Original Article

Utility of Risk Stratification for Paclitaxel Hypersensitivity Reactions

Iris M. Otani, MD[a], Timothy Lax, MD[b], Aidan A. Long, MD[c], Benjamin R. Slawski, NP[c], Carlos A. Camargo, Jr., MD, DrPH[d], and Aleena Banerji, MD[c] *San Francisco, Calif; and Boston, Mass*

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 2017;■:■-■)

Key words: *Paclitaxel hypersensitivity; Paclitaxel reaction; Paclitaxel allergy; Chemotherapy allergy; Chemotherapy hypersensitivity; Chemotherapy; Desensitization; Chemotherapy desensitization*

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

[a]Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, University of California San Francisco, San Francisco, Calif
[b]Division of Allergy and Inflammation, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass
[c]Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Mass
[d]Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Corresponding author: Iris M. Otani, MD, UCSF Medical Center, 400 Parnassus Ave, Box 0359, San Francisco, CA 94143. E-mail: iris.otani@ucsf.edu.

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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 al[10] 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]

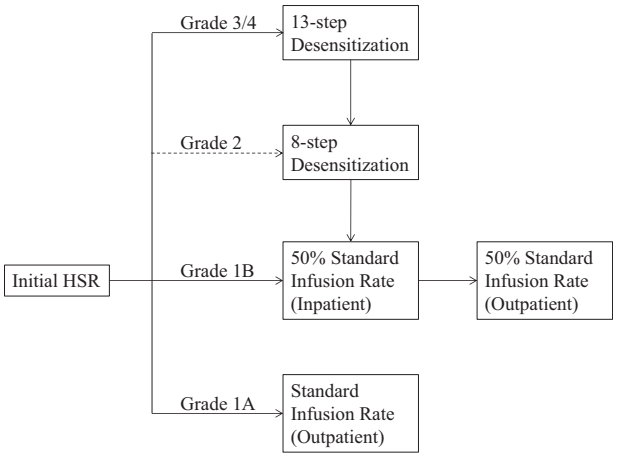

FIGURE 1. Risk stratification protocol for paclitaxel-induced HSRs based on the grade of the initial HSR. Grade 3 or 4 HSRs were considered high risk and patients were risk stratified to receive paclitaxel using 13-step desensitization. Patients with grade 2 HSRs were risk stratified to receive paclitaxel 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.