

Utility of Risk Stratification for Paclitaxel Hypersensitivity Reactions



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What is already known about this topic? Paclitaxel hypersensitivity reactions (HSRs) can be managed by reexposure with or without additional premedications and/or a slower infusion rate, or desensitization. Safe, effective risk stratification strategies are needed to identify patients who can tolerate reexposure without desensitization and patients who need desensitization.

What does this article add to our knowledge? The severity of the initial HSR can be used to safely risk stratify patients to reexposure with additional premedications and a slower infusion rate, or desensitization.

How does this study impact current management guidelines? A management strategy where the initial risk stratification is based on the severity of the initial HSR can be used to safely reintroduce patients to paclitaxel over consecutive dosing.

BACKGROUND: Hypersensitivity reactions (HSRs) are a common impediment to paclitaxel therapy. Management strategies to guide care after a paclitaxel-induced HSR are needed.

OBJECTIVE: The objective was to evaluate the utility and safety of risk stratification on the basis of severity of the initial HSR. **METHODS:** A risk stratification pathway was developed on the basis of a retrospective review of the management and outcome of 130 patients with paclitaxel-induced HSRs at Massachusetts General Hospital. This pathway was then studied prospectively in patients referred to Allergy/Immunology with paclitaxel-induced HSRs.

RESULTS: The study population ($n = 35$) had a mean age of 56.1 ± 12 years and most were women ($n = 33$ [94%]). All 5 patients (15%) with grade 1 initial HSRs were successfully reexposed to paclitaxel, 1 patient at the standard infusion rate and 4 patients at 50% of the standard infusion rate. Thirty patients (85%) with grade 2 to 4 initial HSRs underwent initial paclitaxel desensitization based on the risk stratification

pathway. No patients developed severe HSRs using the pathway. Eleven (31%) patients had HSRs that were mild to moderate in nature (grade 1, $n = 4$ [11%]; grade 2, $n = 6$ [17%]; grade 3, $n = 1$ [3%]) during their first desensitization. Sixteen (46%) of the 35 patients safely returned to the outpatient infusion setting for paclitaxel treatment at 50% of the standard infusion rate. Seven (20%) discontinued paclitaxel before the completion of the risk stratification pathway because of disease progression, completion of therapy, or death.

CONCLUSIONS: A management strategy using the initial HSR severity for risk stratification allowed patients to receive paclitaxel safely. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1266-73)

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Paclitaxel (Taxol, Bristol-Myers Squibb's, New York, NY) is an integral part of standard therapy for multiple malignancies including breast, ovarian, and lung cancer.¹⁻³ Despite paclitaxel's clinical effectiveness, hypersensitivity reactions (HSRs) are a common barrier to its use. In early trials, severe paclitaxel-induced HSRs (bronchospasm and anaphylaxis) were reported in up to 30% of infusions.⁴ Although the frequency of HSRs has been reduced with the use of premedications, which typically include dexamethasone, a histamine-1, and a histamine-2 receptor antagonist, HSRs still occur in 6% to 11% of patients receiving paclitaxel, of which 1% to 2% are reported as severe.⁵⁻⁷

Clinical manifestations of paclitaxel-induced HSRs include those frequently associated with histamine-mediated HSRs including flushing, pruritus, chest/throat tightness, bronchospasm, and hypotension as well as atypical symptoms such as back pain and hypertension.^{7,8} The exact mechanism of

Abbreviations used

CTCAE- Common Terminology Criteria for Adverse Events

HSR- Hypersensitivity reaction

paclitaxel-induced HSRs has not yet been elucidated. HSRs primarily occur during the first 2 cycles of therapy, suggesting that prior sensitization is not necessary and is therefore less likely to be IgE-mediated. This is supported by several studies in which most patients with paclitaxel-induced HSRs tolerate subsequent reexposure without desensitization, an observation that is not consistent with an IgE-mediated allergy.^{5,9}

Management strategies for paclitaxel-induced HSRs have included reexposure with additional premedications and/or a slower infusion rate, desensitization, or discontinuation of the drug.^{5,8,9} Guidelines for risk stratification are needed to safely determine the optimal management strategy for individual patients. For example, a proportion of patients with paclitaxel-induced HSRs tolerate readministration of the drug without additional HSRs.^{5,10} On the other hand, a small number of patients continue to experience HSRs when reexposed without desensitization. These HSRs can be severe and fatalities have been reported.¹¹ Drug desensitization is a safe and effective method to administer paclitaxel even for severe cases of anaphylaxis, but is resource intensive, incurs patient burden, and should be used for select patients who truly need desensitization.^{8,12}

A risk stratification pathway based on skin testing and the severity of the initial HSR that safely allowed 164 patients with taxane-induced HSR to receive subsequent treatment with taxanes was recently published.¹³ Because skin testing can be costly and time-consuming for cancer patients already taxed with high costs and frequent health care visits, a risk stratification pathway based on clinical grading of the initial HSR without skin testing would be of benefit to patients, provided the pathway is safe. We present our experience with a novel risk stratification strategy based on characterization of the initial outpatient HSR.

METHODS

A risk stratification pathway was developed after reviewing the outcomes in 2 cohorts of patients following paclitaxel-induced HSR (Figure 1). The first cohort (cohort A) was previously described by Banerji et al¹⁰ and consisted of 107 patients who experienced paclitaxel-induced HSRs in the Massachusetts General Hospital outpatient chemotherapy infusion center and were reexposed to paclitaxel in the outpatient infusion center between January 2006 and February 2011. All patients were reexposed to paclitaxel at the standard infusion rate along with the standard premedications for the chemotherapeutic agents involved as determined by the oncologist.¹⁰ The second cohort (cohort B) included 23 patients referred to Allergy/Immunology with a clinical history of paclitaxel-induced HSRs who all underwent desensitization between June 2011 and June 2013 according to our standard of care at the time. For each cohort of patients, the medical record was reviewed for the following information: age, sex, oncology diagnosis, medical history, characterization of initial HSR, and treatment of the initial HSR (including type of desensitization received if applicable). HSRs were graded according to a modified National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) as in previous publications (Table I).¹⁶⁻¹⁸

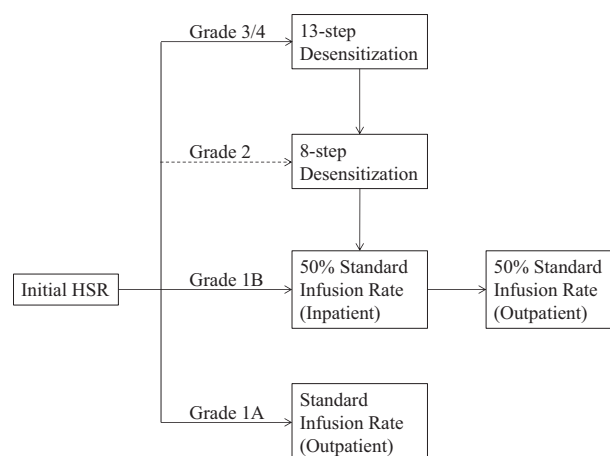


FIGURE 1. Risk stratification protocol for paclitaxel-induced HSRs based on the grade of the initial HSR. Grade 3 or 4 HSRs were considered high risk and patients were risk stratified to receive paclitaxel using 13-step desensitization. Patients with grade 2 HSRs were risk stratified to receive paclitaxel using 8-step desensitization. * Patients with grade 1B HSRs were reexposed to paclitaxel at half of the standard infusion rate. Patients with grade 1A HSRs were reexposed at the standard infusion rate. All patients reexposed to paclitaxel, regardless of the severity of the initial HSR or the method chosen for reexposure, received our institution's previously published standard premedication regimen of 10 mg of cetirizine and loratadine orally the night prior, the morning of, and immediately before the paclitaxel infusion along with the standard premedications for the chemotherapeutic agents involved as determined by the oncologist.^{14,15} *Outcomes of this study suggest that patients with grade 2 HSRs would possibly benefit from starting with a 13-step desensitization protocol. Larger studies are needed to determine the optimal management strategy for this subset of patients.

Development of risk stratification pathway

Patients' characteristics and grade of initial HSRs are described in Table II. Outcomes of cohort A are presented in Table III.

Based on the outcomes in these 2 cohorts of patients, grade 1A initial HSRs were considered low risk for a recurrent HSR (Tables III and IV) and were risk stratified to be reexposed to paclitaxel at the standard infusion rate.

Based on the observation that 1 of 16 (6%) patients with a grade 1B initial HSR reexposed to paclitaxel without desensitization had a moderate (grade 2) HSR (Table III), patients with grade 1B initial HSRs were risk stratified to be reexposed to paclitaxel at 50% of the standard infusion rate as an inpatient. If 50% of the standard infusion rate was tolerated as an inpatient, the patient was transferred to the outpatient infusion center to receive paclitaxel at the 50% slowed infusion rate.

Patients with grade 2 initial HSRs were risk stratified to receive paclitaxel using an 8-step desensitization protocol based on a higher risk of breakthrough reactions compared with patients with grade 1 initial HSRs and despite the fact that 50% (1 of 2) of the patients with grade 2 initial HSRs had a breakthrough HSR when paclitaxel was administered via 8-step desensitization (Table IV). If no reaction occurred with desensitization, patients were then advanced to 50% of the standard infusion rate first as an inpatient and then outpatient.

TABLE I. Grading of HSRs: Signs and symptoms used to grade the severity of the initial HSR to paclitaxel

Grade 1A	Grade 2	Grade 3	Grade 4	Grade 5
Cutaneous rash	Urticaria	Symptomatic bronchospasm	Anaphylaxis	Death
Flushing	Nausea/vomiting	Dyspnea	Hypotension	
Generalized pruritus	Throat tightness	Hypoxia		
Grade 1B	Asymptomatic bronchospasm	Wheezing		
Grade 1A signs/symptoms plus:	Chest tightness			
Back pain				
Hypertension				

TABLE II. Characteristics of patients reviewed to develop risk stratification pathway*

Characteristic	Cohort A (n = 107)	Cohort B (n = 23)
Age (y), mean $\pm$ SD	55.7 $\pm$ 12.2	58.5 $\pm$ 14.1
Sex: female (%)	69	100
BMI (kg/m ²), mean $\pm$ SD	27 $\pm$ 6.4	27 $\pm$ 5.7
Type of malignancy (%)		
Ovarian	18	65
Endometrial	0	30
Lung	32	0
Breast	23	0
Lymphoma	0	4
Other	27	27
Stage (%)		
1	8	13
2	14	9
3	30	52
4	48	26
Reaction severity (%)		
Grade 1A	15	13
Grade 1B	17	22
Grade 2	35	35
Grade 3	28	17
Grade 4	6	13

BMI, Body mass index; IQR, interquartile range; NA, not applicable.

*Demographic and clinical characteristics of patients who experienced HSRs to paclitaxel in the outpatient infusion center (outpatient, n = 107) and patients who underwent inpatient desensitization between June 2011 and June 2013 (inpatient, n = 23) are described.

Based on the observation that patients with grade 3 or 4 initial HSRs had higher rates of additional HSRs upon reexposure (reexposure with or without desensitization) compared with patients with grade 1 or 2 initial HSRs, patients with grade 3 or 4 initial HSRs were risk stratified to receive paclitaxel using a 13-step desensitization protocol.

Based on the observation that patients in cohort B who tolerated the first 2 inpatient desensitizations did not experience additional HSRs, patients who tolerated the first two 13-step desensitizations were felt to be at low risk for further HSRs and these patients were advanced under close observation through the risk stratification pathway until 50% of the standard infusion rate was achieved. If 50% of the standard infusion rate was tolerated in the inpatient setting, the patient was transferred to the outpatient infusion center.

Following our standard of care, paclitaxel desensitization was performed using previously published 8-step and 13-step protocols.^{19,20} Details regarding the desensitization protocols used are

presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org. If a patient experienced symptoms concerning for an HSR during the desensitization procedure, the infusion was stopped. The patient was treated with antihistamines, steroids, and/or epinephrine on the basis of severity of the reaction. After symptom resolution, the desensitization was resumed at the last tolerated step and advanced per protocol until the full dose was received.^{15,21}

All patients reexposed to paclitaxel, regardless of the severity of the initial HSR or the method chosen for reexposure, received our institution's previously published standard premedication regimen of 10 mg of cetirizine and loratadine orally the night prior, the morning of, and immediately before the paclitaxel infusion along with the standard premedications for the chemotherapeutic agents involved as determined by the oncologist.^{14,15}

If there were symptoms concerning for an HSR during reexposure with or without desensitization, patients received further paclitaxel infusions using a 13-step desensitization protocol regardless of the grade of the initial HSR.²¹ If there were symptoms concerning for an HSR during the 13-step desensitization, modifications (additional steps) were made to the desensitization protocol.¹⁵

All patients subsequently referred to the Allergy and Immunology at our institution for paclitaxel-induced HSRs between July 2013 and March 2016 underwent paclitaxel re-treatment following this risk stratification pathway. Data on age, sex, oncology diagnosis, medical history, characterization of initial HSR, and treatment outcome were recorded. Institutional review board approval was obtained for this study.

RESULTS

Outcome of risk stratification pathway

From July 2013 to March 2016, 35 patients were referred to Allergy/Immunology at Massachusetts General Hospital for a paclitaxel-induced HSR. The average age was 56 years (range, 29-78 years) and most patients were women (94%) and white (80%) with gynecologic malignancies (n = 25 [72%]). Most patients had an initial HSR of grade 3 (n = 13 [37%]) or grade 4 (n = 13 [37%]) (Table V).

Patients (n = 35) were risk stratified according to the pathway outlined in Figure 1. Initial risk stratification and treatment outcomes are presented in Table VI.

All 5 patients with grade 1 initial HSRs were successfully reexposed to paclitaxel without the use of desensitization. Four patients (1 with delayed grade 1A and 3 with grade 1B initial HSRs) tolerated reexposure with paclitaxel at 50% of the standard infusion rate. These 4 patients were subsequently able to transfer to the outpatient setting to receive paclitaxel and did not develop additional HSRs.

Five patients with grade 2 initial HSRs had varied outcomes. Three patients received an 8-step desensitization protocol

TABLE III. Outcomes of paclitaxel reexposure in cohort A*

Initial HSR grade	No. of patients	No. of patients reexposed	No. of patients with recurrent HSRs	Recurrent HSR grade
1A	16	13 (81%)	1 (7.7%)	One grade 1A
1B	18	16 (89%)	1 (6.3%)	One grade 2
2	37	31 (84%)	2 (6.5%)	One grade 1A, 1 grade 2
3	30	18 (60%)	2 (11.1%)	Two grade 3
4	6	2 (33%)	1 (50%)	One grade 4
Total patients	107	80 (75%)	7 (8.8%)	

*The frequency and severity of the initial paclitaxel-induced HSRs, the number of patients reexposed to paclitaxel, and the frequency and severity of recurrent HSRs among patients reexposed to paclitaxel are described. All patients were reexposed to paclitaxel at the standard infusion rate along with the standard premedications for the chemotherapeutic agents involved as determined by the oncologist.

TABLE IV. Outcomes of paclitaxel desensitization in cohort B*

Initial HSR grade	n	8-Step	HSRs (grade 2 or higher)	13-Step	HSRs (grade 2 or higher)
1A	3	1	0	2	0
1B	1	0	0	1	0
2	9	2	1 (50%)	7	0
3	4	2	2 (100%)	2	0
4	6	0	0	6	2 (33%)

*The frequency (n) and severity (initial HSR grade) of the initial paclitaxel-induced HSRs, the number of patients reintroduced to paclitaxel using an 8-step desensitization protocol (8-step) and a 13-step desensitization protocol (13-step), and the number of recurrent HSRs grade 2 or higher during paclitaxel reintroduction are described.

according to the pathway. One patient experienced an additional grade 2 HSR, required progressively cautious desensitizations, and completed therapy using a modified, more cautious 14-step desensitization protocol (13-step modified with an additional 15 mL/h rate step for solution 2). Another patient tolerated paclitaxel administered using 8-step desensitization and at a 50% standard infusion rate as an inpatient. However, this patient subsequently developed a grade 2 HSR during the first outpatient infusion of paclitaxel at 50% of the standard infusion rate, and completed paclitaxel treatment using 8-step desensitization. The third patient who tolerated 8-step desensitization was not advanced along the risk stratification protocol because of patient preference (patient expressed desire to receive paclitaxel using the more cautious desensitization protocol). Given the development of an additional grade 2 HSR in 2 of the first 3 patients who were reintroduced to paclitaxel using 8-step desensitization, caution was exercised for the next 2 patients. They were reintroduced to paclitaxel using a 13-step desensitization protocol. One patient advanced without additional HSRs to 50% of the standard infusion rate and returned to the outpatient setting. The other patient received paclitaxel with a 13-step desensitization protocol, experienced an additional grade 1A HSR, and completed therapy using a modified desensitization protocol (an additional 7.5 mL/h rate step for solution 1). Taken together, these data indicate that patients with grade 2 initial HSRs would possibly benefit from starting with a 13-step desensitization protocol.

Of the 25 patients with grade 3 or 4 initial HSRs, 18 of 25 (72%)—nine grade 3 and 9 grade 4—tolerated the first 2 infusions using a 13-step desensitization protocol. Ten (40%)—5 grade 3 and 5 grade 4—were advanced stepwise to a 50% standard infusion rate, and 9 (36%), tenth patient deceased, were transferred to the outpatient setting where paclitaxel was infused at 50% of the standard rate. A total of 48

TABLE V. Patients managed prospectively using the risk stratification pathway*

Characteristic	n	%
Total no. of patients	35	
Female	33	94
White	28	80
Other drug allergies	22	63
Atopic disease	5	14
Age (y), mean $\pm$ SD	56.1 $\pm$ 12	
Type of malignancy		
Gynecologic	25	71.7
Breast cancer	6	8.5
Lung cancer	3	17
Gastric	1	2.8
Stage		
1-2	8	22
3-4	26	75
3	15	42
4	12	34
Unstaged	1	3
Reaction severity		
Grade 1A	1	3
Grade 1A (delayed)	1	3
Grade 1B	3	9
Grade 2	4	11
Grade 3	13	37
Grade 4	13	37

*Baseline demographic and clinical characteristics of patients who were prospectively reintroduced to paclitaxel using the risk stratification pathway are described.

outpatient infusions were safely administered without any further HSRs. The remaining 8 (32%) patients tolerated paclitaxel using a 13-step desensitization protocol, with 2 patients advancing to an 8-step protocol. Five patients discontinued paclitaxel before completion of the risk stratification protocol because of disease progression (n = 2; 1 grade 3 and 1 grade 4 initial HSR), completion of therapy (n = 2, both with grade 3 initial HSRs), or death (n = 1, grade 3 initial HSR). Three patients, all with grade 4 initial HSRs, were not advanced along the risk stratification protocol because of patient preference (patients expressed desire to receive paclitaxel using the slower, more cautious desensitization protocol). Taken together, these data indicate that 13-step desensitization followed by advancement through the pathway is safe for patients with grade 3 or 4 initial HSRs.

TABLE VI. Clinical characteristics and outcomes of patients managed prospectively using the risk stratification pathway

Age (y)	Cancer type	Cancer stage	Initial HSR grade	Initial protocol	Reaction/step at which reaction occurred*	Outcome
51	B	IIA	1A	Standard infusion rate	None	Successfully rechallenged
57	O	IV	Delayed 1A	50% of standard†	None	Able to advance to 50% as outpatient
45	O	IC	1B	50% of standard	None	Able to advance to 50% as outpatient
53	E	IIIB	1B	50% of standard	None	Able to advance to 50% as outpatient
61	O	IC	1B	50% of standard	None	Able to advance to 50% as outpatient
54	O	IIIB	2	8-Step	None	Tolerated and continued 8-step desensitization (patient preferred over progressing to 50% as outpatient)
52	O	IIIA	2	8-Step	Yes (grade 2) 50% outpatient	Advanced to 50% as outpatient but then developed grade 2 reaction. Subsequently tolerated 8-step desensitizations
44	C	IB	2	8-Step	Yes (grade 2) 8-Step solution 2 Step 1 10 mL/h	Tolerated and continued 14-step desensitization protocol as inpatient (13-step modified with additional 15 mL/h step for solution 2)
39	B	IIB	2	13-Step	None	Able to advance to 50% as outpatient
35	B	IIB	2	13-Step	Yes (grade 1A) 13-Step Solution 1 Step 3 10 mL/h	Tolerated and continued 14-step desensitization protocol as inpatient (13-step modified with additional 7.5 mL/h step for solution 1)
73	E	IB	3	13-Step	None	Able to advance to 50% as outpatient
50	O	IIIC	3	13-Step	None	Able to advance to 50% as outpatient
59	O	IIIC	3	13-Step	None	Able to advance to 50% as outpatient
43	O	IV	3	13-Step	None	Able to advance to 50% as outpatient
51	C	IIB	3	13-Step	None	Able to advance to 50% as outpatient
55	O	IV	3	13-Step	None	Tolerated first 2 desensitizations; deceased
30	B	IIB	3	13-Step	None	Tolerated first 2 desensitizations; finished treatment
76	L	IIIA	3	13-Step	None	Tolerated first 2 desensitizations; finished treatment
58	G	IV	3	13-Step	None	Tolerated first 2 desensitizations; progressed
63	O	IIIC	3	13-Step	Yes (grade 3) 13-step NR	Subsequently tolerated 13-step desensitization as inpatient
29	B	II	3	13-Step	Yes (grade 2) 13-Step NR	Subsequently tolerated 13-step desensitization as inpatient
59	O	IIIA	3	13-Step	Yes (grade 2) 13-Step Solution 2 Step 3 20 mL/h	Continued 15-step desensitization protocol as inpatient (13-step modified with additional 15 mL/h step for solution 2 and additional 70 mL/h step for solution 3) for 3 cycles. On the third cycle, patient experienced grade 1A HSR. Tolerated and completed treatment with 17-step desensitization protocol
54	B	III	3	13-Step	Yes (grade 2) 13-Step Solution 3 Step 3 20 mL/h	Treatment discontinued because of neutropenia and progressive neuropathy
78	E	II	4	13-Step	None	Able to advance to 50% as outpatient
71	O	IIIC	4	13-Step	None	Able to advance to 50% as outpatient
54	L	IIIA	4	13-Step	None	Able to advance to 50% as outpatient
72	E	IVA	4	13-step	None	Able to advance to 50% as outpatient
57	L	IV	4	13-Step	None	Able to advance to 50% as outpatient; deceased
64	O	IIIC	4	13-Step	None	Tolerated 8-step desensitization; progressed
64	O	IIIC	4	13-Step	None	Tolerated and continued 13-step desensitization (patient preferred over progressing to 8-step desensitization)

(continued)

TABLE VI. (Continued)

Age (y)	Cancer type	Cancer stage	Initial HSR grade	Initial protocol	Reaction/step at which reaction occurred*	Outcome
63	E	IVB	4	13-Step	None	Tolerated and continued 13-step desensitization (patient preferred over progressing to 8-step desensitization)
52	O	U	4	13-Step	None†	Tolerated and continued 8-step desensitization (patient preferred over progressing to 50% as outpatient)
71	O	IC	4	13-Step	Yes (grade 1A) 13-Step Solution 2 Step 4 40 mL/h	Tolerated and continued 15-step desensitization protocol as inpatient (13-step modified with additional 7.5 mL/h for solution 2 and additional 5 mL/h step for solution 3)
73	O	IIIC	4	13-Step	Yes (grade 1A) 13-Step Solution 3 Step 2 20 mL/h	Tolerated and continued modified desensitization protocol as inpatient (details regarding exact modification NR)
52	O	IV	4	17-Step	Yes (grade 2) 17-Step Solution 3 Step 2 10 mL/h	Tolerated 19-step modified desensitization protocol as inpatient (17-step modified with additional 5 mL/h and 7.5 mL/h steps for solution 3); deceased

B, Breast; C, cervical; E, endometrial; G, gastric; L, non–small-cell lung carcinoma; NR, not recorded in medical record for review; O, ovarian; U, unstaged.

*These reactions all occurred during the initial reexposure to paclitaxel. The method of reexposure is described in the “Initial Protocol” column.

†The risk stratification protocol/pathway does not delineate what to do for a delayed grade 1A reaction. Given the atypical nature of the delayed reaction, caution was exercised and paclitaxel was readministered at 50% the standard rate.

‡Delayed rash after initial 12-step desensitization, unclear if related to paclitaxel administration, that did not recur after subsequent paclitaxel administrations.

Of the 25 patients with grade 3 or 4 initial HSRs, 8 patients were not able to advance through the pathway. Four patients with grade 3 initial HSRs experienced additional symptoms during the first 13-step desensitization (3 grade 2 and 1 grade 3). Three continued to receive paclitaxel as an inpatient using a 13-step or more cautious protocol (Table VI). Paclitaxel was discontinued in 1 patient because of neutropenia and progressive neuropathy.

Three patients with grade 4 initial HSRs experienced additional symptoms during the first desensitization. Two of these 3 patients initially underwent 13-step desensitization and 1 patient initially underwent 17-step desensitization (see Table E1, C) because this patient required epinephrine to treat the grade 4 initial HSR. All 3 patients were able to tolerate a more cautious desensitization protocol with increased number of steps compared with the initial desensitization.

DISCUSSION

Paclitaxel-induced HSRs pose an impediment to optimal first-line treatment of multiple malignancies.^{1-3,5-7} A risk stratification strategy was recently published, showing that it is possible for patients to receive optimal paclitaxel-containing regimens despite a history of paclitaxel-induced HSRs.¹³ We present additional experience managing paclitaxel-induced HSRs along with a novel symptom-guided management strategy where risk stratification is based on the characterization of the initial HSR. This prospective safety assessment of a symptom-guided risk stratification pathway is imperative as it allows health care facilities without access to

skin testing or significant experience with desensitization a pathway to safely manage their patients.

Prospectively, we were able to show that 35 patients could indeed be safely reexposed to paclitaxel using this novel risk stratification pathway. Half of the patients, including 10 patients with grade 3 or 4 initial HSRs, were able to return to the outpatient setting for paclitaxel treatment at 50% of the standard infusion rate. Among patients with grade 3 or 4 initial HSRs, 48 potential inpatient admissions for desensitization were avoided. Although 11 of 35 (31%) patients had additional HSRs, all patients safely completed scheduled paclitaxel with the use of desensitization. These findings support the symptom-guided risk stratification pathway based on the severity of the initial HSR to identify patients who are likely to develop additional HSRs and safely administer paclitaxel to these patients.

For patients with grade 3 or 4 initial HSRs who are at risk for developing additional HSRs upon reexposure, desensitization has been shown to be an effective management strategy.^{5,8,13,22} It has been hypothesized that patients who tolerated the first 2 desensitizations after a moderate or severe HSR could safely have paclitaxel infusions advanced to return to the outpatient setting.⁵ Indeed, of the 18 patients in our study with grade 3 to 4 initial HSRs who tolerated the first 2 infusions, 10 were able to advance to 50% of the standard infusion rate and return to the outpatient setting. Although the other 8 patients did not advance along the risk stratification pathway for various reasons (disease progression, completion of therapy, patient preference, death), none of them had additional HSRs, suggesting that they might also have been able to return to the outpatient setting. These findings suggest that this risk stratification pathway is a safe way to allow

patients who initially experienced grade 3 or 4 HSRs to return to outpatient dosing of paclitaxel.

Of note, 1 patient who had grade 2 initial HSR in the outpatient setting and 2 patients who had grade 4 initial HSRs in the outpatient setting preferred to continue desensitization because of anxiety surrounding recall of the initial reaction despite the inconvenience of inpatient admissions and prolonged wait times associated with scheduled inpatient admissions. This highlights the importance of careful selection of those patients who can be reexposed in the outpatient setting. If reexposed in the standard outpatient setting, HSR of this severity can be traumatic for the patient and complicated to manage given the limitation in staffing, resources, and experience treating anaphylaxis, leading to potentially more adverse outcomes for patients including death.⁷ Retrospective and prospective assessment of paclitaxel reexposure after HSR showed that patients with grade 1A initial HSR could safely be reexposed at a standard infusion rate with additional premedications in the outpatient setting.

At our institution, desensitization is an inpatient procedure to ensure adequate staff and monitoring of patients. Therefore, our risk stratification pathway included a step to transition from 50% standard infusion rate inpatient to 50% standard infusion rate outpatient. Institutions that have the capability of safely performing desensitization as an outpatient procedure would be able to optimize our risk stratification pathway further.

Furthermore, a paclitaxel infusion at 50% of the standard rate can take 6 hours, a duration comparable to the time it takes to perform the 13-step desensitization. The importance of progressing to a 50% standard rate lies in ease of administration, decreased utilization of resources needed only for desensitization (pharmacist experience and resources to mix dilute solutions, nurse monitoring every 15 minutes), and the inpatient bed requirement at our institution. The first 2 benefits stand true even for institutions that are able to perform desensitization as an outpatient procedure.

A limitation of this study is that the prospective assessment consisted of only 35 patients. Although the outcomes of the 5 grade 2 HSRs included in this study suggest that patients with grade 2 initial HSRs should possibly be reintroduced to paclitaxel using a 13-step desensitization protocol, larger studies are needed to determine the optimal management strategy for this subset of patients. Furthermore, because a sample size calculation was not performed before starting the prospective arm of the study, it is possible that larger studies are needed to ensure sufficient generalizability to the general population.

Another limitation is that we focused on safety in creating our first paclitaxel risk stratification pathway. Although we decided not to advance further than a 50% standard rate to minimize the risk of recurrent HSRs, other studies have shown that standard reinfusions can be safely achieved and that limiting the rate to 50% may not be necessary.^{5,13,23} Other studies, including a study from our institution, also suggest that the risk of recurrent reaction decreases with repeat exposures.^{5,10,13} However, we decided not to advance patients further along the risk stratification pathway if they had breakthrough HSRs during desensitization to minimize the risk of recurrent HSRs. This study was aimed at showing that risk stratification based on the clinical grade of the initial HSR is a safe strategy to use for the management of paclitaxel HSR, and future studies are needed to refine the pathway.

In conclusion, paclitaxel-induced HSRs frequently occur during the first 2 exposures to paclitaxel and can be severe in nature. Regardless of the severity of the initial HSR, patients can continue to receive paclitaxel safely. Our findings show that a risk stratification pathway based on the grade of the initial HSR can be used to safely identify and manage patients with paclitaxel-induced HSRs while reducing the need for desensitization. Until objective testing is developed that can reliably risk stratify individuals with a history of paclitaxel-induced HSRs, a conservative approach based on clinical criteria is prudent and safe in a real-world setting.

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TABLE E1. Desensitization protocols for paclitaxel

A. 13-Step protocol							
Solution		Concentration (mg/mL)				Amount infused (mL)	
1		0.00348				9.38	
2		0.0348				18.75	
3		0.345				250	
Step	Solution	Infusion duration (min)	Cumulative time (min)	Infusion rate (mL/h)	Set volume to infuse (mL)	Dose per step (mg)	Cumulative drug dosage (mg)
1	1	15	15	2.5	0.63	0.0022	0.0022
2	1	15	30	5	1.25	0.0044	0.0066
3	1	15	45	10	2.5	0.0087	0.0153
4	1	15	60	20	5	0.0174	0.0327
5	2	15	75	5	1.25	0.0435	0.0762
6	2	15	90	10	2.5	0.087	0.1632
7	2	15	105	20	5	0.174	0.3372
8	2	15	120	40	10	0.348	0.6852
9	3	15	135	10	2.5	0.8631	1.5483
10	3	15	150	20	5	1.7263	3.2746
11	3	15	165	40	10	3.4526	6.7272
12	3	15	180	60	15	5.1789	11.9061
13	3	163	343	80	217.5	75.0939	87

B. 8-Step protocol							
Solution		Concentration (mg/mL)				Amount infused (mL)	
1		0.0348				18.75	
2		0.345				250	
Step	Solution	Infusion duration (min)	Cumulative time (min)	Infusion rate (mL/h)	Set volume to infuse (mL)	Dose per step (mg)	Cumulative drug dosage (mg)
1	1	15	15	5	1.25	0.0435	0.0435
2	1	15	30	10	2.5	0.087	0.1305
3	1	15	45	20	5	0.174	0.3045
4	1	15	60	40	10	0.348	0.6525
5	2	15	75	10	2.5	0.8635	1.516
6	2	15	90	20	5	1.727	3.2429
7	2	15	105	40	10	3.4539	6.6968
8	2	15	120	80	232.5	80.3032	87

C. 17-Step protocol							
Solution		Concentration (mg/mL)				Amount infused (mL)	
1		0.000348				4.7	
2		0.00348				9.375	
3		0.0348				18.75	
4		0.345				250	
Step	Solution	Infusion duration (min)	Cumulative time (min)	Infusion rate (mL/h)	Set volume to infuse (mL)	Dose per step (mg)	Cumulative drug dosage (mg)
1	1	15	15	1.3	0.325	0.00011	0.0001131
2	1	15	30	2.5	0.625	0.00022	0.0003306
3	1	15	45	5	1.25	0.00044	0.0007656
4	1	15	60	10	2.5	0.00087	0.0016356
5	2	15	75	2.5	0.625	0.00218	0.0038106
6	2	15	90	5	1.25	0.00435	0.0081606

(continued)

TABLE E1. (Continued)

Step	Solution	Infusion duration (min)	Cumulative time (min)	Infusion rate (mL/h)	Set volume to infuse (mL)	Dose per step (mg)	Cumulative drug dosage (mg)
7	2	15	105	10	2.5	0.0087	0.0168606
8	2	15	120	20	5	0.0174	0.0342606
9	3	15	135	5	1.25	0.0435	0.0777606
10	3	15	150	10	2.5	0.087	0.1647606
11	3	15	165	20	5	0.174	0.3387606
12	3	15	180	40	10	0.348	0.6867606
13	3	15	195	10	2.5	0.86313	1.54989299
14	4	15	210	20	5	1.72626	3.27615778
15	4	15	225	40	10	3.45253	6.72868736
16	4	15	240	60	15	5.17879	11.9074817
17	4	163.125	403.125	80	217.5	75.0925	87

Target dose is set at 87 mg.

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