

Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions

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Background: The optimal approach to patients with hypersensitivity reactions (HSRs) to taxanes has not been established.

Objective: We sought to assess the safety and efficacy of risk stratification based on the severity of the initial HSR and skin testing for guiding taxane reintroduction in patients with an HSR to these agents.

Methods: Data on 164 patients treated for a taxane-related HSR from April 2011 to August 2014 at the Dana-Farber Cancer Institute and Brigham and Women's Hospital were collected retrospectively. Patients were re-exposed to taxanes either through desensitization, challenge, or regular infusion based on the severity of the initial HSR and skin test response. Depending on the initial risk stratification and tolerance to re-exposure, patients were then treated with shorter desensitization protocols, challenge, or both with the aim of resuming regular infusions, except in patients with a severe immediate initial HSR.

Results: Of 138 patients desensitized, 29 (21%) had an immediate and 20 (14%) had a delayed HSR with the procedure. Of 49 patients challenged, 2 (4%) had a mild immediate and 1 (2%) had a delayed HSR with the procedure. No patients had a severe immediate HSR with desensitization or challenge. Thirty-six (22%) patients eventually resumed regular infusions. These patients were more likely to have negative skin test responses and to have experienced a delayed or mild immediate initial HSR.

Conclusions: Risk stratification based on the severity of the initial HSR and skin testing to guide taxane reintroduction is safe and allows a significant number of patients to resume regular infusions. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: Taxane, paclitaxel, docetaxel, hypersensitivity, skin test, allergy, risk stratification, desensitization, challenge

Antineoplastics are the third leading cause of fatal drug-induced anaphylaxis in the United States,¹ and taxanes are among the most frequently implicated antineoplastics in these reactions, with more than 300 fatalities reported to the US Food and Drug Administration since their commercialization.²⁻⁴ Although an immunologic mechanism has not been demonstrated, the term immediate hypersensitivity reaction (HSR) is used to designate adverse reactions with features suggestive of mast cell/basophil degranulation that occur during taxane infusions.⁵⁻⁷

Taxanes are an integral part of the chemotherapeutic regimen used in gynecologic malignancies and are frequently administered in patients with various cancers, including breast, prostate, and lung cancers.^{8,9} In early clinical trials paclitaxel and docetaxel caused a high rate of immediate HSRs, usually during first or second exposure.^{5,10} Premedication with antihistamines and corticosteroids for paclitaxel and with corticosteroids alone for docetaxel successfully reduced the risk of immediate HSRs to 10% or less.^{5,11-15} However, severe immediate HSRs still occur in around 1% of patients.^{11,12,16}

Immediate HSRs to taxanes are generally attributed to the surfactants used in their formulation (Cremophor EL for paclitaxel and polysorbate 80 for docetaxel).^{2,9} These molecules can cause complement activation, resulting in anaphylatoxin formation.¹⁷ Nanoparticle albumin-bound paclitaxel (nab-paclitaxel; Abraxane, Celgene, Summit, NJ) is a newer paclitaxel formulation that does not contain Cremophor EL.¹⁸ It is administered without premedication and causes mild immediate HSRs in around 4% of patients.¹⁹ Severe and even fatal immediate HSRs have also been reported with nab-paclitaxel, suggesting that some patients react to the taxane moiety rather than to the surfactants.¹⁸ A case of an IgE-mediated HSR to paclitaxel demonstrated by a positive immunoblot assay and skin test result was recently published.²⁰ Since then, other groups have reported patients with HSRs to either paclitaxel or docetaxel and a positive skin test (ST+) response, suggesting that an IgE-mediated mechanism might be implicated in some cases.^{21,22}

After an immediate taxane-induced HSR, most patients appear to tolerate a regular or slowed reinfusion with or without added premedication.^{2,5,12,23} However, severe immediate HSRs can occur with those reinfusions, and 2 fatalities have been reported in such circumstances.^{2,5,24,25} Rapid drug desensitization is a safe and effective method of reintroducing taxanes in patients with past immediate HSRs.^{4,21,25} Yet this method is time-consuming, necessitates a 1:1 nursing ratio, and might not be necessary to prevent HSRs in most patients.²

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Abbreviations used

BWH: Brigham and Women's Hospital
 DFCI: Dana-Farber Cancer Institute
 HSR: Hypersensitivity reaction
 nab-paclitaxel: Nanoparticle albumin-bound paclitaxel
 OR: Odds ratio
 ST+: Positive skin test
 ST-: Negative skin test

In an effort to maximize safety while allowing patients who do not require desensitization to resume regular infusions, a risk stratification strategy to guide taxane reintroduction based on the severity of the initial HSR and skin testing was developed at our institution (Fig 1). The safety and outcomes of this approach are presented.

METHODS**Study design**

This study is a collaboration between the Dana-Farber Cancer Institute (DFCI) and Brigham and Women's Hospital (BWH) Drug Hypersensitivity and

Desensitization Center and was approved by the BWH institutional review board (protocol 2013P001672). All patients with a taxane-induced HSR treated at the BWH Drug Hypersensitivity and Desensitization Center between April 2011 and August 2014 were included. Files of patients treated between January 2008 and April 2011 were also reviewed to assess whether any had increases in mast cell/basophil mediator levels after a severe immediate HSR. Data were retrospectively collected through review of patients' electronic medical records.

Patient evaluation

Two types of taxane-induced HSRs were observed: immediate and delayed. Immediate HSRs were defined as an adverse reaction with onset during the infusion or 1 hour or less after and with features suggestive of mast cell/basophil degranulation. Delayed HSRs were defined as an adverse reaction with onset of greater than 1 hour after the infusion and with features suggestive of either a cell-mediated HSR (eg, a maculopapular rash) or a mast cell/basophil-mediated HSR (eg, flushing with onset ≤ 48 hours after the infusion). The severity of immediate HSRs was graded, as previously described (Table I).^{26,27} Patients with severe cutaneous adverse drug reactions (eg, desquamative/blistering skin reactions) were advised to avoid all taxanes.

Skin testing

Paclitaxel was diluted to a concentration of 1 mg/mL and docetaxel to a concentration of 0.4 mg/mL with normal saline for skin prick tests.

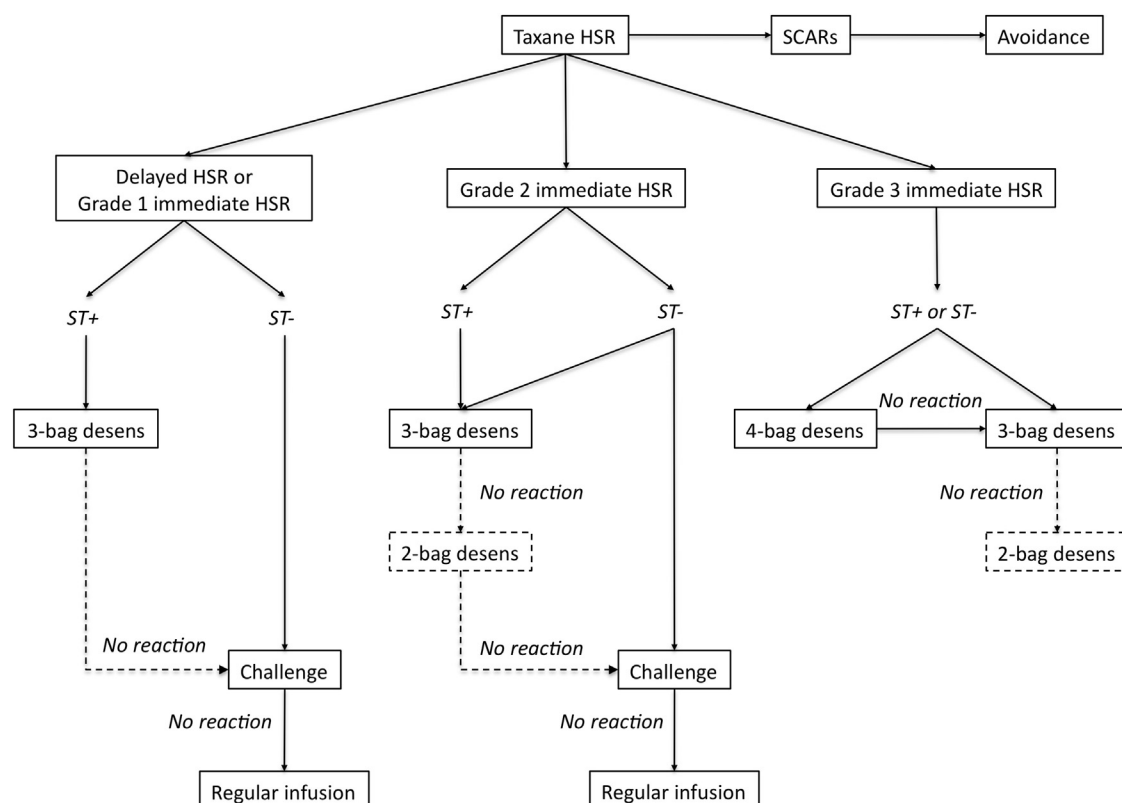


FIG 1. Approach to taxane reintroduction in patients with HSRs. In patients with an HSR with desensitization or challenge, premedication is generally adjusted for the next procedure, which is administered by using either the same or a longer protocol. Patients in whom the HSR does not recur are then treated with a shorter desensitization protocol, challenge, or regular infusion, according to the algorithm. Each procedure is usually repeated several times before proceeding with a shorter desensitization protocol, challenge, or regular infusion to ensure the patient's tolerance. Dotted lines represent procedures that were incorporated in the algorithm after September 2013. See Table I for a description of the grading of immediate HSRs and Tables E1 and E2 for a description of the desensitization and challenge protocols. SCARs, Severe cutaneous adverse drug reactions include Stevens-Johnson syndrome and desquamative/blistering skin reactions.

TABLE I. Severity grading system of immediate HSRs

Grade	Severity	Description
1	Mild	Symptoms are limited to the skin (eg, flushing) or involve a single organ/system and are mild (eg, mild back pain).
2	Moderate	Symptoms involve at least 2 organs/systems (eg, flushing and dyspnea), but there is no significant decrease in blood pressure or oxygen saturation.
3	Severe	Symptoms typically involve at least 2 organs/systems, and there is a significant decrease in blood pressure (systolic ≤ 90 mm Hg and/or syncope) and/or oxygen saturation ($\leq 92\%$).

Adapted from Brown.²⁶

Intradermal tests were performed at 0.001 and 0.01 mg/mL for paclitaxel and 0.04 and 0.4 mg/mL for docetaxel. These concentrations were shown to be nonirritating in 10 negative control subjects and by 2 other independent groups.²⁰⁻²³ Paclitaxel skin testing was progressively introduced into our practice, followed by docetaxel skin testing, explaining why half of the patients who reacted to docetaxel underwent skin tests to paclitaxel. Skin tests were generally performed at least 2 weeks after the HSR to minimize the possibility of a false-negative result, as previously described,²⁷ and positivity was defined as a wheal measuring at least 3 mm larger than that elicited by the negative control. The size of the wheal-and-flare reaction of any ST+ response and the concentration at which it was positive were documented in the patient's medical record.

Management of patients with HSRs to taxanes

Risk stratification based on the severity of the initial HSR and skin test result guided taxane reintroduction (Fig 1). Patients with an ST+ response were re-exposed through desensitization, regardless of the severity of the initial HSR. After September 2013, given the safety profile of taxane desensitization in our cohort,²⁸ patients with ST+ responses who tolerated desensitization were progressively treated with shorter desensitization protocols, challenge, or both with the aim of resuming regular infusions except in those with an initial severe (grade 3) immediate HSR (Fig 1, dotted lines). Patients who did not undergo skin tests or those with an equivocal result were managed as if they had ST+ responses.

Patients with a negative skin test (ST-) response and a delayed or mild (grade 1) immediate HSR were re-exposed to taxanes through challenge, whereas those with a grade 3 immediate HSR were re-exposed through desensitization. The decision to perform desensitization or challenge in patients with moderate (grade 2) immediate HSRs and ST- responses was based on each patient's comorbidities (eg, uncontrolled asthma and/or significant impairment in FEV₁, unstable or symptomatic coronary heart disease, and poor Eastern Cooperative Oncology Group performance status) and comfort with the procedure (eg, patients reluctant to be retreated with taxanes despite adequate reassurance were treated with desensitization).

HSRs during desensitization or challenge were managed as previously described.²⁷ In patients with reactions, the next procedure was performed with the same or a longer protocol and often with added premedication. If the HSR did not recur, the patient could then be treated with a shorter desensitization protocol, challenge, or regular infusion, according to the algorithm. To ensure the patient's tolerance, each procedure could be repeated several times before proceeding along the algorithm. Patients who refused to undergo a challenge or to resume regular infusions were maintained on desensitization or challenge procedures until their treatment ended.

For details on premedication, desensitization, and challenge procedures, see the [Methods section](#) and [Tables E1](#) and [E2](#) in this article's Online Repository at www.jacionline.org.

TABLE II. Characteristics of patients at the time of the initial HSR

Characteristics	HSR to paclitaxel (n = 142*)	HSR to docetaxel (n = 22†)
Age (yr)		
Median	59	59
Range	25-81	33-73
Sex, no. (%)		
Female	141 (99)	10 (45)
Male	1 (1)	12 (55)
Race or ethnic group, no. (%)		
White	127 (89)	21 (95)
African American	2 (1)	0
Asian	8 (6)	1 (5)
Other/unknown	5 (4)	0
Cancer site, no. (%)		
Ovarian, fallopian, peritoneal	93 (65)	1 (5)
Endometrial	32‡ (23)	1 (5)
Breast	11 (8)	5 (23)
Prostate	0	10 (45)
Other	7‡ (5)	5 (23)
Cancer stage, no. (%)		
I or II	27 (19)	5 (23)
III	68 (48)	2 (9)
IV	47 (33)	15 (68)
Atopy,§ no. (%)		
Yes	50 (35)	6 (27)
No	92 (65)	16 (73)
History of drug-induced HSR, no. (%)		
Yes	49 (35)	2 (9)
No	93 (65)	20 (91)
Prior HSR to nontaxane chemotherapy, no. (%)		
Platinum	4¶ (3)	0
Other	3¶ (2)	2 (9)
None	136 (96)	20 (91)

*Three of these patients also reacted to docetaxel after reacting to paclitaxel.

†One of these patients also reacted to cabazitaxel after reacting to docetaxel.

‡One patient was concomitantly given a diagnosis of endometrial and non-small cell lung cancer.

§Defined as the presence of any of the following: history of allergic asthma and/or rhinoconjunctivitis, food allergy, atopic dermatitis, or Hymenoptera allergy.

||Any drug except chemotherapeutic agents.

¶One patient had a prior HSR to platinum and doxorubicin.

Statistical analysis

Comparisons were made for categorical variables by using the Fisher exact test when the variable was dichotomous and the χ^2 test when the nominal variable exceeded 2 categories. The Mann-Whitney *U* test was used to compare continuous variables. A *P* value of less than .05 was considered significant. Multivariate analysis was performed by using binary logistic regression (if the dependent variable was dichotomous) or multinomial logistic regression (if the dependent variable exceeded 2 categories) when more than 1 independent variable was associated with the outcome of interest in univariate analysis. Statistical analysis was performed with SPSS statistical software (version 19; SPSS, Chicago, Ill).

RESULTS

Characteristics of patients and initial taxane-induced HSRs

One hundred sixty-four patients were evaluated for a suspected taxane-induced HSR (Table II). Most (142/164 [87%]) initially

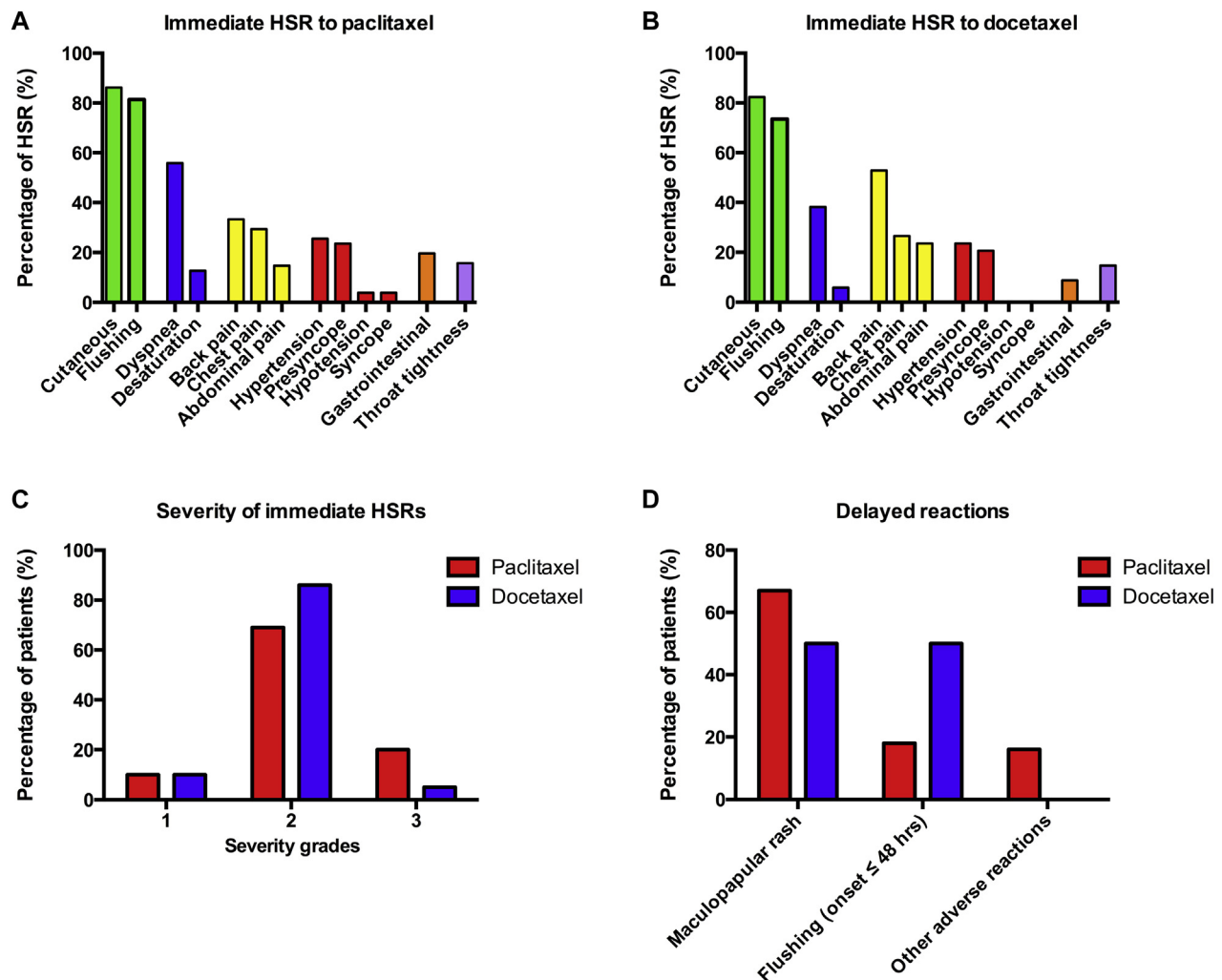


FIG 2. Clinical features of taxane-induced HSRs. **A**, Immediate HSRs to paclitaxel. **B**, Immediate HSRs to docetaxel. **C**, Severity of immediate HSRs to paclitaxel and docetaxel. For patients with more than 1 immediate HSR, only the most severe HSR is represented. See Table 1 for a definition of severity grades. **D**, Delayed reactions to paclitaxel and docetaxel. Onset of maculopapular rash (median, 7 days; range, 1-15 days) and flushing (median, 0.5 days; range, 0.5-2 days) after infusion is shown. Other adverse reactions consisted of isolated pruritus ($n = 5$), dyspnea/bronchospasm ($n = 2$), and acute inflammation of actinic keratosis ($n = 1$).

reacted to paclitaxel, and 22 (13%) reacted to docetaxel. Patients with paclitaxel-induced HSRs were almost exclusively female (99%), whereas those with docetaxel-induced HSRs were more commonly male (55%) because paclitaxel is mainly used to treat advanced gynecologic malignancies and docetaxel to treat metastatic prostate cancer.

Most patients (131/164 [80%]) reacted on the first or second exposure despite the use of standard premedication in more than 90% of cases (see Fig E1 in this article's Online Repository at www.jacionline.org). A majority of patients experienced at least 1 immediate HSR (119/164 [73%]), of which 107 (90%) were grade 2 or 3 (Fig 2, A-C). Twenty-seven percent (45/164) of patients presented exclusively with a delayed HSR (Fig 2, D, and see Fig E2 in this article's Online Repository at www.jacionline.org). Twenty-eight (17%) patients experienced more than 1 HSR, and 12 of those had both types of reactions (immediate and delayed, see Fig E2 in this article's Online Repository at www.jacionline.org). Before allergy evaluation, 24 patients were

retreated with taxanes after an initial HSR and had a recurrent reaction. The recurrent HSR was more severe than the initial reaction in 42% (10/24). Importantly, 4 patients with an initial HSR that was delayed (maculopapular rash, $n = 3$; flushing ≤ 48 hours after infusion, $n = 1$) had a recurrent reaction that was immediate. Forty patients were also evaluated for a suspected HSR to a platinum drug (see the Results section in this article's Online Repository at www.jacionline.org).

Mast cell/basophil mediators after an immediate taxane-induced HSR

After an immediate HSR, mast cell/basophil mediator levels were measured in 7 patients treated between April 2011 and August 2014 and in 2 patients treated between January 2008 and April 2011. Levels were increased in 2 (22%) of 9 patients (see Table E3 in this article's Online Repository at www.jacionline.org). In 1 patient (treated in 2014) the 24-hour urine

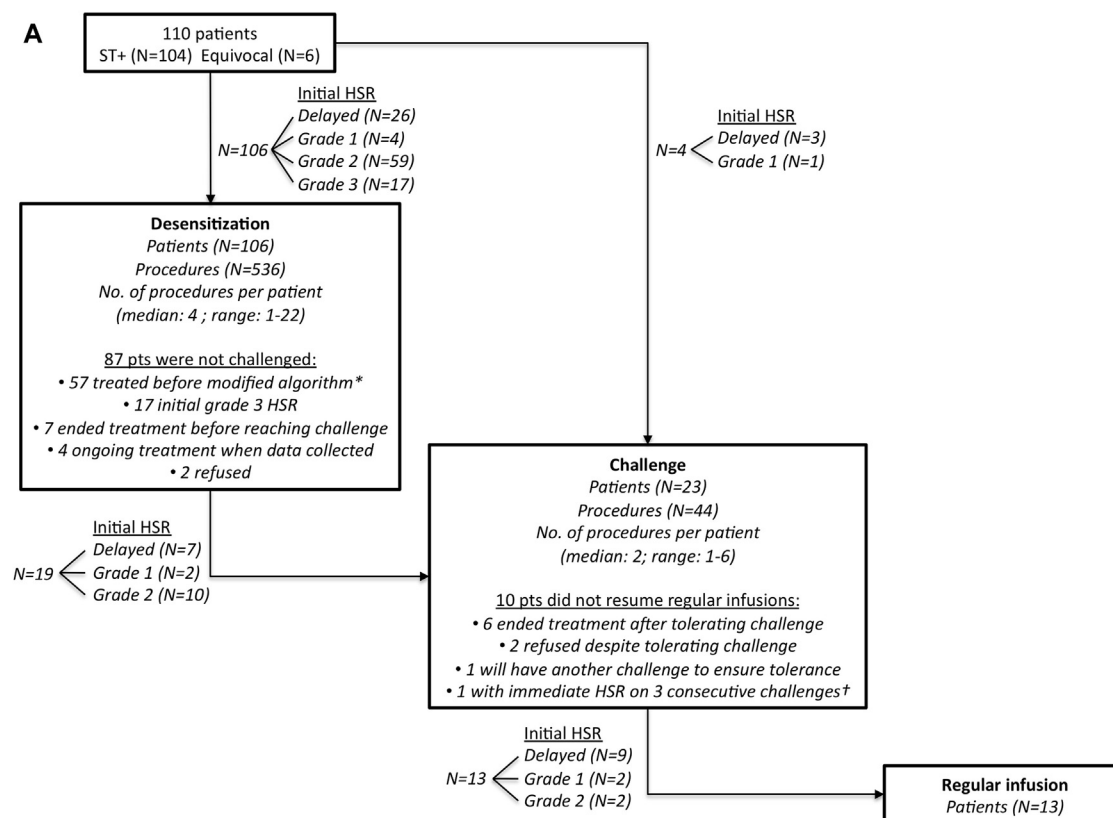


FIG 3. Management of patients with HSRs to taxanes. Patients were treated according to the algorithm presented in Fig 1. **A**, Patients with a positive or equivocal skin test response. **B**, Patients with an ST– response. **C**, Patients not skin tested. See Table 1 for a description of the severity grades of immediate HSRs. *Modifications made to the algorithm in September 2013 are shown as dotted lines in Fig 1. †See Table III for a description of patients with HSRs to challenge. ‡One patient had a delayed initial HSR, tolerated 3 regular infusions, and then had an immediate grade 3 HSR. On re-evaluation, she had converted to an ST+ response. The other patient had an initial immediate grade 1 HSR, tolerated 5 regular infusions, and then had a grade 2 immediate HSR. She was not re-evaluated.

N-methylhistamine/creatinine ratio was increased (406 $\mu\text{g/g}$; normal, ≤ 200 $\mu\text{g/g}$) around 24 hours after the HSR and had returned to within normal limits when measured 4 months after the HSR (150 $\mu\text{g/g}$). The other (treated in 2010) had a significant increase in total and mature tryptase levels (total, 44 ng/mL; mature, 8.5 ng/mL; normal levels, ≤ 11.4 and < 1 ng/mL, respectively), which returned to normal when measured 1 month after the HSR (total, 7 ng/mL; mature, < 1 ng/mL).

Taxane skin test results

Skin testing was performed in 145 patients: 103 (71%) had positive results, 35 (24%) had negative results, 6 (4%) had equivocal results, and 1 (0.7%) had results that converted from negative to positive (see Table E4 in this article's Online Repository at www.jacionline.org). The latter patient initially experienced a delayed HSR (maculopapular rash), had an ST– response, and then tolerated 1 challenge procedure and 3 regular infusions before experiencing an immediate HSR. On re-evaluation, she had converted to an ST+ response.

Nineteen patients were not skin tested either because they were evaluated before taxane skin testing was implemented (15/19) or because they were evaluated within 2 weeks of their

HSR (4/19). Patients with an immediate grade 2 or 3 HSR were significantly more likely to have ST+ responses than patients with a delayed or grade 1 immediate HSR (odds ratio [OR], 2.8; 95% CI, 1.3–6.1; $P = .01$; see Table E5 in this article's Online Repository at www.jacionline.org). Immediate HSRs experienced by patients with ST+ responses were more frequently characterized by flushing compared with those with ST– responses (86% vs 64%, $P = .02$, see Fig E3 in this article's Online Repository at www.jacionline.org). Among patients who only had delayed reactions, reaction characteristics did not predict the skin test result (see Fig E3).

Management of patients with taxane-induced HSRs

Patients were treated as shown in Fig 3 according to the algorithm presented in Fig 1. Thirty-six (36/164 [22%]) patients eventually resumed regular infusions. These patients were more likely to have ST– responses than to have any other skin test result (positive, equivocal, or not done; OR, 9.6; 95% CI, 3.6–25.6) or to have experienced a delayed or immediate grade 1 initial HSR than an immediate grade 2 or 3 initial HSR (OR, 8.2; 95% CI, 3.1–21.4; see Tables E6 and E7 in this article's Online Repository at www.jacionline.org). These findings were expected considering

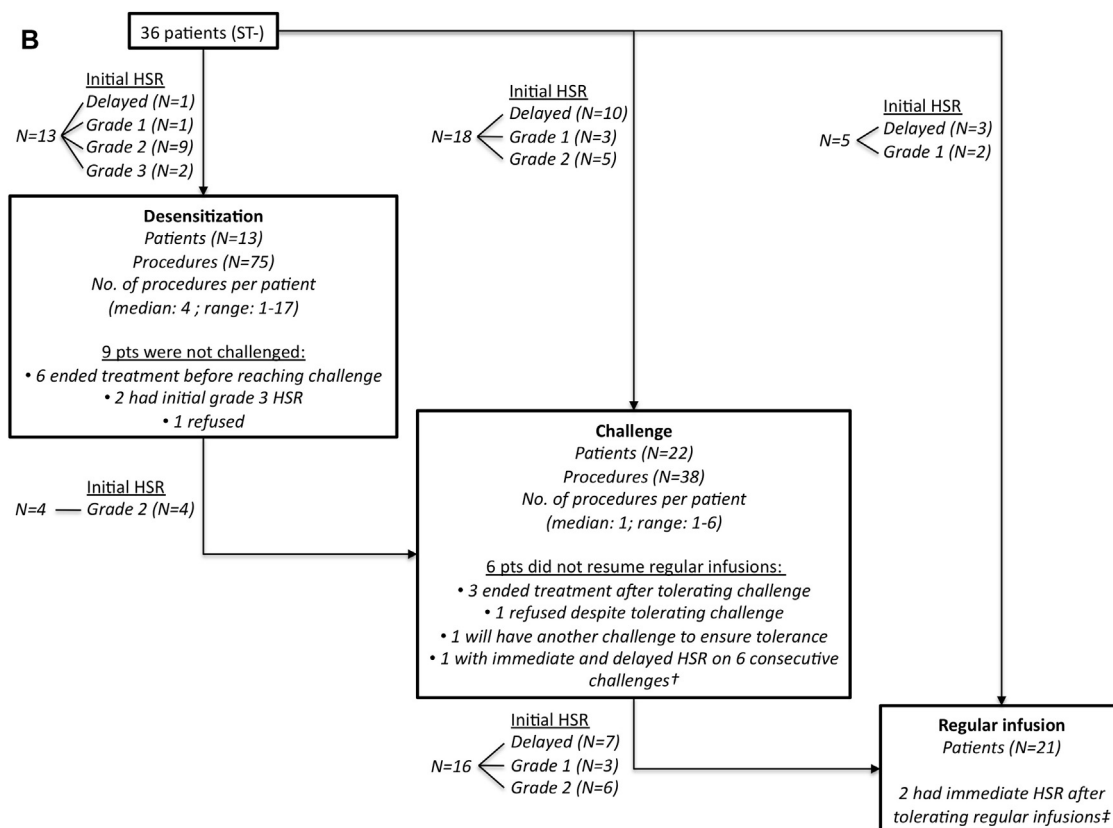


FIG 3. (Continued).

the retreatment strategy depicted in Fig 1. Two patients had an immediate HSR after tolerating 3 or more regular infusions. One was re-evaluated and found to have converted from an ST– response to an ST+ response and was thereafter desensitized.

Safety of desensitization

Of 138 patients desensitized, 29 (21%) had an immediate and 20 (14%) had a delayed HSR with the procedure (Fig 4, A-C). Most immediate reactions were grade 1 (24/29 [83%]), and none were severe (grade 3). Five patients had grade 2 immediate HSRs, which resolved rapidly after a temporary pause in the infusion and the appropriate treatment. Immediate HSRs most commonly occurred during the last step of the protocol (Fig 4, D), and all patients completed the desensitization procedure. Six patients with an immediate HSR during desensitization also experienced a delayed reaction after desensitization. Importantly, 4 patients with an initial delayed HSR (maculopapular rash, $n = 3$; flushing ≤ 48 hours after the infusion, $n = 1$) had an immediate grade 1 HSR during desensitization. One patient had pneumonitis after the first and second paclitaxel desensitization and discontinued treatment.

Overall, the risk of an immediate or delayed HSR with desensitization progressively decreased with repeated exposures (Fig 4, E). This finding was not attributable to a depletion of patients susceptible to a reaction because most patients (42/49 [86%]) who either had an immediate or delayed HSR with desensitization subsequently tolerated at least 1 desensitization, 8

(16%) tolerated at least 1 challenge, and 3 (6%) tolerated regular infusions. Only 3 patients with an HSR were not re-exposed since their treatment had ended. Premedication was adjusted in 53% (26/49) of patients with either an immediate or delayed HSR with desensitization, and of those, 73% (19/26) did not experience another reaction.

Safety of challenge

Of 49 patients challenged, 2 (4%) had a grade 1 immediate and 1 (2%) had a delayed HSR with the procedure (Table III). One patient subsequently tolerated regular infusions, but HSRs recurred on repeated challenge in the other 2 patients.

Factors associated with an HSR during desensitization or challenge

Atopy was associated with an increased risk of an immediate HSR during desensitization or challenge (OR, 4.9; 95% CI, 2.0-11.8; Tables IV and V). Older patients (OR, 1.1; 95% CI, 1.0-1.1) and those with ovarian, fallopian, or peritoneal cancer (OR, 8.1; 95% CI, 1.8-37.4) were more likely to experience a delayed HSR with desensitization or challenge (Tables IV and V). In the subgroup of patients with an initial delayed HSR, those with flushing with onset at 48 hours or less after infusion were at increased risk of having either an immediate or delayed HSR with desensitization or challenge compared with patients with any other type of delayed reaction (OR, 8.3; 95% CI, 1.4-50.5;

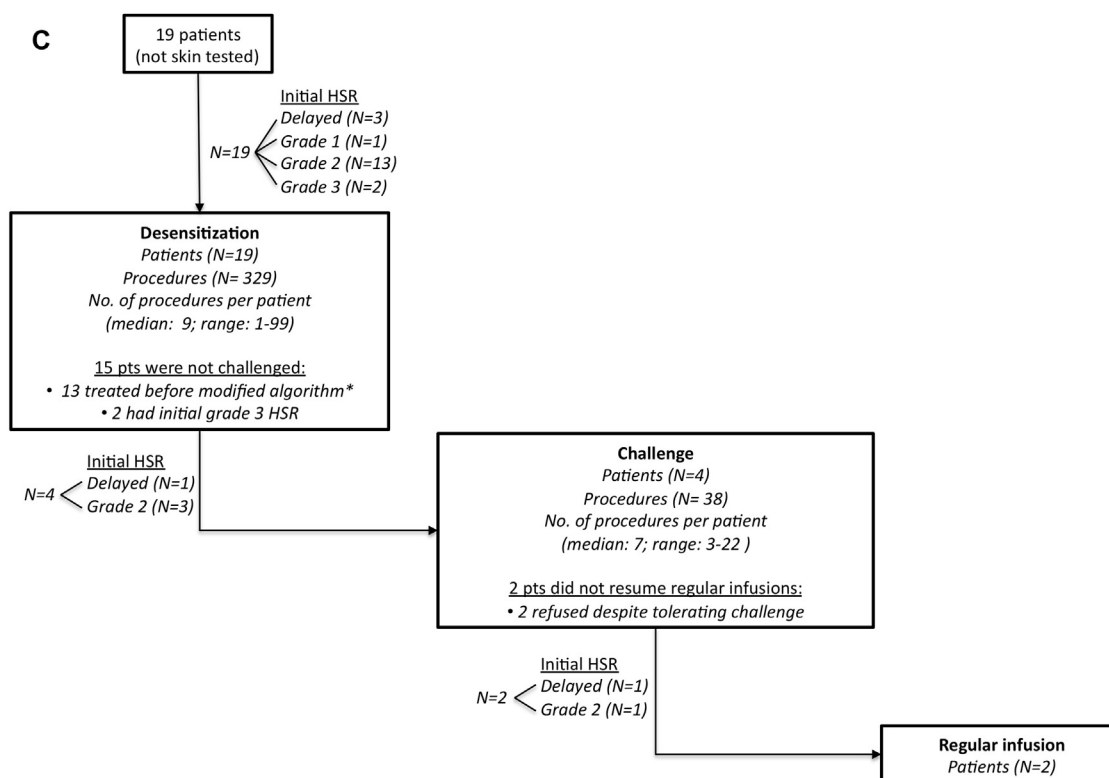


FIG 3. (Continued).

$P = .02$; Table IV). The severity of the initial HSR, as well as the skin test result, was not significantly associated with the occurrence of an immediate or delayed HSR with desensitization or challenge. Patients who experienced an immediate (1/31 [3%]) or delayed (3/21 [14%]) HSR with desensitization or challenge were less likely to resume regular infusions ($P = .007$) than those who did not (32/112 [29%]).

DISCUSSION

In this study patients with delayed or immediate HSRs to taxanes were re-exposed to these agents either through desensitization, challenge, or regular infusion based on the severity of the initial HSR and skin test result. Depending on the initial risk stratification and tolerance to re-exposure, patients were then treated with shorter desensitization protocols and/or challenge with the aim of resuming regular infusions except in patients with a severe immediate initial HSR. This approach proved to be safe because no patient had a severe immediate HSR on re-exposure, and it also allowed a significant proportion (22%) of patients to resume regular infusions. To our knowledge, this study, which includes 164 patients, of whom 107 had a moderate-to-severe immediate initial HSR, represents the largest cohort of patients treated for taxane-induced HSRs reported to date. Importantly, no patient was judged ineligible for retreatment, and only 1 patient stopped treatment prematurely because of an adverse reaction (paclitaxel-induced pneumonitis).

In contrast, another retreatment strategy used in patients with immediate HSRs to taxanes consists of a rapid rechallenge within 30 minutes of the initial reaction¹² and in administration

of the next cycle as a regular^{12,23} or slowed infusion with or without added premedication.² An advantage of this approach is that it allows many patients (40%,²³ 68%,² and 89%¹²) to resume regular infusions without having to undergo desensitization. However, in 2 of those studies, an important number of patients were not retreated with taxanes (25%² and 40%²³), most commonly those with a more severe initial HSR. In the study by Alvarez-Cuesta et al,²³ the main reason for not being retreated with a regular infusion was that the patient did not consent to the procedure, showing another limitation of this approach. Furthermore, severe immediate HSRs on re-exposure (with hypotension and/or requiring treatment with epinephrine) were reported in these 2 studies affecting 1 (1%) of 80² and 2 (8%) of 26²³ patients. Moreover, 2 fatalities were previously reported during re-exposure with either a slowed or regular infusion.^{5,24} It should be emphasized that the absence of a recurrent reaction with the rapid rechallenge procedure (within 30 minutes of the initial HSR) does not ensure tolerance of the next cycle. In the study by Markman et al,¹² a rate of 1.6 HSRs per patient (71 HSRs in 44 patients) was reported, and in our study (before allergy evaluation) 12 patients who tolerated a rapid rechallenge had a recurrent immediate HSR with the next cycle, which was severe in 3 patients (see Fig E2).

Differences in populations could account for discrepancies between the different studies on taxane re-exposure. For instance, in the study by Banerji et al,² all patients with a paclitaxel-induced HSR were included. In this study only patients referred for an allergy evaluation were included, possibly selecting patients at higher risk of a recurrent reaction because those who tolerated a rechallenge by their oncologist were not included. Also, in this study 99% of patients with a paclitaxel-induced HSR were

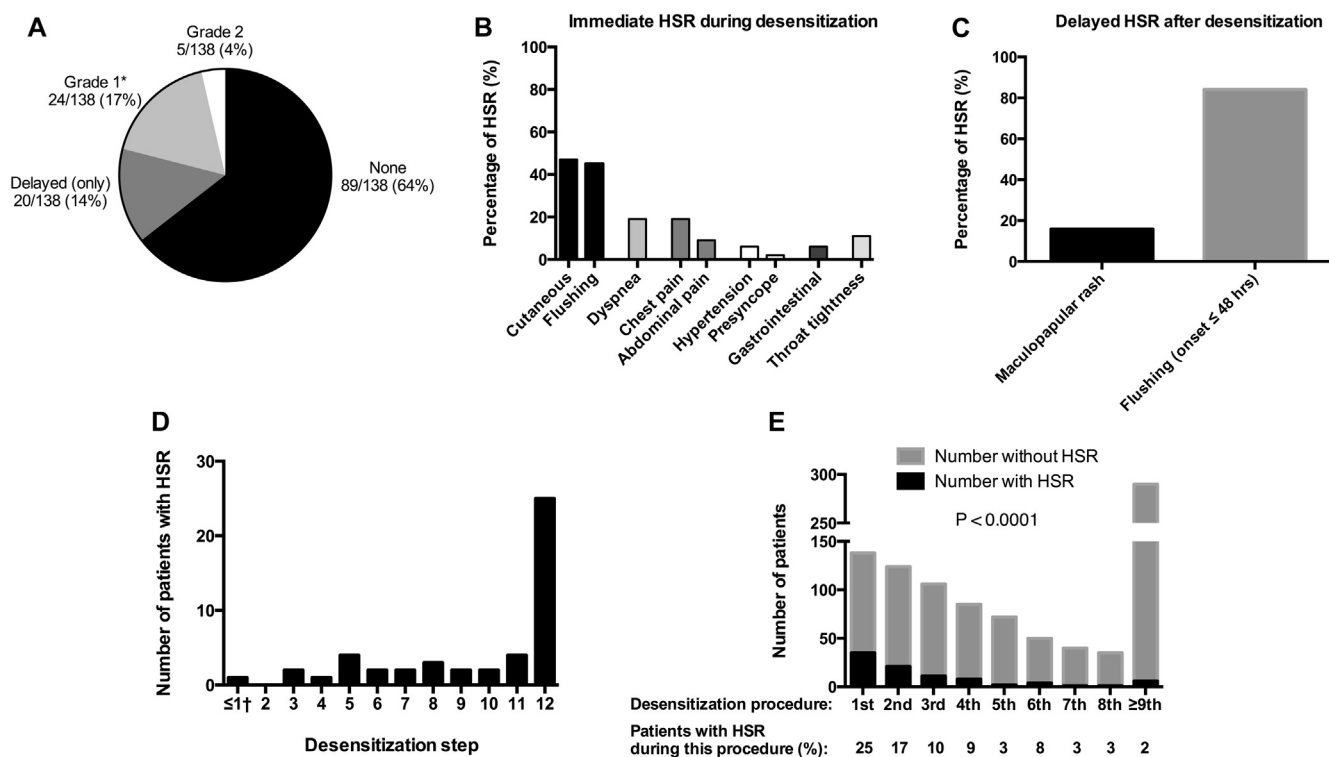


FIG 4. Risk and timing of HSRs in patients desensitized to taxanes: 138 patients underwent 940 desensitization procedures. **A**, Type and severity of HSRs with desensitization. *Six patients with an immediate grade 1 HSR also experienced a delayed HSR. **B**, Characteristics of immediate HSRs during desensitization (29 patients experienced a total of 47 HSRs). **C**, Description of delayed HSRs after desensitization (26 patients experienced a total of 44 HSRs). Onset of flushing in a median of 1 day (range, 0.5-2 days) and of maculopapular rash in a median of 1 day (range, 0.5-7 days) after desensitization. **D**, Timing of immediate HSRs during desensitization. †Patients who reacted during the first 5 steps of a 4-bag/16-step protocol are depicted as reacting at step 1 or less. **E**, Risk of HSR at each desensitization procedure.

TABLE III. Characteristics of patients with HSRs to challenge

Age (y)	Sex	Initial HSR	ST result	Taxane used for re-exposure	Desensitization	HSR with challenge	Resumed regular infusions
59	F	Delayed maculopapular rash	Negative	Paclitaxel	ND	Delayed maculopapular rash on first 2 challenges; tolerated third challenge	Yes
64	F	Delayed flushing	Negative	Paclitaxel	ND	Immediate grade 1 on challenges 2 and 6; delayed flushing on challenges 1-5	No
72	M	Immediate grade 2	Positive	Docetaxel and cabazitaxel	Tolerated one 3-bag and one 2-bag desensitization to docetaxel	Immediate grade 1 on challenge 1 with docetaxel and on challenges 1-2 with cabazitaxel	No

F, Female; M, male; ND, not done.

female, 35% were atopic, and most (65%) had ovarian cancer compared with 69% of female patients, 21% of atopic patients, and 18% of patients with ovarian cancer in the study by Banerji et al.

A common finding in many studies on taxane-induced HSRs is the decreasing risk of reaction with repeated exposures (Fig 4, E).^{2,5,12} This finding argues for a progressive approach to taxane reintroduction, starting with the safest method for re-exposure (desensitization) when the risk is highest and progressively shortening the protocol or proceeding with challenge with the aim of resuming regular infusions as the risk decreases (Fig 1).

Patients with delayed taxane-induced HSRs, consisting of either a maculopapular rash or flushing with onset of 48 hours or less after the infusion might be at risk of an immediate reaction on re-exposure.²⁴ In this study 9 patients with an initial delayed HSR had an immediate reaction on re-exposure (Table IV and see Fig E2). Interestingly, those with flushing with onset of 48 hours or less after infusion were at increased risk for a recurrent HSR (immediate or delayed).

Mast cell/basophil activation appears to be implicated in at least a subset of immediate taxane-induced HSRs, as shown in Table E3 and in a previous report of a patient with an increased N-

TABLE IV. Characteristics of patients with an immediate, delayed, or no HSR with desensitization or challenge

Characteristics	No HSR (n = 112)	Immediate HSR (n = 31*)	Delayed HSR only (n = 21)	P value
Age (y)				.1
Median	59	56	63	
Range	25-79	37-73	40-81	
Sex, no. (%)				.8
Female	102 (91)	29 (94)	20 (95)	
Male	10 (9)	2 (6)	1 (5)	
Race or ethnic group, no. (%)				.8
White	100 (89)	29 (94)	19 (90)	
Other/unknown	12 (11)	2 (6)	2 (10)	
Cancer site, no. (%)				.03
Ovarian, fallopian, peritoneal	61 (54)	14 (45)	19 (90)	
Endometrial	29 (26)	7† (23)	1 (5)	
Breast	9 (8)	7 (23)	0	
Prostate	7 (6)	2 (6)	1 (5)	
Other	6 (5)	2‡ (6)	0	
Cancer stage, no. (%)				.1
I or II	19 (17)	9 (29)	4 (19)	
III	44 (39)	16 (52)	10 (48)	
IV	49 (44)	6 (19)	7 (33)	
Atopy,‡ no. (%)				.002
Yes	30 (27)	19 (61)	7 (33)	
No	82 (73)	12 (39)	14 (67)	
History of drug-induced§ HSR, no. (%)				.5
Yes	36 (32)	7 (23)	8 (38)	
No	76 (68)	24 (77)	13 (62)	
Prior HSR to non-taxane chemotherapy, no. (%)				.3
Yes	5 (4)	3 (10)	0	
No	107 (96)	28 (90)	21 (100)	
Taxane cycle causing an HSR				1.0
Median	1	1	1	
Range	1-30	1-30	1-54	
Patients with recurrent HSRs on rechallenge before allergy evaluation				.2
Yes	16 (14)	7 (23)	1 (5)	
No	96 (86)	24 (77)	20 (95)	
Taxane used for re- exposure				.8
Paclitaxel	95 (85)	26 (84)	19 (90)	
Docetaxel	15 (13)	5 (16)	2 (10)	
Other¶	2 (2)	0	0	
Type and severity of initial HSR				.2
Delayed	32 (29)	5 (16)	9 (43)	
Maculopapular rash	23 (21)	3 (10)	5 (24)	
Flushing (onset ≤48 h)	2 (2)	2 (6)	3 (14)	
Other	7 (6)	0	1 (5)	
Immediate				
Grade 1	10 (9)	1 (3)	1 (5)	
Grade 2	54 (48)	21 (68)	11 (52)	
Grade 3	16 (14)	4 (13)	0	
Skin test result				.09

(Continued)

TABLE IV. (Continued)

Characteristics	No HSR (n = 112)	Immediate HSR (n = 31*)	Delayed HSR only (n = 21)	P value
Negative	29 (26)	4 (13)	3 (14)	
Positive	71 (63)	17 (55)	15 (71)	
Equivocal	3 (3)	2 (6)	1 (5)	
Not done	9 (8)	8 (26)	2 (10)	

*Seven of these patients also experienced delayed HSRs after desensitization or challenge.

†One patient was concomitantly given a diagnosis of endometrial and non-small cell lung cancer.

‡Defined as the presence of any of the following: history of allergic asthma and/or rhinoconjunctivitis, food allergy, atopic dermatitis, or Hymenoptera allergy.

§Any drug except a chemotherapeutic agent.

||Three of these patients were also exposed to cabazitaxel (2 did not react, and 1 had an immediate HSR).

¶Includes nab-paclitaxel and cabazitaxel.

methylhistamine/creatinine ratio after a severe immediate taxane-induced HSR.²⁵ The lack of a tryptase level increase to greater than the upper limit of normal in the other patients does not rule out a mast cell-mediated reaction because tryptase is not a sensitive marker of anaphylaxis, especially in the absence of hypotension.^{29,30}

The concept that IgE-mediated HSRs could occur on the first exposure to a given drug was recently demonstrated for cetuximab-induced HSRs in which pre-existing IgE antibodies, acquired through tick bites, cause these reactions.^{31,32} As for taxanes, evidence of an IgE-mediated mechanism is currently lacking. However, several findings raise such a possibility. Exposure to yew tree pollen (the tree from which paclitaxel is derived) leads to development of anti-paclitaxel IgG, especially among atopic subjects.³³ In the present study, which was conducted in a region in which yew trees are common, most patients had ST+ responses, and atopy was associated with an increased risk of a recurrent immediate HSR on re-exposure. Skin test positivity correlated with the severity of the initial reaction and with flushing during the initial immediate HSR. Cutaneous symptoms during an immediate HSR to chemotherapy were recently found to predict a recurrent reaction on re-exposure.²³ Arguing against an IgE-mediated phenomenon is the fact that only 31% of patients with ST+ responses in our cohort were atopic, although atopy might not be a prerequisite to acquire paclitaxel sensitivity through yew tree pollen exposure. Also, atopy has previously been implicated as a risk factor for HSRs to radiocontrast media, which are non-IgE mediated in most cases.^{6,34,35} Finally, an ST+ response could indicate a direct activating effect of the taxane moiety or its surfactant on mast cells rather than an IgE-mediated reaction. Interestingly, risk factors for delayed HSRs differed from the ones for immediate HSRs, possibly pointing toward distinct mechanisms.

This study has several limitations. First, it did not show that patients with a more severe initial HSR and/or who had an ST+ response were at increased risk of a recurrent reaction on taxane reintroduction. This might be explained by the fact that patients were stratified according to these characteristics and therefore were treated differently, with a more conservative approach used in patients with ST+ responses and those with a grade 2 or 3 initial immediate HSR. The rationale behind this approach is that the safety of a rechallenge has not been established in patients with a severe immediate HSR because

TABLE V. Multivariate analysis of factors associated with an HSR to desensitization or challenge

Outcomes and contributing factors	OR	95% CI	P value
Immediate HSR*			
Age†	1.0	0.97-1.04	.8
Atopy‡	4.9	2.0-11.8	.001
Ovarian, fallopian, peritoneal cancer§	0.5	0.2-1.2	.1
Negative skin test response	0.4	0.1-1.4	.2
Delayed HSR*			
Age†	1.1	1.0-1.1	.02
Atopy‡	1.3	0.4-3.7	.7
Ovarian, fallopian, peritoneal cancer§	8.1	1.8-37.4	.007
Negative skin test response	0.5	0.1-1.8	.5

*Compared with no HSR.

†Age was included in the model because it increased its accuracy to 70.7%.

‡Defined as the presence of any of the following: history of allergic asthma and/or rhinoconjunctivitis, food allergy, atopic dermatitis, or Hymenoptera allergy (compared with no atopy).

§Compared with any other type of cancer.

||Compared with any other skin test outcome (positive, equivocal, or not done).

these patients are less likely to be rechallenged or included in such studies^{2,12,23} and are generally more reluctant to undergo a challenge.²³ As for patients with ST+ responses, a more conservative approach was used empirically because an ST+ response to a nonirritating concentration suggests the possibility of an IgE-mediated mechanism and a risk of anaphylaxis.⁶

Second, our cohort is not representative of all patients with taxane-induced HSRs because those who were rechallenged by their oncologist and tolerated the procedure were not included.

Third, given the high ST+ responses observed in our cohort, our findings might not be directly applicable to other populations in which ST+ responses are less prevalent.^{20,21} Although the presented strategy for taxane re-exposure appears to be generally safe, practitioners less familiar with these procedures should remain cautious because its safety has not been established in other settings.

Finally, this study did not address the risk of using nab-paclitaxel after an HSR to paclitaxel. However, given the high cost of nab-paclitaxel and the limited data available on its use after a paclitaxel-induced HSR, this option might not be cost-effective and cannot be considered safer than paclitaxel desensitization.³⁶⁻³⁸

In conclusion, a risk stratification strategy based on the severity of the initial HSR and skin testing to guide taxane reintroduction appears to be safe because no patient had a severe immediate HSR on re-exposure. This approach also allowed a significant number of patients to resume regular infusions. Although this study raises the possibility of an IgE-mediated mechanism underlying a subset of taxane-induced HSRs, further studies are needed to clarify the mechanisms of these reactions.

Clinical implication: Risk stratification based on the severity of the initial HSR and skin testing to guide taxane reintroduction is safe and allows a significant number of patients to resume regular infusions.

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METHODS

Premedication

All patients were premedicated with H₁-blockers (either 10 mg of oral cetirizine, 50 mg of oral or intravenous diphenhydramine, or 50 mg of oral hydroxyzine), 99% (163/164) with H₂-blockers (either 50 mg of intravenous ranitidine or 20 mg of intravenous famotidine), 65% (106/164) with montelukast (10 mg), 50% (77/164) with aspirin (325 mg), and 2% (3/164) with zileuton (600 mg) 30 minutes before desensitization or challenge. Corticosteroids (10–20 mg of oral or intravenous dexamethasone) were administered to 95% (156/164) of patients, as recommended.^{E1,E2} Fifteen patients received H₁-blockers (combined with corticosteroids in 6 and with aspirin in 2), 4 received aspirin (combined with montelukast in 2), and 3 received corticosteroids alone for 2 to 7 days after desensitization.

Setting of desensitization or challenge procedures

Patients with a grade 3 immediate HSR were initially desensitized in the BWH intensive care unit. If no reaction occurred, subsequent desensitizations were performed in the DFCI desensitization unit. All other patients were desensitized or challenged in the DFCI desensitization unit with 1:1 nursing.

Desensitization protocols

Three different desensitization protocols were used depending on the severity of the initial HSR, the patient's comorbidities (eg, uncontrolled asthma and/or significant impairment in FEV₁, unstable or symptomatic coronary heart disease, and poor Eastern Cooperative Oncology Group performance status), skin test results, and tolerance of previous desensitizations: 4-bag/16-step, 3-bag/12-step, and 2-bag/8-step desensitizations (Table E1). After 1 or 2 uneventful desensitizations or in patients with a low reaction risk (eg, delayed HSR), the final rate of the infusion could be increased from 80 to 120 mL/h for 15 minutes and then to 160 mL/h for the remainder of the infusion. If an HSR occurred after a rate increase, the final rate was limited at 80 mL/h, premedication was adjusted for the next procedure, or both.

Challenge protocols

The target dose was diluted in 250 mL of normal saline, and infusion was started at 10 mL/h and progressively increased up to 160 mL/h. Although all patients who tolerated this challenge protocol tolerated at least 1 regular infusion, the protocol was modified in September 2013 so as to use approximately 10-fold increments between steps and a final infusion rate

that matched that of a regular infusion (Table E2). This change was made to ensure that the challenge protocol could elicit any HSR that might be elicited by a regular infusion.

RESULTS

Platinum skin testing and management

All 6 patients with an immediate HSR during or shortly after their carboplatin infusion but 1 hour or less after their paclitaxel infusion had a positive carboplatin skin test result, and 2 of these also had a positive paclitaxel skin test result. Patients reacted in median during their seventh lifetime carboplatin exposure (range, 1–8). All 6 patients were re-exposed to carboplatin through desensitization.

Among 34 patients with a delayed HSR after paclitaxel/platinum infusions, 15 (44%) had positive responses to both agents, 11 (32%) had positive responses only to paclitaxel, and 2 (6%) had positive responses only to carboplatin. Three (9%) patients had negative responses to both agents, and 3 (9%) others had negative responses to only paclitaxel because they were not skin tested to platinum. Patients, regardless of the platinum skin test result, reacted in median after their first lifetime platinum exposure (range, 1–11). All 17 patients with a negative platinum skin test response (or not skin tested) resumed regular infusions uneventfully. Most patients with ST+ responses (15/17 [88%]) were desensitized to platinum, and 2 of them later tolerated a challenge and resumed regular infusions. The 2 other patients with ST+ responses were directly challenged and tolerated 3 and 5 regular infusions, respectively, before having an immediate HSR during a platinum infusion.

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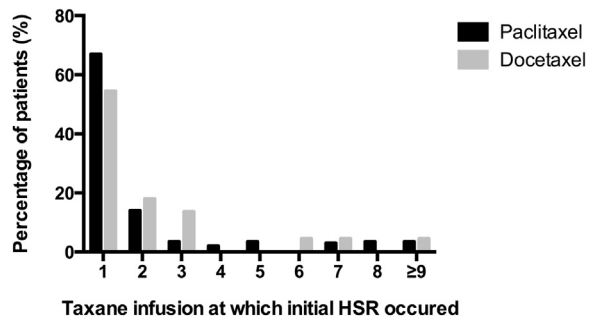


FIG E1. Taxane infusion at which the initial HSR occurred. Patients with initial HSRs to paclitaxel (n = 142) and docetaxel (n = 22) are shown.

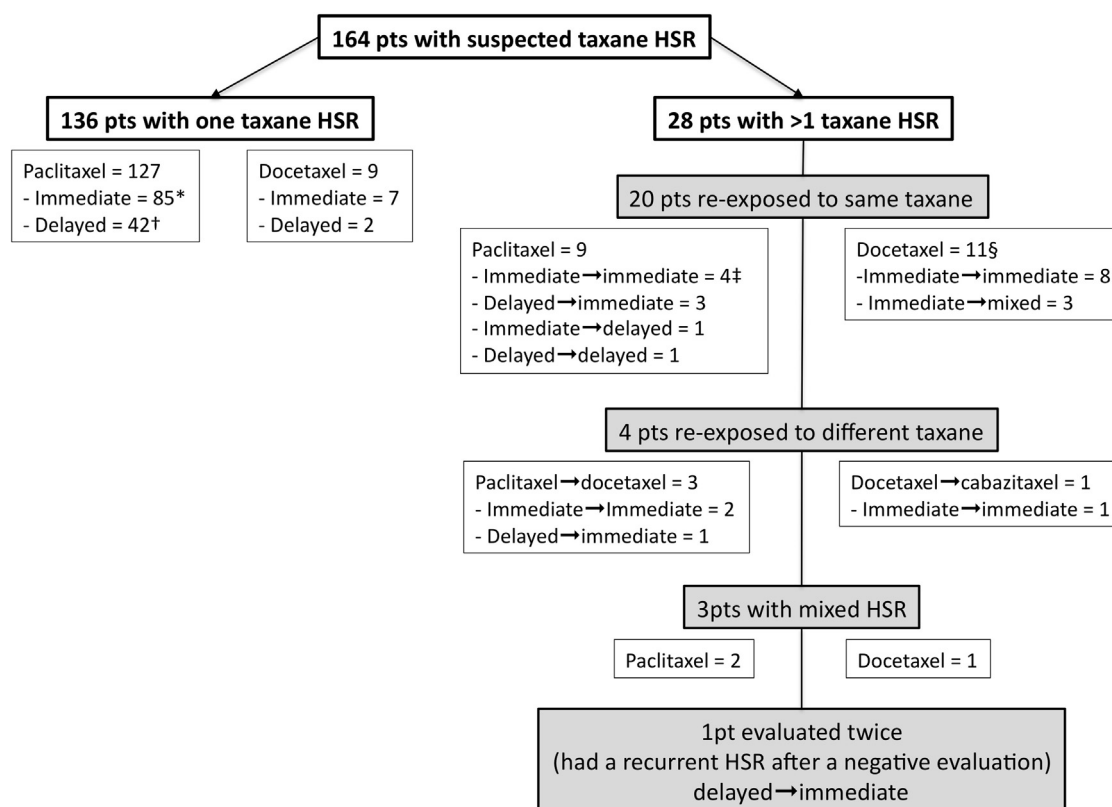


FIG E2. Patterns of taxane-induced HSRs. *In 5 of these patients, the immediate HSR occurred during carboplatin infusion and 1 hour or less after paclitaxel infusion. One patient had an immediate HSR 45 minutes into the paclitaxel infusion, which recurred 15 minutes into the carboplatin infusion. †In 34 of these patients, the delayed HSR occurred after a paclitaxel and carboplatin infusion. ‡One patient tolerated a rapid rechallenge within 30 minutes of the initial HSR but had a recurrent immediate HSR at the next cycle. §Eleven patients tolerated a rapid rechallenge within 30 minutes of the initial HSR but had a recurrent immediate HSR at the next cycle. Mixed HSR is defined as the occurrence of an immediate HSR during a taxane infusion followed several hours to days later by a delayed HSR.

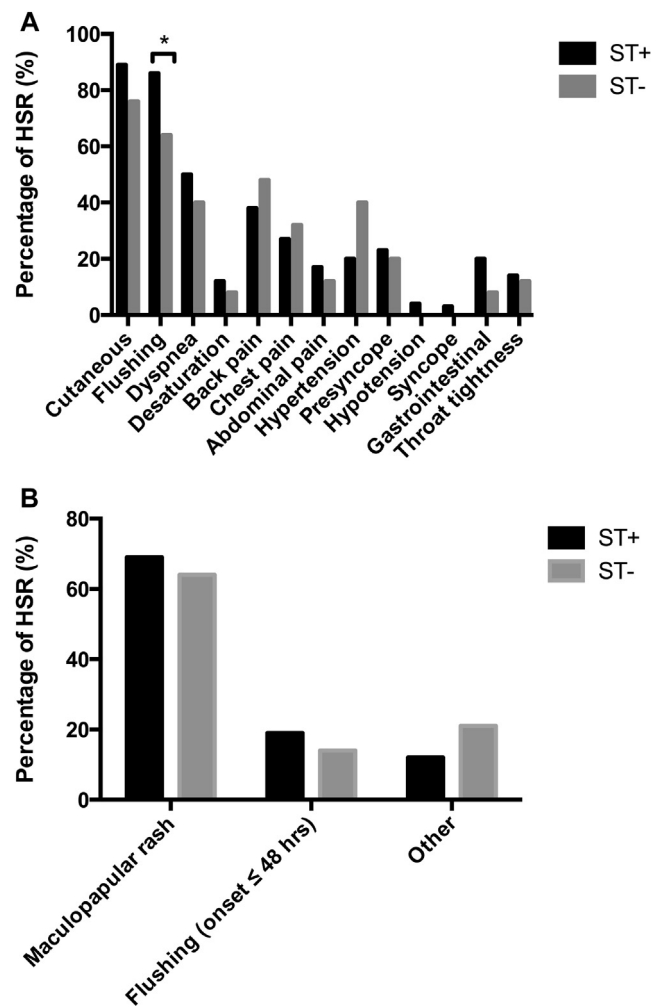


FIG E3. Comparison of clinical features of HSRs in patients with ST+ and ST- responses. **A**, Immediate HSRs. * $P = .02$. **B**, Delayed reactions.

TABLE E1. Desensitization protocols for paclitaxel (294 mg)

Bag	Volume (mL) per bag	Concentration (mg/mL) per bag	Amount (mL) of bag infused	Dose infused (mg) per bag		
4-Bag/16-step protocol						
Solution 1	250	0.00118	9.38	0.011		
Solution 2	250	0.0118	9.38	0.111		
Solution 3	250	0.118	18.75	2.213		
Solution 4	250	1.167	250	291.665		
Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused (mg) per step	Cumulative dose (mg)
1	1	2.5	15	0.625	0.001	0.001
2	1	5	15	1.25	0.001	0.002
3	1	10	15	2.5	0.003	0.005
4	1	20	15	5	0.006	0.011
5	2	2.5	15	0.625	0.007	0.018
6	2	5	15	1.25	0.015	0.033
7	2	10	15	2.5	0.030	0.063
8	2	20	15	5	0.059	0.122
9	3	5	15	1.25	0.148	0.270
10	3	10	15	2.5	0.295	0.565
11	3	20	15	5	0.590	1.155
12	3	40	15	10	1.18	2.335
13	4	10	15	2.5	2.917	5.252
14	4	20	15	5	5.834	11.086
15	4	40	15	10	11.667	22.753
16	4	80	174.4	232.5	271.262	294.0
Total time (hours) = 6.67						
Bag	Volume (mL) per bag	Concentration (mg/mL) per bag	Amount (mL) of bag infused	Dose infused (mg) per bag		
3-Bag/12-step protocol						
Solution 1	250	0.0118	9.38	0.111		
Solution 2	250	0.118	18.75	2.213		
Solution 3	250	1.167	250	291.676		
Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused (mg) per step	Cumulative dose (mg)
1	1	2.5	15	0.625	0.007	0.007
2	1	5	15	1.25	0.015	0.022
3	1	10	15	2.5	0.030	0.052
4	1	20	15	5	0.059	0.111
5	2	5	15	1.25	0.148	0.259
6	2	10	15	2.5	0.295	0.554
7	2	20	15	5	0.590	1.144
8	2	40	15	10	1.18	2.324
9	3	10	15	2.5	2.917	5.241
10	3	20	15	5	5.834	11.075
11	3	40	15	10	11.667	22.742
12	3	80	174.4	232.5	271.328	294.0
Total time = 5.67 h						
Bag	Volume (mL) per bag	Concentration (mg/mL) per bag	Amount (mL) of bag infused	Dose infused (mg) per bag		
2-Bag/8-step protocol						
Solution 1	250	0.118	18.75	2.213		
Solution 2	250	1.167	250	291.787		
Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused (mg) per step	Cumulative dose (mg)
1	1	5	15	1.25	0.148	0.148
2	1	10	15	2.5	0.295	0.443

(Continued)

[illegible]

Bag	Volume (mL) per bag	Concentration (mg/mL) per bag	Amount (mL) of bag infused	Dose infused (mg) per bag
Paclitaxel (135-175 mg/m ²) infused every 3 wk over 3 h (example = 294 mg)				
Solution 1	250	1.176	250	294

Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused (mg) per step	Cumulative dose (mg)
1	1	2	15	0.5	0.588	0.588
2	1	8	15	2	2.352	2.940
3	1	80	185.625	247.5	291.06	294.0
Total time = 3.59 h						

Bag	Volume (mL) per bag	Concentration (mg/mL) per bag	Amount (mL) of bag infused	Dose infused (mg) per bag
Paclitaxel (50-80 mg/m ²) infused weekly over 1 h (example = 134 mg)				
Solution 1	250	0.536	250	134

Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused (mg) per step	Cumulative dose (mg)
1	1	2.5	15	0.625	0.335	0.335
2	1	25	15	6.25	3.35	3.685
3	1	250	58.35	243.125	130.32	134.0
Total time = 1.47 h						

TABLE E3. Mast cell/basophil mediator levels measured at the time of HSR to paclitaxel

Patient	Tryptase		Delay between HSR and tryptase test	24-h Urine N-methylhistamine (normal, ≤ 200 $\mu\text{g/g}$)	Clinical features of HSR		
	Total (normal, ≤ 11.4 ng/mL)	Mature (normal, < 1 ng/mL)			Severity grade	Hypotension	Oxygen desaturation
1	7.1	ND	0 h, 18 min	ND	3	No	Yes
2	7.8	ND	0 h, 51 min	ND	2	No	No
3	6.2	ND	1 h, 43 min	ND	2	No	No
4	3.1	ND	2 h, 30 min	ND	3	No	Yes
5	5.2	ND	>12 h	406	3	No	Yes
6*	2.3	ND	8 h, 14 min	ND	3	No	No
7	8.8	ND	1 h, 23 min	ND	3	No	Yes
8	44.0	8.5	1 h, 16 min	ND	3	Yes	Yes
9	5.6	<1	5 h, 6 min	ND	3	Yes	Yes

ND, Not done.

*Patient had to be intubated because of tongue angioedema.

TABLE E4. Taxane skin test results

	HSR to paclitaxel (n = 142), no (%)	HSR to docetaxel (n = 22), no (%)	
No. of patients skin tested	127 (89)	18 (82)	
Skin test to:	Paclitaxel (n = 127)	Paclitaxel (n = 11*)	Docetaxel (n = 9*)
Positive response†	91 (71)	6 (55)	8 (89)
SPT	5 (4)	0	0
Size of SPT response (mm), median (range)			
Wheal	4 (3-5)	—	—
Flare	15 (4-25)	—	—
IDT‡	86 (67)§	6 (55)	8 (89)
First concentration	60 (47)	5 (45)	7 (78)
Second concentration	25 (20)	1 (9)	1 (11)
Size of IDT (mm), median (range)			
Wheal	7 (3-14)	6 (3-8)	6 (3-10)
Flare	15 (0-30)	13 (8-24)	11 (0-14)
Equivocal	5 (4)	1 (9)	0
Negative¶	32 (25)	4 (36)	1 (11)

Skin tests were performed at a median of 17 days (range, 8 days to 16 years) after the HSR.

IDT, Intradermal test; SPT, skin prick test.

*A total of 18 patients underwent skin tests, and 2 of them underwent skin tests to paclitaxel and docetaxel.

†A total of 104 patients had an ST+. One of them (with a paclitaxel-induced HSR) was skin tested twice and converted from an ST- to an ST+ response. This patient is also included among patients with ST- responses. Another (with a docetaxel-induced HSR) had positive responses to paclitaxel and docetaxel.

‡Concentrations used for IDTs were 0.001 mg/mL (first concentration) and 0.01 mg/mL (second concentration) for paclitaxel and 0.04 mg/mL (first concentration) and 0.4 mg/mL (second concentration) for docetaxel. Concentrations used for SPTs were 1 mg/mL for paclitaxel and 0.4 mg/mL for docetaxel.

§The concentration and size of the positive IDT response was not recorded in 1 patient.

||Sizes in millimeters (wheal/flare) of the equivocal skin test results were 4/0, 0/40, 0/10, and 0/31 for paclitaxel and 0/8 for docetaxel.

¶A total of 36 patients had an ST- response. One of them (with a paclitaxel-induced HSR) later converted to an ST+ response and is also included among patients with ST+ responses. Another (with a docetaxel-induced HSR) had negative responses to paclitaxel and docetaxel.

TABLE E5. Comparison of patients with ST+ and ST– taxane responses

Characteristics	ST+ response (n = 103*)	ST– response (n = 35*)	P value
Age (y)			.6
Median	60	60	
Range	25-79	29-78	
Sex, no. (%)			1.0
Female	94 (91)	32 (91)	
Male	9 (9)	3 (9)	
Race or ethnic group, no. (%)			.5
White	92 (89)	30 (86)	
Other/unknown	11 (11)	5 (14)	
Cancer site, no. (%)			.5
Ovarian, fallopian, peritoneal	61 (59)	19 (54)	
Endometrial	21† (20)	9 (26)	
Breast	11 (11)	1 (3)	
Prostate	6 (6)	3 (9)	
Other	5‡ (5)	3 (9)	
Cancer stage, no. (%)			1.0
I or II	20 (19)	7 (20)	
III	45 (44)	15 (43)	
IV	38 (37)	13 (37)	
Atopy,‡ no. (%)			.7
Yes	32 (31)	9 (26)	
No	71 (69)	26 (74)	
History of drug-induced§ HSR, no. (%)			.2
Yes	28 (27)	15 (43)	
No	75 (73)	20 (57)	
Prior HSR to non-taxane chemotherapy, no. (%)			1.0
Yes	4 (4)	1 (3)	
No	99 (96)	34 (97)	
Taxane implicated in initial HSR			1.0
Paclitaxel	90 (87)	31 (89)	
Docetaxel	13 (13)	4 (11)	
Taxane cycle causing HSR			.4
Median	1	1	
Range	1-10	1-54	
Patients with recurrent HSR on rechallenge before allergy evaluation			1.0
Yes	16 (16)	5 (14)	
No	87 (84)	30 (86)	
Type and severity of initial HSR			.01
Delayed	26 (25)	13 (37)	
Immediate			
Grade 1	5 (5)	6 (17)	
Grade 2	56 (54)	14 (40)	
Grade 3	16 (16)	2 (6)	

*The patient who converted from an ST– response to an ST+ response was not included in this analysis.

†One patient was given a concomitant diagnosis of endometrial and non-small cell lung cancer.

‡Defined as the presence of any of the following: history of allergic asthma and/or rhinoconjunctivitis, food allergy, atopic dermatitis, or Hymenoptera allergy.

§Any drug except chemotherapeutic agent.

||Comparison between delayed or immediate grade 1 and immediate grade 2 or 3 HSRs.

TABLE E6. Characteristics of patients who resumed regular infusions compared with those who did not

Characteristics	Resumed regular infusions (n = 36)	Did not resume regular infusions (n = 128)	P value
Age (y)			.7
Median	58	59	
Range	29-78	25-81	
Sex, no. (%)			.07
Female	36 (100)	115 (90)	
Male	0	13 (10)	
Race or ethnic group, no. (%)			.8
White	32 (89)	116 (91)	
Other/unknown	4 (11)	12 (9)	
Cancer site, no. (%)			.3
Ovarian, fallopian, peritoneal	24 (67)	70 (55)	
Endometrial	9 (25)	28* (22)	
Breast	2 (6)	14 (11)	
Prostate	0	10 (8)	
Other	1 (3)	7* (5)	
Cancer stage, no. (%)			.8
I or II	7 (19)	25 (20)	
III	14 (39)	56 (44)	
IV	15 (42)	47 (37)	
Atopy, [†] no. (%)			.7
Yes	11 (31)	45 (35)	
No	25 (69)	83 (65)	
History of drug-induced [‡] HSR, no. (%)			.008
Yes	18 (50)	33 (26)	
No	18 (50)	95 (74)	
Prior HSR to non-taxane chemotherapy, no. (%)			1.0
Yes	2 (6)	6 (5)	
No	34 (94)	122 (95)	
Taxane cycle causing HSR			.9
Median	1	1	
Range	1-30	1-54	
Patients with recurrent HSR on rechallenge before allergy evaluation			.1
Yes	2 (6)	22 (17)	
No	34 (94)	106 (83)	
Taxane used for re-exposure			.02
Paclitaxel	36 (100)	104 (81)	
Docetaxel	0	22 (17) [§]	
Other	0	2 (2)	
Type and severity of initial HSR			<.001
Delayed	20 (56)	26 (20)	
Immediate			
Grade 1	7 (19)	5 (4)	
Grade 2	9 (25)	77 (60)	
Grade 3	0	20 (16)	
Skin test result			<.001
Negative	21 (58)	15 (12)	
Positive	11 (31)	92 (72)	
Equivocal	2 (6)	4 (3)	
Not done	2 (6)	17 (13)	

*One patient was given a concomitant diagnosis of endometrial and non-small cell lung cancer.

[†]Defined as the presence of any of the following: history of allergic asthma and/or rhinoconjunctivitis, food allergy, atopic dermatitis, or Hymenoptera allergy.

[‡]Any drug except chemotherapeutic agent.

[§]Three of those patients were also exposed to cabazitaxel.

^{||}Includes nab-paclitaxel and cabazitaxel.

TABLE E7. Multivariate analysis of factors associated with resuming regular infusions

Outcome and contributing factors*	OR	95% CI	P value
Resumed regular infusions			
Negative skin test response [†]	9.6	3.6-25.6	<.001
Delayed or immediate grade 1 initial HSR [‡]	8.2	3.1-21.4	<.001
History of drug-induced HSR [§]	2.2	0.9-5.8	.1

*Taxane used for re-exposure could not be included in the multivariate analysis because no patient who resumed regular infusions was re-exposed to another taxane than paclitaxel.

[†]Compared with any other skin test outcome (positive, equivocal, and not done).

[‡]Compared with patients with initial immediate grade 2 or 3 HSRs.

[§]Any drug except chemotherapeutic agent (compared with no history of drug-induced HSR).