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.

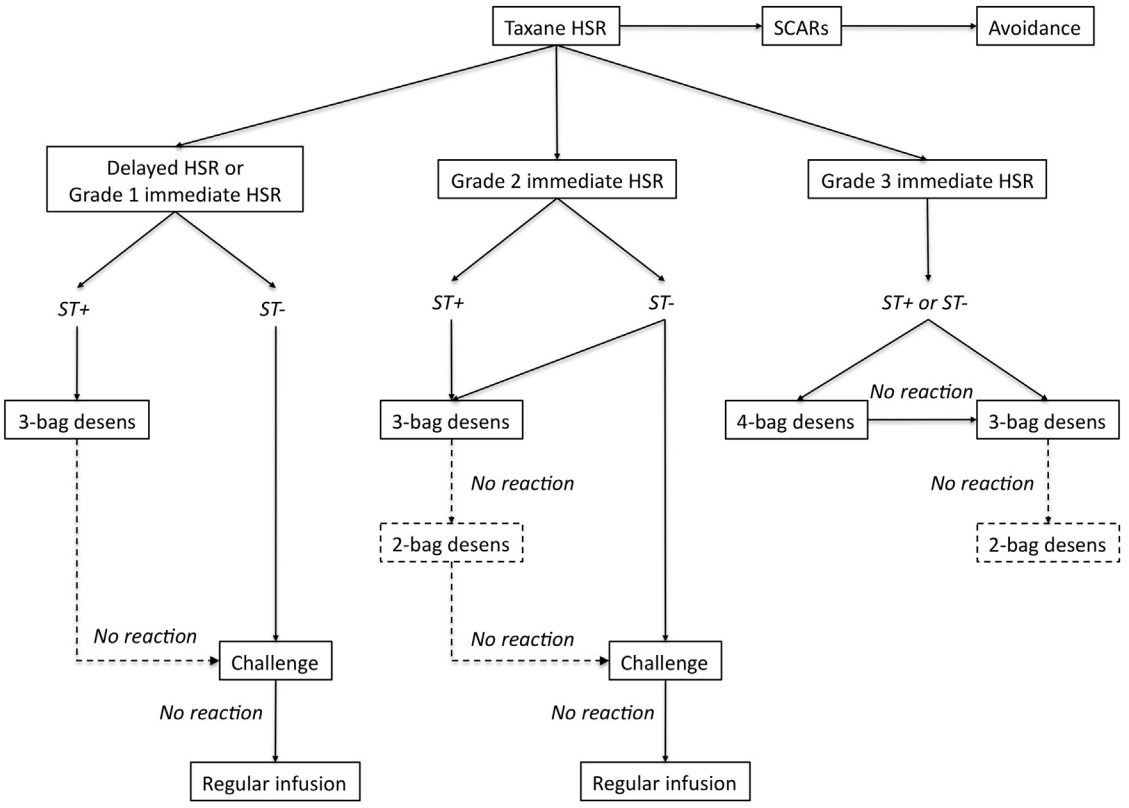

FIG 1. Approach to taxane reintroduction in patients with HSRs. In patients with an HSR with desensitization or challenge, premedication is generally adjusted for the next procedure, which is administered by using either the same or a longer protocol. Patients in whom the HSR does not recur are then 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.