior platinum doses received prior to the platinum HSR was 10.3. Twenty-five patients had a platinum-free interval of at least 12 months (52.1%). Most of the initial platinum HSR at our institution were moderate (high-risk) in severity (79.2%), and approximately half of the patients completed a rechallenge on the same day following their initial HSR (Fig. 1).

Characteristics of initial HSR symptoms are presented in Table 4. The most common symptoms of HSR were cutaneous manifestations followed by nausea/vomiting followed by respiratory complaints. Transient hypertension was the most common sign of moderate (high-risk) reactions while persistent tachycardia was the most common

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

Characteristics (n = 43)	Mean or frequency	Range or %
Age (years)	63.0	44–80
Race		
White	44	91.7
African American	4	8.3
Allergy history		
No	17	35.4
Yes	31	64.6
Cancer type		
Ovarian/fallopian tube/primary peritoneal	27	56.3
Endometrial	13	27.0
Cervical	8	16.7
Platinum agent		
Carboplatin	36	75.0
Cisplatin	12	25.0
Line of chemotherapy when HSR occurred	2.7	1–8
Number of prior platinum doses	10.25	0–37
Treatment-free interval (months)	19.1	0–93
Platinum-free interval		
No prior platinum	12	25.0
<12 months	11	22.9
≥12 months	25	52.1
Severity of initial HSR		
Moderate-(high-risk)	38	79.2
Severe	10	20.8
Same day rechallenge following initial HSR		
No	16	33.3
Yes	22	45.8
Not applicable – delayed reaction	10	20.8

manifestation of severe platinum HSR. Presyncope/syncope was rarely encountered in this cohort. There were no occurrences of angioedema, anaphylaxis or death.

Ultimately, a total of 295 desensitization cycles were attempted while 285 cycles were completed resulting in a success rate of 96.6% (Table 5). The standard protocol was the most commonly utilized PD (50.8%) followed by the shortened desensitization protocol (40.7%). Only 5 patients were treated with the prolonged desensitization protocol. The mean number of desensitization cycles received by each patient was 5.1 (1−32). Nineteen of 24 patients initially tried the shortened protocol and completed this including the two patients re-classified as severe HSR on records review. Six patients were converted to the standard protocol. Five of 6 patients converted to the standard protocol and completed this. One patient was transitioned to the standard protocol but had a benzodiazepine reaction requiring step-down care and was not subsequently re-challenged with platinum. Twenty four patients started on the standard protocol and only 1 patient did not complete this and had to be escalated to the prolonged protocol.

Thirty-one patients (64.6%) experienced breakthrough reactions during desensitization. Twenty five of the 31 patients experiencing breakthrough reactions had a breakthrough reaction during the first desensitization cycle. Of these patients, 4 (16%) had severe reactions and all of these patients were in the shortened protocol cohort. Eleven

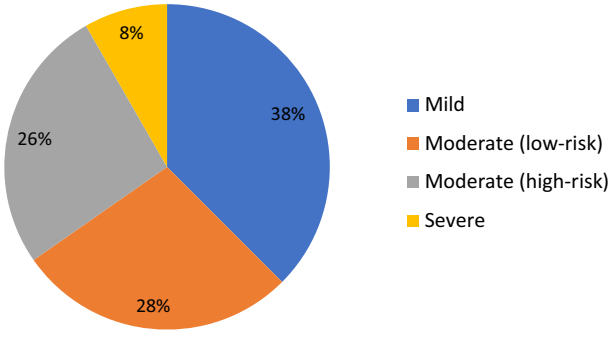

Fig. 1. Severity of breakthrough reactions encountered during desensitization.

Table 4
Symptoms of initial moderate (high-risk) and severe platinum hypersensitivity reactions.

Characteristics of initial HSR symptoms	Frequency	Percentage
Cutaneous		
Flushing	24	50.0
Itching	16	33.3
Rash/hives	20	41.7
Respiratory		
Chest tightness/dyspnea	8	16.7
Coughing	5	10.4
Chest pain	7	14.6
Oxygen desaturation (<93%)		
≤10 min	7	14.6
>10 min	4	8.3
Cardiovascular		
Hypertension (>150/90)		
≤10 min	21	43.8
>10 min	3	6.3
Hypotension (<90/60)		
≤10 min	6	12.5
>10 min	0	0
Tachycardia (HR > 100)		
≤10 min	14	29.2
>10 min	9	18.8
Bradycardia (HR <60)		
≤10 min	1	2.1
>10 min	0	0
Neurological		
Presyncope/syncope	3	6.3
Others		
Nausea/vomiting	13	27.1
Abdominal pain/discomfort	7	14.6
Angioedema	4	8.3

patients had moderate (high-risk) reactions (44%) while 10 (40%) had mild to moderate (low-risk) reactions. Of these 31 patients, 18 (58.1%) had breakthrough reactions during the first desensitization cycle alone and were successfully treated without subsequent reactions resulting in administration of 223 desensitization cycles (75.6%) with no breakthrough reactions. Approximately 64% of breakthrough reactions

Table 5
Description of desensitization experience.

Characteristics	Mean or frequency	Range or %
Desensitization protocols[a]		
Shortened[b]	24	40.7
Standard	30	50.8
Prolonged	5	8.5
Number of desensitization cycles attempted	295	–
Number of desensitization cycles completed	285	–
Mean number of desensitization cycles attempted per patient	5.1	1–32
Breakthrough reactions during desensitization cycles		
Present	72	24.4
Absent	223	75.6
Reason for discontinuation of desensitization protocol		
Regimen change due to disease progression	20	31.7
Regimen change due to toxicities (not including breakthrough reactions)	5	7.9
Completion of therapy	21	33.3
Transfer of care/transition to hospice	4	6.3
Currently on therapy	2	
Continued breakthrough reactions		
Switched to more intense desensitization protocol	5	7.9
Changed to non-platinum containing regimen	2	1.6
Changed to alternative platinum regimen	4	6.3

[a] Frequency >43 as several patients were on multiple desensitization protocols due to change to an alternative platinum regimens or continued breakthrough reactions.

[b] Two patients had initial reactions to carboplatin and were started on a shortened desensitization. Upon recurrence, they were started on a shortened desensitization for cisplatin. This was included as a separate occurrence of the shortened protocol due the change in platinum. Two patients were mistakenly clinically classified as moderate (high-risk) HSRs and received the shortened protocol but were able to successfully complete all cycles.

during desensitization were either mild or moderate (low-risk) in severity. There was no difference in incidence of breakthrough reactions between carboplatin (64.4%) and cisplatin (61.5%) PD.

As noted above, the shortened protocol was initially used for patients with moderate (high-risk) HSR. However, 65.0% (13/20) patients experienced breakthrough reactions with 40.1% of those reactions being moderate (high-risk) to severe HSR. Of concern, 4 of these patients (20.0%) had severe reactions. The first patient had a moderate (high-risk) HSR during her first shortened desensitization and was given an increased dose of dexamethasone prior to her next shortened PD. The patient then had a severe breakthrough reaction with her second attempted shortened PD cycle and was hospitalized overnight for observation. She was discharged within 24 h with no residual effects and then elected for an alternative therapy. A second patient with a severe breakthrough reaction on the shortened PD was transitioned to the standard PD after her breakthrough reaction but developed persistent hypoxia and mental status changes secondary to benzodiazepine administration. She was then changed to a non-platinum containing regimen. The third and fourth patients subsequently successfully completed the prolonged, 16-step protocol in an acute care bed without requirement for ICU admission. Of note, there were only two instances in which epinephrine administration was required for breakthrough reactions per protocol.

In an attempt to decrease the incidence and severity of breakthrough reactions, all patients with moderate (high-risk) or severe HSR subsequently underwent desensitization using the standard PD. Approximately 61% of patients undergoing desensitization with the standard PD had breakthrough reactions of all severities. Thirty-nine percent of patients had moderate (high-risk) reactions. Importantly, no patients had severe breakthrough reactions when using the standard PD compared to 20.0% of patients undergoing desensitization with the shortened protocol ($p = 0.0656$). Furthermore, only 2 patients undergoing standard PD for moderate (high-risk) HSR (2/24, 8.3%) were unable to complete their desensitization cycles (with 1 of these patients being the aforementioned patient with an adverse reaction to benzodiazepines) compared to 5 patients (5/20, 25%) undergoing the shortened PD.

The most commonly noted reasons for discontinuation of a desensitization protocol were completion of therapy (33.3%) and regimen change due to disease progression (31.7%). Of note, 5 patients were switched to more intense PD due to continued HSR (7.9%) and were all able to successfully completing subsequent PD cycles. There were no deaths or ICU admissions due to breakthrough reactions during platinum desensitization. There was one stepdown admission in the cohort due to benzodiazepine administration.

4. Discussion

The outpatient PD described here is a highly effective treatment of patients with moderate (high-risk) to severe platinum HSR. To our knowledge, this is the first report of a rapid, outpatient PD for patients with moderate (high-risk) to severe HSR which is the equivalent of CTCAE v 3.0 grade 3 reactions and NCCN classification of severe reactions. In terms of efficacy, 96.6% of the desensitization cycles attempted were completed (285/295) while 887.5% (42/48) of patients were able to complete desensitization without undergoing a prolonged PD. Experienced medical professionals are essential to recognize the signs and symptoms of platinum HSR and actively manage the potentially life threatening acute reactions that can occur [14,15]. Though a significant proportion of patients experienced subsequent breakthrough reactions during desensitization, it is important to note that a majority of these reactions were low to moderate (low-risk) in severity and were limited to the first cycle of desensitization. Only one of the patients undergoing PD in an outpatient infusion center required hospitalization due to a breakthrough reaction and was subsequently discharged the next day. Furthermore, none of the patients experiencing breakthrough reactions during a PD required had long-term morbidity or had significant toxicities emphasizing the safety of this regimen in a center with experience in the treatment of platinum HSR.

During the initial implementation of the new protocol and standardized desensitization program a majority of patients with moderate (high-risk) to severe HSR underwent desensitization with the shortened, 4-step protocol. However, we noted breakthrough reactions in 65% of patients with 20% of these reactions being severe in nature. In an attempt to reduce the rate of these breakthrough reactions, we subsequently recommended that all patients undergo desensitization with the standard 16-step, 1 solution protocol. While 61% of patients still experienced breakthrough reactions, only 39.0% of these patients had moderate (high-risk) breakthrough reactions. No patients had severe breakthrough reactions supporting the use of the standard, 16-step, 1-solution PD in patients with moderate (high-risk) and severe platinum HSR.

A number of PD have been described in the literature [16–20]; however, there is little literature regarding the use of desensitization protocols in patients with moderate or severe reactions. A recent study by Altwerger et al. described their successful experience with a 4 step, 3.5 h desensitization protocol [13]. In this study, 129 patients underwent desensitization and were able to complete a total 788 cycles with prevention of reactions in 96% of patients. This sample included both patients with a history of previous platinum HSR (56/129) and patients with positive skin testing (73/129). Of the patients with a prior platinum HSR only 2.3% of those patients had a CTCAE grade 3 reaction or higher. This is contrast to our report in which 100% of patients had the equivalent of CTCAE grade 3–4 reactions or severe reactions per NCCN classifications (Table 6). Seventy-five percent of patients in the Altwerger et al. study had no breakthrough reactions during desensitization compared to only 31.8% of patients in our study. We hypothesize that the increased rate of breakthrough reactions noted in our study is likely due to the exclusive inclusion of patients with clinically-documented moderate (high-risk) to severe HSR. Of note, Altwerger and colleagues did report one death in a patient receiving her 13th desensitization cycle while we did not have any mortalities or the need for critical care in our cohort undergoing desensitization.

To ensure safety and efficacy of desensitization, it is important that the severity of HSR be appropriately categorized so the appropriate desensitization protocol may be selected. Both the National Comprehensive Cancer Network (NCCN) guidelines and the Common Terminology Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute (NCI) are commonly used to define HSR [15]. While these definitions may provide guidance for documentation, they are often vague and heavily rely on a patient's subjective experiences. In an attempt to overcome these limitations, Brown and colleagues published a simplified system for grading the severity of anaphylaxis based on highlighting the importance of hypotension, hypoxia and central nervous system involvement in grading HSR [21]. The modified, clinical classification system utilized at our institutions allows us to overcome some of the limitations and vague definitions of the currently used systems by combining both subjective patient symptoms with objective signs (Table 1). This allowed us to maintain the categories of mild and severe HSRs while separating the group of moderate reactions into two sub-groups (moderate-low and moderate-high-risk/standard) allowing us to select the most appropriate PD for the patient.

While both an outpatient 4-step and 16-step, 1-solution PD were utilized in our patients with moderate (high-risk) or severe reactions, we believe the 16-step PD provided greater benefits to our patients than the 4-step protocol. Firstly, patients receiving the 16-step PD had less severe breakthrough reactions compared to those receiving the 4-step protocol. Secondly, compared to more intensive regimens in the literature, patients can initiate desensitization in either an outpatient infusion center or in outpatient acute observation beds. By avoiding hospital admissions and prolonged infusion, cost and patient inconvenience should be decreased. Additionally, patients can be treated in a timelier

manner under direct supervision of their primary practitioner as the standard, 16-step one solution protocol for carboplatin requires only 4.25 h for completion. Finally, this protocol utilized varying rates of a single solution rather than requiring multiple dilutions which simplifies the desensitization process and potentially decreasing the risk of errors in medication preparation or administration potentially improving patient safety. Finally, despite our patients having moderate (high-risk) to severe reactions, 93% of these patients were able to complete desensitization allowing these patients to receiving further platinum treatment for platinum-sensitive disease.

Limitations of this study include the retrospective nature of the project and our sample size. However, in one small study of carboplatin HSR, the incidence of grade 1–2 reactions as defined by the CTCAE v3.0 was 66.7% while the incidence of grade 3–4 reactions was 33.3% [9]. We chose to report our patient with high-risk HSR separately from those with lower risk HSR to attempt to better define the patient populations and the PD protocols utilized. Smaller numbers are expected when limiting the population to higher risk patients. It is also important to note that these desensitization cycles were undertaken at an institution where a multi-disciplinary team experienced with HSR is in place within the areas the patients are receiving the PD. Therefore, this protocol may not be suitable for institutions where there is a lack of healthcare professionals experienced in platinum HSR or in centers where immediate intervention and assessment is not available.

The outpatient 16-step PD established at our institution for patients with a history of moderate (high-risk) to high HSR is timely, effective and safe. Additionally, given the reliance on a single-solution, this particular protocol is likely easier to administer when compared to other regimens requiring multiple dilutions. Ninety-seven percent of attempted desensitization cycles were completed illustrating the effectiveness of the protocol. Safety is demonstrated in the fact that 75% of patients undergoing standard desensitization had either no to moderate (low-risk) breakthrough reactions. No patients treated with the standard PD had severe breakthrough reactions. In institutions with multidisciplinary teams experienced with management of HSR this protocol offers a feasible, safe, and effective option for management of patients with a history of moderate (high-risk) or severe HSR but careful patient selection and close monitoring are essential for success. Further clinical studies are warranted to confirm these results.

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CRediT authorship contribution statement

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