

Management of Hypersensitivity Reactions to Taxanes



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KEYWORDS

- Taxane • Paclitaxel • Docetaxel • Allergy • Hypersensitivity • Skin test
- Desensitization and challenge

KEY POINTS

- The incidence of immediate hypersensitivity reaction (HSR) to taxanes varies greatly between molecules from 10% with paclitaxel to less than 1% with cabazitaxel.
- Two mechanisms could account for immediate HSRs to taxanes: complement activation caused by the emulsifying agents (Cremophor EL and polysorbate 80) used in their formulation and an IgE-mediated reaction.
- Almost all patients who experienced an immediate HSR to taxanes can be safely retreated and many of those do not require desensitization.
- The decision to re-expose a patient to taxanes through desensitization or challenge should be based on the severity of the reaction and on the skin test result.
- Because the risk of recurrent reaction decreases with repeated exposures to taxanes, desensitization protocols can be progressively shortened in patients with good tolerance with the aim of eventually resuming regular infusions.

INTRODUCTION

Paclitaxel (taxol) is a taxane antineoplastic agent that is widely used in the treatment of various types of cancers, such as ovarian, breast, and lung cancer.¹ However, it causes immediate hypersensitivity reactions (HSRs) in around 10% of patients despite premedication with antihistamines and a corticosteroid.^{2–4} Docetaxel (taxotere) is another taxane molecule and is used for treating a wide variety of cancers.⁵ It must also be administered along with a corticosteroid premedication to reduce the incidence of immediate HSRs.^{5–7} The newer taxanes, nanoparticle albumin-bound

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(nab)-paclitaxel (abraxane) and cabazitaxel (jevtana) can also cause immediate HSRs, although more rarely than the older taxanes.^{8–11} This article reviews the clinical presentation, diagnosis, and management of HSRs to taxanes and discusses the different options for their safe readministration.

TERMINOLOGY

The International Consensus on drug allergy defines HSRs as reactions that clinically resemble an allergic reaction even if an immunologic mechanism has not been demonstrated.¹² It also differentiates between immediate and nonimmediate HSRs depending on the onset of the reaction (immediate, ≤ 1 hour after drug administration; nonimmediate, >1 hour). Occasionally, immediate HSRs to taxanes can occur a few hours after the infusion. This terminology is used in this review.

EPIDEMIOLOGY

Table 1 gives a brief description of the different taxanes in clinical use and the incidence of immediate HSRs associated with each molecule.

Paclitaxel

Phase I studies of paclitaxel revealed that a high percentage of patients suffered from immediate HSRs, most commonly during the first administration of the drug.^{13–15} Premedication with antihistamines and a corticosteroid was soon implemented to mitigate this important adverse event.¹³ Currently, around 10% of patients treated with paclitaxel will develop an immediate HSR despite premedication.^{2–4} Two premedication regimens can be used. Both regimens contain an H1 (diphenhydramine) and an H2 (ranitidine, cimetidine, or famotidine) antihistamine given 30 to 60 minutes before the infusion.^{1,4} They differ in that the standard regimen consists of 2 doses of dexamethasone administered the night before and the morning of the infusion, whereas the simplified protocol consists of a single dose of dexamethasone given 30 to 60 minutes before the infusion.⁴ Although the single-dose protocol could entail a slightly higher risk of reaction, both protocols are considered acceptable options for premedication.^{4,16,17}

Docetaxel

Early clinical trials of docetaxel were also complicated by a high incidence of immediate HSRs and by an adverse event specific to this taxane: fluid retention caused by capillary protein leak.^{18–21} Premedication with dexamethasone given for 3 days starting the day before docetaxel administration helped reduce the incidence of immediate HSRs to around 5% and that of fluid retention to between 3.5% and 16.5%.^{6,7,22,23}

Nab-Paclitaxel

Nab-paclitaxel is a newer paclitaxel formulation that does not contain Cremophor EL, which is considered responsible for most immediate HSRs to paclitaxel.^{8,24,25} Thus, it can be infused without premedication and at a faster rate than paclitaxel.⁸ Although, immediate HSRs are much less frequent than with paclitaxel,^{10,11} severe and even fatal reactions have been reported with nab-paclitaxel.⁸ Given its ease of administration and safety profile, nab-paclitaxel is increasingly used in place of conventional paclitaxel despite its much higher cost.²⁶

Table 1
Description of the different taxanes in clinical use

	Paclitaxel	Docetaxel	Nab-Paclitaxel	Cabazitaxel
Solubilizer	Cremophor-EL	Polysorbate 80	Human serum albumin	Polysorbate 80
FDA-approved indications	Ovarian cancer, breast cancer, non-small cell lung carcinoma, AIDS-related Kaposi sarcoma	Breast cancer, prostate cancer, non-small cell lung carcinoma, head and neck cancer, gastric adenocarcinoma	Breast cancer, non-small cell lung carcinoma, pancreatic adenocarcinoma	Prostate cancer
Administration	Over 3 h every 3 wk or over 1 h every week	Over 1 h every 3 wk	Over 30 min every 3 wk or weekly	Over 1 h every 3 wk
Premedication	Diphenhydramine Ranitidine Dexamethasone	Dexamethasone	None	Diphenhydramine Ranitidine Dexamethasone
Incidence of immediate HSR	10%	5%	4%	<1% ^a

Abbreviations: AIDS, acquired immune deficiency syndrome; FDA, US Food and Drug Administration.

^a In patients on concomitant prednisone therapy as part of the treatment regimen for prostate cancer.

Cabazitaxel

Cabazitaxel was developed to treat castration-resistant prostate cancer in patients whose tumor had progressed after treatment with docetaxel.^{9,27} It is administered with premedication consisting of antihistamines and a corticosteroid.⁹ Phase III clinical trials in subjects with prostate cancer did not detect any HSR.^{28,29} This is in contrast with a phase II clinical trial performed on subjects with breast cancer that found a 6% incidence of immediate HSRs.³⁰

PATHOPHYSIOLOGY

Taxanes are poorly soluble molecules. Therefore, to allow intravenous administration, emulsifying agents were used in their formulation: Cremophor EL for paclitaxel and polysorbate 80 for docetaxel and cabazitaxel.^{22,27,31} In contrast, nab-paclitaxel uses human serum albumin to create nanoparticles of paclitaxel molecules.²⁴ Cremophor EL and polysorbate 80 are capable of causing complement activation in vitro and it is hypothesized that through production of anaphylatoxins they could trigger immediate HSRs in vivo, thereby explaining why most patients experience immediate HSRs on first exposure to taxanes if no premedication is used.^{32,33} More recently, the possibility of an immunoglobulin (Ig)E-mediated mechanism has been raised based on the finding that a positive skin test result to paclitaxel and/or docetaxel could be elicited in a subset of patients who had experienced an immediate HSR to these molecules.^{34–37} Also, acute elevations in serum tryptase and 24-hour urine N-methylhistamine have been reported following severe immediate HSRs to taxanes, thus indicating mast cell activation.^{34,38} An IgE-mediated mechanism may be more likely if the HSR was severe and involved flushing.³⁴ Interestingly, patients with a positive skin test result generally experienced the HSR on their first exposure to taxane, raising the possibility that sensitization had occurred beforehand.³⁴ Taxanes molecules can be isolated from yew tree pollen, as well as from hazelnut trees and its nuts, providing potential sources of environmental exposure.^{39,40} Finally, atopy seems to be a risk factor for immediate HSR to taxanes and to increase the risk of a recurrent HSR on re-exposure.^{34,38}

CLINICAL FEATURES

Immediate Hypersensitivity Reactions

Immediate HSRs to taxanes generally occur during the first cycle, within minutes of starting the infusion, and usually resolve promptly after the infusion is stopped.^{3,34,41} Cutaneous symptoms (most commonly flushing) are present in most patients.^{34,41} Chest, back, and abdominal pain are also frequently seen, as well as respiratory symptoms.^{34,41} More severe reactions are characterized by oxygen desaturation and/or hypotension.^{34,41} It is clinically useful to divide immediate HSRs as mild (grade 1), moderate (grade 2), and severe (grade 3) because this classification can guide the strategy used for re-exposure (**Table 2**).^{34,41}

Nonimmediate Hypersensitivity Reactions

Nonimmediate HSRs to taxanes usually consist of a skin eruption, described as maculopapular and sometimes as flushing, with onset from several hours to 15 days after the drug infusion.³⁴ The mechanism of these reactions is unknown but a short course of corticosteroids for several days after the infusion is sometimes used to help prevent a recurrence.³⁴ Although in most patients these HSRs usually abide after several exposures, in some they can be the prelude to an immediate HSR.³⁴ Skin testing could be useful in detecting this particular subset of patients.³⁴ Cases of severe

Table 2
Severity grading of immediate hypersensitivity reactions

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

Adapted from Picard M, Pur L, Caiado J, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol* 2016;137(4):1156; with permission.

nonimmediate HSRs (Stevens-Johnson syndrome, toxic epidermal necrolysis, acute interstitial pneumonitis, and subacute cutaneous lupus erythematosus) have been reported in association with paclitaxel, docetaxel, and nab-paclitaxel.^{8,42–50} Re-exposure to taxanes should not be reattempted in those patients.

DIAGNOSTIC TESTS

Although the diagnosis of an immediate HSR to taxane is usually straightforward, several diagnostic tests can be useful to guide the re-treatment strategy and to sometimes rule out an alternative diagnosis.

Tryptase

It could be useful to measure the serum tryptase level within 4 hours of a severe immediate HSR.³⁴ The result should be compared with a baseline tryptase value, which is usually obtained several days or weeks after the reaction. An increase in the tryptase level by a factor of 1.2 times plus 2 ng/ml compared with baseline would indicate mast cell activation even if the absolute value is equal to or less than 11.4 ng/ml.⁵¹ In addition, if the baseline level is greater than the upper limit of normal, it should prompt an investigation for an underlying mast cell disease.⁵² This information should be taken into account when re-exposing the patient to taxanes by using a more prudent approach in patients with documented elevations in mast cell mediators.³⁴

Skin Testing

Skin testing could be useful to identify a subset of patients in whom an IgE-mediated mechanism is present and who would, therefore, benefit from re-exposure through desensitization.^{34–37} The proportion of patients with an IgE-mediated allergy among all patients with immediate HSRs to taxanes varies greatly between populations from less than 10% to around 70%.^{34,35,53} Therefore, the necessity for a skin test may vary according to the likelihood of eliciting a positive result. As previously mentioned, patients with more severe reactions and those whose reaction involved flushing may be more likely to have a positive skin test result.³⁴ Re-exposure to taxane should never be delayed only to allow skin testing, which should ideally be performed at least 2 weeks after the reaction to avoid false-negative results.³⁴ Skin testing concentrations for paclitaxel are 1 mg/ml for a skin prick test (SPT) and up to 0.01 mg/ml for an intradermal test (IDT).³⁴ For docetaxel, SPT and IDT should be performed at

0.4 mg/ml.³⁴ One group has reported that higher concentrations were nonirritating but they encountered false-positive results with paclitaxel at 6 mg/ml IDT.³⁶ Skin testing with nab-paclitaxel and cabazitaxel has not been studied.

DIFFERENTIAL DIAGNOSIS

Several other medications that are often administered shortly before or after taxanes can elicit immediate HSRs. Ondansetron, an antiemetic drug; ranitidine, an H₂ antihistamine; and dexamethasone, a corticosteroid, are often given shortly before the start of the taxane infusion. IgE-mediated reactions have been reported with these drugs, albeit rarely.^{54–56} The possibility that these medications are the cause of the HSR rather than the taxane should be entertained if atypical features are present. For example, if the reaction occurred after several well-tolerated cycles of taxane or if the reaction recurred despite desensitization and very early in its course (eg, during step 1), one should evaluate the possibility that a drug given as premedication is responsible for the reaction through skin testing. Carboplatin is often given right after the end of the taxane infusion and is associated with an increasing incidence of immediate HSRs from the sixth cycle onwards.^{57,58} Therefore, immediate HSRs that occur during or shortly after the end of the carboplatin infusion are more likely to be caused by this medication, especially if prior taxane cycles were well tolerated.³⁴ Finally, dexamethasone can cause facial flushing with onset, usually several hours after intake, which lasts for several days.⁵⁹ However, this condition is usually benign and does not require any treatment.

RE-EXPOSURE TO TAXANES AFTER A HYPERSENSITIVITY REACTION

Almost all patients, regardless of the severity of the immediate HSR, can be safely re-exposed to taxanes either through desensitization or a regular infusion.^{3,34,41} Also, the risk of having a recurrent reaction steadily decreases with repeated exposures regardless of the method used for re-exposure.^{3,13,34,41} After an immediate HSR, many patients will tolerate the next infusion through a regular infusion without the need for desensitization.^{3,13,36,41} However, depending on the population studied, a significant proportion of patients will have a recurrent HSR with this approach that is sometimes more severe than the initial reaction.^{34,36,41} Also, it may be difficult to convince a patient with a recent HSR to receive the same medication without any additional precaution.³⁶ In contrast, desensitization using the 3-bag, 12-step desensitization protocol developed at Brigham and Women's Hospital and Dana-Farber Cancer Institute (BWH-DFCI) has been shown to be safe and has a very high success rate, allowing patients with HSR of any severity to be retreated with taxanes.^{34,38,60,61} A suggested approach to taxane reintroduction is depicted in **Fig. 1**. It is generally agreed that the severity of the initial HSR should guide the method chosen for re-exposure: desensitization versus challenge.^{3,34,36,41} In addition, skin testing could also be useful because a positive skin test result may indicate an IgE-mediated mechanism and thus a higher risk of reaction on re-exposure.^{34,35} Therefore, patients with a positive skin test result should be retreated as if they had a severe HSR (see **Fig. 1**). Patients with mild reactions are often rechallenged by their treating oncologist and referred to an allergy specialist only in the event of a recurrent HSR.^{3,41} Almost all patients with mild HSRs tolerate a rechallenge and can safely continue treatment with regular infusions.^{3,41} In contrast, even if some patients with a severe HSR can tolerate a rechallenge without reaction, it is generally advisable to re-expose those patients through desensitization.^{34,41} A 3-bag, 12-step protocol or, in very severe cases, a 4-bag, 16-step protocol can be used (**Table 3**).³⁴ If no HSR occurs with desensitization,

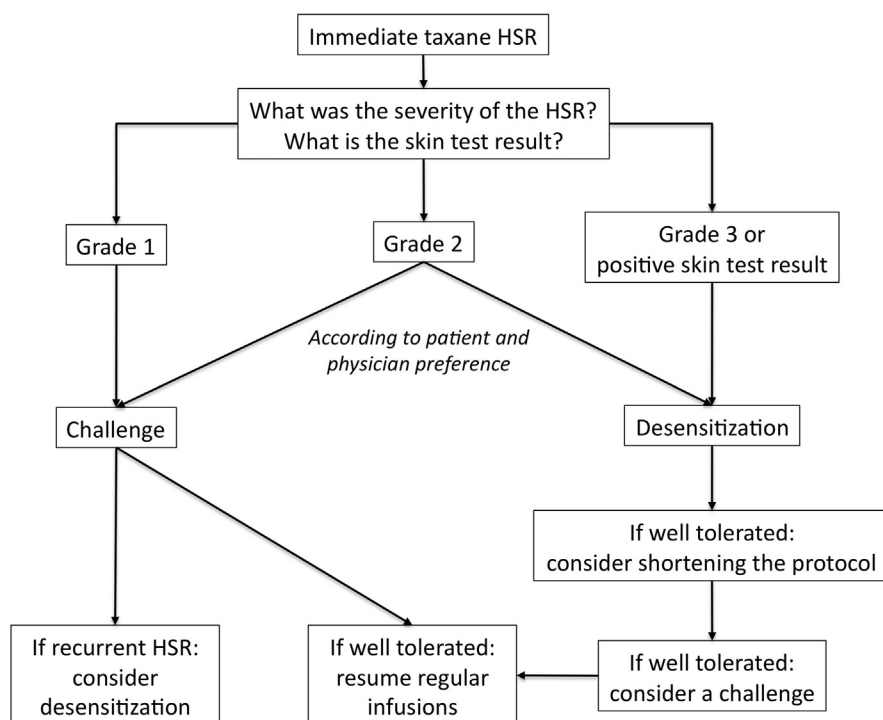


Fig. 1. Suggested approach to taxane re-exposure in patients who experienced an immediate HSR.

the protocol could then be progressively shortened by cutting 1 bag at a time and/or by increasing the final infusion rate to 160 mL/h.³⁴ If a 1-bag desensitization protocol is well-tolerated, a challenge procedure can be attempted and, if well-tolerated, the patient could then resume regular infusions (Table 4).³⁴ For patients with a moderate HSR, the decision between desensitization and challenge is often made on a case-by-case basis. For example, if the patient is reluctant to undergo retreatment with taxanes because of the fear of a recurrent HSR, despite adequate reassurance, or if the physician, based on personal experience, considers that there is a significant risk of recurrent reaction, a desensitization protocol should be chosen.³⁴

DESENSITIZATION PROTOCOLS AND PREMEDICATION

Various desensitization protocols for taxanes have been studied with variable safety outcomes.^{3,7,36,37,62–64} The BWH-DFCI 3-bag, 12-step protocol has been the most studied and has an excellent safety record (see Table 3).^{34,38,60,61} Patients are premedicated, as for regular infusions, before these procedures, which should be performed with a 1-to-1 nursing ratio and under the supervision of an allergist with expertise in drug desensitization.³⁴ When second-generation antihistamines are available, it is customary to replace diphenhydramine with cetirizine.³⁴ In patients with a severe HSR or with a recurrent HSR despite desensitization, it may be useful to add a single dose of montelukast (10 mg) and/or aspirin (325 mg) 30 to 60 minutes before the infusion to the premedication regimen.^{34,65} To alleviate the anxiety associated with these procedures, a benzodiazepine such as lorazepam can be used.³⁴ Approximately

Table 3
Desensitization protocols for taxanes

Example with paclitaxel 250 mg

Volume per bag: 250 mL

Bag A: contains total dose minus cumulative dose administered with previous bags (eg, 250 mg minus (varies depending on the protocol from 1.875 to 1.973 mg)/250 mL)

Bag B: contains 1/10th of the total dose to be administered (eg, 25 mg/250 mL)

Bag C: contains 1/100th of the total dose to be administered (eg, 2.5 mg/250 mL)

Bag D: contains 1/1000th of the total dose to be administered (eg, 0.25 mg/250 mL)

Only Bag A is completely infused. A fraction of the total volume of Bags B, C and D is infused to the patient. What remains is discarded.

Protocols				4-bag	3-bag	2-bag	1-bag
Bag	Step	Infusion rate (mL/h)	Time (minutes)	Cumulative Dose (mg)	Cumulative Dose (mg)	Cumulative dose (mg)	Cumulative dose (mg)
D	1	2.5	15	0.0006	NA	NA	NA
D	2	5	15	0.001	NA	NA	NA
D	3	10	15	0.002	NA	NA	NA
D	4	20	15	0.005	NA	NA	NA
C	5	2.5	15	0.011	0.005	NA	NA
C	6	5	15	0.023	0.018	NA	NA
C	7	10	15	0.048	0.043	NA	NA
C	8	20	15	0.098	0.093	NA	NA

B	9	5	15	0.223	0.218	0.125	NA
B	10	10	15	0.473	0.468	0.375	NA
B	11	20	15	0.973	0.968	0.875	NA
B	12	40	15	1.973	1.968	1.875	NA
A	13	10	15	4.454	4.448	4.356	2.5
A	14	20	15	9.414	9.409	9.319	7.5
A	15	40	15	19.335	19.330	19.244	17.5
A	16	80	174	250	250	250	250
The final infusion rate can be increased to 120 mL/h and then to 160 mL/h if well tolerated, waiting 15 min between steps.							
Duration of the protocols (hours) compared with a regular infusion (3 h)							
4-bag: 6.7							
3-bag: 5.7							
2-bag: 4.7							
1-bag: 3.7							
Increasing the final infusion rate to 160 mL/h reduces the duration of the protocol by approximately 1 hour.							

Abbreviation: NA, not applicable.

Data from Picard M, Pur L, Caiado J, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol* 2016;137(4):1154–64.e1–12.

Table 4
Challenge protocols for taxanes

Paclitaxel (135–175 mg/m²) Infused Every 3 wk Over 3 h (Example = 294 mg)						
<u>Bag</u>	<u>Volume (mL) per Bag</u>	<u>Concentration (mg/mL) per Bag</u>	<u>Amount (mL) of Bag Infused</u>	<u>Dose Infused (mg) per Bag</u>		
<u>Solution 1</u>	<u>250</u>	<u>1.176</u>	<u>250</u>	<u>294</u>		
<u>Step</u>	<u>Solution</u>	<u>Rate (mL/h)</u>	<u>Time (min)</u>	<u>Volume Infused (mL)</u>	<u>Dose Infused (mg) per Step</u>	<u>Cumulative dose (mg)</u>
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 (hours) = 3.59						
Paclitaxel (50–80 mg/m²) Infused Weekly Over 1 h (Example = 134 mg)						
<u>Bag</u>	<u>Volume (mL) per Bag</u>	<u>Concentration (mg/mL) per Bag</u>	<u>Amount (mL) of Bag Infused</u>	<u>Dose Infused (mg) per Bag</u>		
<u>Solution 1</u>	<u>250</u>	<u>0.536</u>	<u>250</u>	<u>134</u>		
<u>Step</u>	<u>Solution</u>	<u>Rate (mL/h)</u>	<u>Time (min)</u>	<u>Volume Infused (mL)</u>	<u>Dose Infused (mg) per Step</u>	<u>Cumulative Dose (mg)</u>
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	290.315	294.0
Total time (hours) = 1.47						

Data from Picard M, Pur L, Caiado J, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol* 2016;137(4):1154–64.e1–12.

20% of patients who undergo desensitization to taxanes will experience an immediate HSR, most commonly during the last step of the protocol.³⁴ However, these reactions are usually mild and almost never severe.³⁴ With repeated exposures, the risk of recurrent reactions steadily decreases to around 2%.³⁴

CHALLENGE PROCEDURE

The goal of the challenge procedure is to insure that the patient will thereafter tolerate a regular infusion of the drug while minimizing the risks associated with such a reaction (see [Table 4](#)). One bag of the medication is prepared as if it was to be administered through a regular infusion protocol.³⁴ However, the infusion is started at a 10-fold to 100-fold slower rate than the regular infusion for 15 minutes, then increased to the regular infusion rate by 10-fold increments.³⁴ Premedication should be administered as for a regular infusion.³⁴

CURRENT CONTROVERSIES

Taxane skin testing remains controversial because most immediate HSRs to these molecules are considered non-IgE-mediated.⁴¹ It is also unclear if the risk of recurrent reaction on re-exposure is increased in patients with a positive skin test result because those patients are usually treated more conservatively than those with a negative result.³⁴ Another caveat is that the proportion of patients with a positive skin test result varies greatly depending on the population studied.^{34–36} Therefore, in a population in which a positive result on taxane skin testing is rare, it may not be necessary to routinely skin test all patients with a taxane HSR. Finally, skin testing may not be feasible in patients who receive weekly treatments of paclitaxel.³⁴ Skin testing is most useful when it affects the retreatment strategy used in a particular patient.³⁴ For example, a patient who experiences a recurrent HSR on re-exposure, either through challenge or desensitization, could benefit from skin testing. If skin testing is positive, it likely indicates an IgE-mediated phenomenon and it argues for pursuing desensitization procedures. In contrast, if skin testing is negative, it remains possible that the patient will eventually tolerate regular infusions and a challenge procedure could be reattempted. Likewise, a patient with a severe HSR would benefit from skin testing because, if it were negative, a challenge procedure could be attempted once tolerance to desensitization is established, whereas, if it were positive, a challenge would be discouraged even if the patient tolerates desensitization.³⁴

Because many patients with an immediate taxane HSR tolerate re-exposure through a regular infusion, it remains to be defined which patients truly benefit from desensitization.^{3,36,41} Some investigators consider desensitization only in patients with a recurrent reaction on rechallenge or who suffered a severe HSR.^{3,36} Recently, Banerji and colleagues⁴¹ reviewed all cases of patients with immediate HSRs to paclitaxel at Massachusetts General Hospital over a 5-year period. They concluded that patients with mild reactions (flushing and/or back pain) could be safely rechallenged, albeit at half the normal infusion rate, and that patients with moderate to severe reactions should be re-exposed through desensitization.⁴¹ It should be kept in mind that severe HSRs, some fatal, have been described during rechallenge procedures to paclitaxel despite a slower infusion rate and added premedication.^{13,36,41,66} In contrast, the safety of desensitization to taxanes using the BWH-DFCI protocol has been clearly established.^{34,38,60,61}

SUMMARY

Although immediate HSRs to taxanes are common, they should not lead to drug discontinuation because almost all patients can be safely retreated with these molecules either through desensitization or rechallenge. The severity of the HSR and the taxane skin test result can help the clinician decide between these 2 options. Future studies on the subject will certainly allow a better understanding of these HSRs and will help refine the approach to retreatment.

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