Original Article

Management of Hypersensitivity Reactions to Carboplatin and Paclitaxel in an Outpatient Oncology Infusion Center: A 5-Year Review

Aleena Banerji, MD[a], Timothy Lax, MD[a], Autumn Guyer, MD[a], Shelley Hurwitz, PhD[b], Carlos A. Camargo, Jr, MD, DrPH[a,c], and Aidan A. Long, MD[a] *Boston, Mass*

What is already known about this topic? Carboplatin and Taxol are frequently associated with drug hypersensitivity reactions. Drug desensitization is a successful way to manage these patients after a hypersensitivity reaction.

What does this article add to our knowledge? The clinical symptoms and timing of hypersensitivity reactions to carboplatin is distinct from hypersensitivity reactions to Taxol. Many patients with Taxol hypersensitivity reactions tolerated rechallenge in the outpatient infusion center without desensitization.

How does this study impact current management guidelines? Desensitization should be offered to all patients with severe hypersensitivity reactions to carboplatin and paclitaxel who need to remain on first-line therapy. Whether patients reactive to paclitaxel with mild-to-moderate reactions can be safely rechallenged with premedications needs further study.

BACKGROUND: A high incidence of hypersensitivity reactions (HSR) to carboplatin and Taxol is limiting the use of carboplatin and Taxol.

OBJECTIVE: We conducted a 5-year study of all patients with HSR to carboplatin or Taxol to better understand the nature of infusion HSR and success or failure of management plans after the initial HSR.

METHODS: We performed a retrospective chart review of all safety reports from the Massachusetts General Hospital outpatient chemotherapy infusion center between January 2006 and February 2011. All the patients with HSRs to carboplatin or Taxol were identified and included in the final analysis. We reviewed patient characteristics, clinical symptoms, timing, and treatment of the initial HSR, and determined if the patient was rechallenged despite an initial HSR.

RESULTS: We identified 152 patients with HSR to carboplatin (n = 45) or Taxol (n = 107). Carboplatin HSR was less severe than Taxol HSR. When comparing the 2 groups, the patients with carboplatin HSRs more commonly described itchy palms and feet, generalized itch, and general urticaria and/or erythema, whereas patients with Taxol HSR more commonly described facial flushing, back pain, and chest or throat tightness (all $P < .05$). Among 40 patients with mild-to-moderate carboplatin HSRs, only 7 were rechallenged, and 100% tolerated rechallenge without desensitization. None of the patients with severe carboplatin HSRs (n = 5) were rechallenged. Most patients (75%) with Taxol HSRs were rechallenged, and 91% tolerated rechallenge without desensitization; the patients with a severe HSR to Taxol were less likely to be rechallenged.

CONCLUSION: The clinical symptoms and timing of carboplatin HSR are distinct from Taxol HSR. Most patients with carboplatin HSR were not rechallenged, whereas most patients with Taxol HSR were successfully rechallenged. **© 2014 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2014;2:428-33)**

Key words: *Drug hypersensitivity; Allergy; Desensitization*

Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (approximately 13% of all deaths) in 2008,[1] and ovarian cancer is responsible for 5% of all cancer deaths among women.[2] Although the incidence of these cancers continues to rise, cancer mortality has declined over the past decade,[3] in large part due to more efficacious chemotherapeutic regimens. Thus, the ability to use first-line chemotherapeutic agents, such as carboplatin or Taxol, (Bristol-Myers Squibb, Hopewell, NJ) in the treatment of patients with cancer is crucial. However, a high incidence of hypersensitivity or hypersensitivity-like reactions (HSR) to important first-line chemotherapeutic agents, such as carboplatin and Taxol, have been recognized and

[a]Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Mass
[b]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass
[c]Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Mass
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Corresponding author: Aleena Banerji, MD, Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114. E-mail: abanerji@partners.org.
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Abbreviations used
BMI- Body mass index
CAD- Coronary artery disease
HSR- Hypersensitivity reaction
HTN- Hypertension
IQR- Interquartile range
NA- Not available

limited their use. A 1% incidence of HSR to carboplatin is documented in patients who received fewer than 6 courses of treatment, but this increased to 27% in patients who received more than 7 treatments.[4] Similarly, Markman et al[5] showed a 9% risk of HSR to Taxol during the first or second infusion in women with pelvic malignancies.

The lack of a standard approach to management after an initial HSR leads to suboptimal outcomes, including needless avoidance of first-line chemotherapeutic agents in patients who could tolerate rechallenge without desensitization or intentional rechallenge with a drug that may cause a recurrent and severe HSR. A better understanding of the nature of infusion HSR and the success or failure of management plans after an HSR would improve decision making and help in the development of a safe and standardized approach for all patients who develop HSR. To address these issues, we performed a 5-year detailed review of all the patients with HSR to carboplatin or Taxol that occurred in the outpatient infusion center at a large academic center. We focused on symptoms, timing, and management of initial HSR, along with outcomes after rechallenge to carboplatin or Taxol despite a history of an HSR.

METHODS

At our institution, any adverse event, including a drug HSR, is filed as a safety report. We performed a retrospective chart review of all safety reports from the Massachusetts General Hospital outpatient chemotherapy infusion center between January 2006 and February 2011. All the patients with HSR to carboplatin or Taxol were selected and included in the analysis. We used the term HSR to include all immune-mediated reactions to carboplatin and Taxol consistent with previously published literature.[4,5] Institutional review board approval was obtained for this study.

HSRs

We compiled information from patient records, including age, sex, body mass index, oncology diagnosis, and medical history. Clinical symptoms, timing, and treatment of the initial HSR were recorded. The severity of the initial HSR was classified by using the Brown classification,[6] in which mild is defined by symptoms of generalized erythema, urticaria, periorbital edema, or angioedema; moderate is defined by symptoms of dyspnea, stridor, wheeze, nausea, vomiting, dizziness, presyncope, diaphoresis, chest or throat tightness, or abdominal pain; and severe is defined by symptoms of cyanosis, hypotension (systolic blood pressure <90 mm Hg in adults), confusion, collapse, or loss of consciousness. If symptoms from different categories were present, then patients were classified by the category of highest severity. An allergy/immunology physician (A.B.) and oncology nurse independently evaluated the reaction and came to an agreement that clinical symptoms met the definition for carboplatin or Taxol HSR based on published literature[4,5] and on the severity classification of the initial HSR.

Outcomes after initial hypersensitivity reaction

All the medical records were further reviewed to determine if the patient was rechallenged to the same chemotherapeutic agent despite initial HSR and if the patient tolerated rechallenge. Clinical symptoms of any subsequent HSR were recorded if the patient did not tolerate rechallenge. The data were analyzed to determine if there were any factors predictive of rechallenge or tolerating rechallenge among patients with HSR to carboplatin or Taxol.

Statistical analysis

Data were summarized by using standard descriptive statistics such as means ± SDs, medians with interquartile ranges or percentages, as applicable. Statistical comparisons included the Wilcoxon rank sum test for ordinal data or the Fisher exact test for binary data. All P values are 2-tailed, with $P < .05$ considered statistically significant. Statistical analysis was performed by using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Overall, there were 476 HSRs to any chemotherapeutic agents at the Massachusetts General Hospital outpatient infusion center from January 2006 to February 2011. We focused on 152 patients with HSRs specifically to carboplatin (n = 45) or Taxol (n = 107).

Patient characteristics

The average age of patients with HSRs to carboplatin or Taxol was approximately 55 years (range, 25-79 years). Most patients in both carboplatin or Taxol groups were women (69% and 96%, respectively). Most patients with carboplatin HSRs were being treated for ovarian cancer (76%), whereas patients with Taxol HSRs were being treated for lung (32%), breast (23%), and ovarian cancers (18%). Comorbid conditions in addition to the primary oncologic diagnosis were reviewed (Table I).

Clinical symptoms and timing of the initial HSR

Carboplatin HSRs were less severe than Taxol HSRs ($P = .02$), with 64% of carboplatin HSRs being classified as moderate to severe compared with 86% of Taxol HSRs (Table I). Compared with patients with Taxol HSRs, patients with an HSR to carboplatin more frequently presented with symptoms of itchy palms and feet, generalized itch, general urticaria and/or erythema, vomiting, hypotension, and coryzal symptoms (all $P < .05$). In contrast, patients with HSRs to Taxol more frequently presented with symptoms of facial flushing, back pain, and chest or throat tightness (all $P < .05$) (Table II). Patients developed HSRs to carboplatin after multiple exposures to the drug, a pattern distinct from patients on Taxol who developed HSRs during the first or second exposure to the drug (Figure 1). Two patients developed delayed Taxol HSRs with initial symptoms during the 13th cycle (breast cancer) and during the 14th cycle, with additional symptoms of chest pressure and chest pain (sarcoma). Symptoms of Taxol HSRs were moderate in severity, with symptoms of facial flushing and of back and throat pain. Both patients were rechallenged, with additional premedications, without desensitization and tolerated the infusion successfully.

Treatment for the initial HSR

Treatment of the initial HSR included glucocorticoids, H1 and H2 blockers, intravenous fluids, oxygen therapy, and inhaled

TABLE I. Demographic and clinical characteristics of patients with HSRs to carboplatin or Taxol in the outpatient infusion center

	Carboplatin (n = 45)	Taxol (n = 107)	*P* value
Age (y), mean ± SD	56.6 ± 10.2	55.7 ± 12.2	.67
Women (%)	96	69	.004
BMI (kg/m^2), mean ± SD	26.5 ± 5.0	27.0 ± 6.4	.97
Initial HSR cycle no., median (IQR)	8 (7-11)	1 (1-2)	<.0001
Ovarian cancer (%)	76	18	<.0001
Lung cancer (%)	11	32	.007
Breast cancer (%)	2	23	.002
CAD (%)	2	4	.63
Diabetes (%)	4	10	.35
HTN (%)	42	43	.93
Atopy (%)	33	21	.09
History of drug allergy (%)	49	59	.29
Rechallenged (%)	16	75	<.0001
Infusion tolerated in rechallenged patients (%)	100	91	.41
Initial HSR severity (%)			.02
Mild	36	14	
Moderate	53	73	
Severe	11	13	

BMI, Body mass index; *CAD,* coronary artery disease; *HTN,* hypertension; *IQR,* interquartile range.

TABLE II. Clinical symptoms of initial carboplatin or Taxol HSR

	Carboplatin (%) (n = 45)	Taxol (%) (n = 107)	*P* value
Abdominal pain	18	12	.39
Back pain	2	35	<.0001
Chest pain	4	12	.14
Chest or throat tightness	18	34	.04
Chills	0	2	.35
Coryzal symptoms	20	2	.001
Cough	7	9	.57
Cyanosis	7	10	.46
Diaphoresis	2	5	.47
Dizziness	4	8	.38
Dyspnea	18	32	.07
Facial flushing	42	70	.001
General urticaria and/or erythema	31	7	<.0001
Generalized itch	29	6	<.0001
Hypertension	0	5	.14
Hypotension	13	4	.03
Itchy palms or feet	44	1	<.0001
Nausea	18	7	.07
Rigors	0	3	.25
Tachycardia (%)	18	16	.81
Vomiting (%)	13	2	.004

β-agonists. Treatment of HSRs was similar in both groups except that patients with carboplatin HSRs were more frequently treated with H2 blockers, whereas patients with Taxol HSRs were more frequently treated with oxygen supplementation (Table III). Despite the moderate-to-severe nature of many HSRs, epinephrine was not used to treat any HSRs to carboplatin or Taxol over the 5-year period.

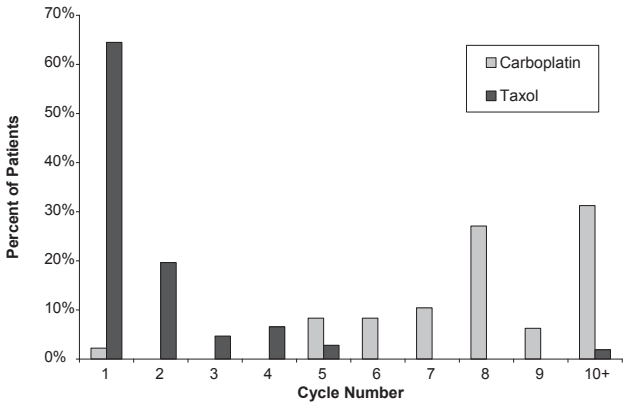

FIGURE 1. Reaction cycle number in patients with HSR to carboplatin or Taxol.

TABLE III. Treatment of carboplatin or Taxol HSRs

	Carboplatin (%) (n = 45)	Taxol (%) (n = 107)	*P* value
Glucocorticoids	53	53	.86
H1 blocker	89	85	.81
H2 blocker	16	3	.005
β-agonist	2	7	.26
Intravenous fluids	38	32	.55
Oxygen	18	33	.05

Outcomes after the initial HSR

Seven patients were rechallenged to carboplatin after the initial HSR. These patients had a mild (n = 4) or moderate (n = 3) initial HSR, and all 7 patients (100%) tolerated rechallenge in the outpatient infusion center without having undergone desensitization. The other 38 patients, including all 5 patients with a severe initial HSR (n = 5) to carboplatin were not rechallenged in the outpatient infusion center. Fifteen patients who were not rechallenged did not receive any further carboplatin therapy, and the other 23 patients, including 4 patients with severe HSRs, were referred to the allergy department for further management. Most (64% [14/22]) of the patients referred to the allergy department after the initial HSR were skin test positive to carboplatin, and all were referred for desensitization due to concerning HSRs. One patient referred to the allergy department did not undergo skin testing or receive any further carboplatin treatment. All 4 patients referred to the allergy department with severe HSR were skin test positive to carboplatin. The fifth patient with a severe HSR was not referred to the allergy department because carboplatin therapy was no longer deemed necessary. There was no statistical difference in clinical symptoms, timing, or treatment of initial HSR between patients with carboplatin HSRs who were rechallenged versus those who were not rechallenged; however, these data are from a small number of patients (Table IV).

Most patients (75%) with Taxol HSRs were rechallenged, and the majority (91%) tolerated rechallenge in the outpatient infusion center without having undergone desensitization

TABLE IV. Patients with carboplatin HSR who were rechallenged compared with those who were not rechallenged

	Rechallenged (n = 7)	Not rechallenged (n = 38)	*P* value
Age (y), mean ± SD	58.3 ± 15.3	56.3 ± 9.2	.47
Women (%)	100	95	.53
BMI (kg/m^2), mean ± SD	25.5 ± 6.7	26.7 ± 4.8	.58
Initial HSR cycle no., median (IQR)	8 (5-12)	8 (7-11)	.97
CAD (%)	0	3	.66
Diabetes (%)	0	5	.53
HTN (%)	43	42	.97
Atopy (%)	71	26	.02
History of drug allergy (%)	43	50	.73
Initial HSR severity (%)			.15
Mild	57	32	
Moderate	43	55	
Severe	0	13	
Infusion tolerated during rechallenge (%)	100	NA	
Symptoms of initial HSR (%)			
Back pain	0	3	.66
Chest or throat tightness	14	16	.92
Coryzal symptoms	14	21	.68
Cyanosis	0	8	.44
Dyspnea	14	18	.79
Facial flushing	29	42	.50
General urticaria and/or erythema	14	32	.35
Generalized itch	14	26	.50
Hypotension	0	16	.26
Itchy palms or feet	43	29	.47
Vomiting	0	16	.26

BMI, Body mass index; *CAD,* coronary artery disease; *HTN,* hypertension; *IQR,* interquartile range.

TABLE V. Patients with Taxol HSRs who were rechallenged compared with those who were not rechallenged

	Rechallenged (n = 80)	Not rechallenged (n = 27)	*P* value
Age (y), mean ± SD	55.7 ± 12.9	55.6 ± 9.7	.83
Women (%)	69	70	.87
BMI (kg/m^2), mean ± SD	26.8 ± 6.0	27.8 ± 7.5	.79
Initial HSR cycle no., median (IQR)	1 (1-1)	1 (1-2)	.04
CAD (%)	5	0	.23
Diabetes (%)	6	22	.02
HTN (%)	38	59	.05
Atopy (%)	20	22	.80
Drug allergy (%)	58	63	.62
Initial HSR severity (%)			.09
Mild	18	4	.07
Moderate	76	63	.18
Severe	6	33	.0004
Infusion tolerated during rechallenge (%)	91	NA	NA
Symptoms of initial HSR (%)			
Back pain	34	30	.69
Chest or throat tightness	31	41	.37
Coryzal symptoms	0	0	.56
Cyanosis	5	22	.008
Dyspnea	24	56	.002
Facial flushing	69	67	.84
General urticaria and/or erythema	6	7	.83
Generalized itch	8	0	.14
Hypotension	1	15	.004
Itchy palms or feet	0	4	.08
Vomiting	1	4	.41

BMI, Body mass index; *CAD,* coronary artery disease; *HTN,* hypertension; *IQR,* interquartile range; *NA,* not available.

(Table V). There were 8 patients with facial flushing as the only symptom of Taxol HSR and 7 patients with back pain with or without facial flushing. The majority (14 [93%]) of this specific subset of patients with Taxol HSR were rechallenged, and all tolerated rechallenge. A few of these patients were given antihistamine premedications (n = 3) or antihistamine premedications with a slowed infusion (n = 4). Patients with diabetes, hypertension, or a severe initial HSR to Taxol were less likely to be rechallenged. Specifically, patients on Taxol and with initial HSR symptoms, including cyanosis, dyspnea, or hypotension, suggestive of a moderate-to-severe reaction by the Brown classification[6] were less likely to be rechallenged to Taxol in the outpatient infusion center. However, 5 patients with an initial severe Taxol HSR were rechallenged, and 4 of these patients (80%) tolerated rechallenge in the outpatient infusion center. The fifth patient developed hypotension, shortness of breath, cough, lightheadedness, and facial flushing near the end of his rechallenge dose. The Taxol infusion was stopped, and he was given 125 mg of methylprednisolone. His symptoms completely resolved within 1 hour, likely related to cessation of the Taxol infusion. He tolerated subsequent Taxol infusions with additional antihistamine and steroid premedication in the outpatient infusion center without desensitization. Despite initial HSR, an allergy/immunology specialist was not consulted for the management of this 1 patient. All the patients on carboplatin and Taxol who were rechallenged successfully tolerated at least 2 additional treatments without any HSRs.

DISCUSSION

Our 5-year review at the Massachusetts General Hospital outpatient infusion center identified 45 patients with HSRs to carboplatin and 107 patients with HSRs to Taxol. To our knowledge, this is one of the largest studies of patients with carboplatin or Taxol HSRs in an outpatient infusion center. We report distinct differences between the clinical symptoms and timing of HSRs to carboplatin and Taxol, including increased severity of Taxol HSRs compared with carboplatin HSRs. Most patients with HSRs to carboplatin were not rechallenged, but a few patients with mild-to-moderate reactions were rechallenged successfully without having undergone desensitization. A substantial number of patients with Taxol HSRs were rechallenged, and most tolerated rechallenge in the outpatient infusion center without having undergone desensitization. Patients with Taxol HSRs with symptoms of dyspnea, cyanosis, and hypotension were less likely to be rechallenged. Despite the moderate-to-severe

nature of many HSRs, epinephrine was not used to treat any HSR in this case series. These novel preliminary findings have important clinical and research implications for the management of patients with HSRs to carboplatin or Taxol.

Carboplatin and Taxol HSRs differ in clinical presentation and timing, differences that suggest different pathophysiologies. Similar to our findings, prior studies reported that carboplatin HSRs are frequently associated with cutaneous symptoms, including palmar pruritus, general pruritus, erythema, or urticaria,[7-9] and develop only after multiple exposures to the drug. These symptoms suggest an IgE-mediated pathophysiology.[7,8] Skin testing has successfully been used to identify patients at risk for recurrent HSRs to carboplatin, which supports the notion that these HSRs are IgE mediated, although IgE-independent mechanisms also are possible.[7,8,10] This pattern differs from Taxol HSRs in which patients describe flushing, back pain, and chest or throat tightness without pruritus, usually during the first or second exposure to Taxol.[5] HSRs to Taxol are not fully understood but generally are not considered to be IgE mediated and may be a result of direct effects on immune cells.[11] Cremophor EL (polyoxyethylated castor oil) (BASF Corp., Florham Park, NJ), the excipient found in Taxol has been reported to induce histamine release and hypotension, and, therefore, may be responsible in part for the HSRs.[11-13] Along those lines, an albumin-bound form of Taxol, Abraxane (Celgene, Summit, NJ), that does not contain Cremophor EL has been associated with little to no incidence of HSRs.[11,14] Pulmonary oil microembolism reactions from castor oil, classically associated with dyspnea, chest tightness, and flushing, should be considered in the differential diagnosis of Taxol HSRs. However, the majority of patients with pulmonary oil microembolism reactions develop symptoms hours after the infusion instead of during the infusion, which argues against this in our observations.

Moderate-to-severe HSRs are associated with symptoms of dyspnea, dizziness, hypotension (systolic blood pressure <90 mm Hg in adults), collapse, or loss of consciousness, which are symptoms consistent with previously published criteria for anaphylaxis.[15] Regardless of the trigger of anaphylaxis, epinephrine is well recognized as the first-line treatment[16] and it is well documented in the literature that any delay in using epinephrine for anaphylaxis can be associated with worse outcomes.[16] Despite the moderate-to-severe nature of many HSRs, including patients who met criteria for anaphylaxis, epinephrine was not used to treat any carboplatin or Taxol HSRs. Cremophor-associated Taxol HSRs are thought to be non-IgE reactions rather than IgE-mediated anaphylactic reactions. However, when the clinical symptoms of a non-IgE HSR meet criteria for anaphylaxis, epinephrine should still be considered. Despite different clinical patterns, symptoms, and timing of HSRs, treatment of both carboplatin, and Taxol HSRs was very similar with the use of antihistamines, steroids, β-agonists, and intravenous fluids. Patients with carboplatin HSRs were more often treated with H2 blockers, likely due to more frequent symptoms of nausea and/or vomiting, whereas Taxol HSRs were more commonly treated with oxygen, likely due to more frequent symptoms of chest or throat tightness and dyspnea. Analysis of these findings suggests that we need to better understand the relationship between the pathophysiology of the HSR and optimal treatment of the HSR, especially the role of epinephrine for treatment of moderate-to-severe HSRs. In addition, better education of health care providers who manage anaphylaxis-like symptoms in the infusion center is needed.

Several prior publications, along with our own experience, support desensitization as an acceptable method of managing patients who develop HSRs to chemotherapeutic agents.[7,8,10,17-20] However, a smaller number of publications suggest that slowed infusions with additional premedications instead of desensitization can be used successfully in patients with mild-to-moderate HSRs.[12,21-23] Our review identified a large number of patients with typical Taxol HSRs along with a few mild-to-moderate carboplatin HSRs that were rechallenged successfully in the outpatient infusion center. Analysis of these observations indicates that, although desensitization is an acceptable approach, it might not always be absolutely necessary. For example, patients with Taxol HSRs most frequently presented with flushing or back pain. Our initial observations indicate that patients with flushing and or back pain alone would likely tolerate further infusions with antihistamine premedications, and the infusion slowed to 50% of the standard rate. However, we would still encourage desensitization for all patients with Taxol HSRs and with symptoms of dyspnea, cyanosis, or hypotension. Skin testing is useful in the management of carboplatin HSRs; therefore, we suggest evaluation by an allergist/immunologist familiar with these techniques for all patients with carboplatin HSRs.[8,10] The majority of factors to consider in determining if rechallenge is safe for any particular patient remains unclear, and we must exercise caution because fatalities have been reported with Taxol infusion[24] and during Taxol rechallenge despite the use of premedications.[25] In addition, although we understand the most common timing for HSRs to occur, we still have a limited ability in preventing HSRs from occurring in the first place. Further studies to understand factors predictive of HSRs and successful rechallenge after the initial HSR are needed.

The current study has several limitations including an inability to characterize the factors used by each individual oncologist in deciding when to proceed with rechallenge. Also, we did not have sufficient data to accurately define how the rechallenge was performed. Some patients were given antihistamines for premedication before rechallenge, whereas other patients underwent slowed infusions during the rechallenge. Although premedications and slowed infusion are contributing factors to the success of rechallenge,[23] these patients did not need desensitization. We are trying to better understand these factors to optimize management plans for patients after development of an HSR.

In summary, we describe a large group of patients with HSRs to carboplatin or Taxol and identified very different presentations for the clinical symptoms and timing of the initial HSR. Although most patients with carboplatin HSRs were not rechallenged, a few patients with mild-to-moderate carboplatin HSRs tolerated rechallenge successfully. In contrast, the majority of patients with Taxol HSRs were rechallenged successfully in the outpatient infusion center without having undergone desensitization. Although drug desensitization is acceptable, alternative approaches to managing patients with drug HSRs to carboplatin or Taxol should be considered, especially for patients with mild-to-moderate HSRs. Although these novel findings are provocative, we still need further studies to help identify factors that will guide us in optimizing management of patients after they develop an HSR to carboplatin or Taxol.

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