

Role of Skin Tests in the Diagnosis of Immediate Hypersensitivity Reactions to Taxanes: Results of a Multicenter Study



Mauro Pagani, MD^a, Sevim Bavbek, MD^b, Adile Berna Dursun, MD^c, Patrizia Bonadonna, MD^d, Maria Caralli, MD^e, Josefina Cernadas, MD^f, Gabriele Cortellini, MD^g, Maria Teresa Costantino, MD^h, Asli Gelincik, MDⁱ, Giuseppe Lucchini, MD^j, and Mariana Castells, MD, PhD^k Mantua, Verona, Rimini, Italy; Ankara and Istanbul, Turkey; Madrid, Spain; Porto, Portugal; and Boston, Mass

What is already known about this topic? The role of skin tests in the diagnosis of hypersensitivity reactions (HSRs) to taxanes is not clear. Some experiences with discordant results are reported in scientific literature.

What does this article add to our knowledge? In this prospective multicenter study, we analyzed 84 patients with HSRs to paclitaxel or docetaxel, observing a 16.7% rate of positive intradermal test results, especially in subjects with severe reactions involving the skin.

How does this study impact our current management guidelines? Skin tests for taxanes are useful in the allergological workup, in particular for patients with grade 3 reactions that appear with cutaneous symptoms. Graded challenge and desensitization are useful procedures for subsequent treatment.

BACKGROUND: Immediate hypersensitivity reactions (HSRs) to taxanes have been increasing in recent years, but the importance of skin tests in allergological workup has not been established.

OBJECTIVE: In our study we tried to evaluate the role of prick and intradermal tests in the diagnosis of HSRs to paclitaxel and docetaxel.

METHODS: In this multicenter prospective study, we enrolled patients with immediate HSRs to the aforesaid agents. Skin tests

were performed on these subjects and if results were negative, intradermal tests with the culprit drug were conducted. Patients with grade 1 reactions subsequently underwent graded challenge; in cases of grade 2 or 3 reactions and/or positive test results, the culprit drug was administered with a desensitization schedule. Skin tests were also performed in 30 control subjects exposed to the taxanes without HSRs.

RESULTS: A total of 84 patients (63 with HSRs to paclitaxel and 21 to docetaxel) were recruited in the period July 2015 to July 2017 by 8 centers; 58 patients (69%) developed grade 2 or 3 reactions. Prick test results were negative in all the cases, whereas intradermal test results were positive in 14 patients (10 with paclitaxel [15.9%] and 4 with docetaxel [19%]). The positivity of skin tests significantly correlated with grade 3 reactions and cutaneous involvement during HSRs. Graded challenge was performed in 16 patients without problems and 58 subjects underwent desensitization, which was well tolerated in all but 2 cases. In the control group, skin test results were negative in all the patients. **CONCLUSIONS:** Skin tests for taxanes seem useful and can be performed in the allergological workup of subjects with HSRs to these agents, especially in cases of severe reactions with cutaneous involvement. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:990-7)

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INTRODUCTION

Hypersensitivity reactions (HSRs) to chemotherapy have been increasing in recent years and represent a crucial obstacle to the standard treatment of cancer patients, because they prevent the

^aMedicine Ward, Medical Department ASST of Mantova, Mantua, Italy

^bDivision of Immunology and Allergy, Department of Chest Diseases, Ankara University School of Medicine, Ankara, Turkey

^cRecep Tayyip Erdogan Üniversitesi, Department of Chest Disease, Ankara, Turkey

^dAllergy Unit, Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

^eAllergy Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain

^fAllergy Department, University Hospital S.João, Porto, Portugal

^gInternal Medicine and Rheumatology Department, Azienda Sanitaria Romagna, Rimini Hospital, Rimini, Italy

^hAllergy Unit, Medical Department, ASST of Mantova, Mantua, Italy

ⁱIstanbul Faculty of Medicine, Department of Internal Medicine, Division of Immunology and Allergic Diseases, Istanbul University, Istanbul, Turkey

^jBiostatistical Service ASST of Mantova, Mantua, Italy

^kDivision of Rheumatology, Immunology and Allergy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass

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Corresponding author: Mauro Pagani, MD, Via Bugatte, 1 46020 Borgo Mantovano, Mantova, Italy. E-mail: mauro.pagani@asst-mantova.it.

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Abbreviations used

HSR-hypersensitivity reaction

*ST--*negative skin test result

*ST+-*positive skin test result

administration of the most efficacious drugs against neoplasms. In this scenario, taxanes are a class of chemotherapeutic drugs particularly responsible for this type of adverse effect, which are even lethal in some cases.^{1,2}

Taxanes are used in clinical practice for the treatment of a number of cancers, namely, gynecological malignancies and breast, lung, and prostate cancers.³

The taxane group includes paclitaxel and the newer formulations of nab-paclitaxel, docetaxel, and cabazitaxel.

Paclitaxel is a natural compound derived from the bark of the Pacific yew tree (*Taxus brevifolia*). Antineoplastic activity occurs by interfering with the dynamics of microtubules and causes mitotic inhibition and cell death. The drug formulation includes Cremophor EL, a solubilizer and emulsifying agent, and was introduced into clinical practice in the 1980s.^{4,5} Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a newer, different paclitaxel formulation that does not contain Cremophor EL, which has been replaced by serum albumin to encapsulate paclitaxel molecules in particles of 130 nm.⁶ Nab-paclitaxel was developed in an attempt to reduce the toxicity associated with conventional taxane formulations, namely, HSRs.⁷ Docetaxel was synthesized at the end of 1980s in the search for a more soluble product. It is extracted from *Taxus baccata*, but despite a higher solubility than paclitaxel, its drug formulation requires polysorbate 80, a solubilizing agent, for intravenous administration.⁸ Along with Cremophor EL, it is considered responsible for HSRs to paclitaxel; therefore, polysorbate 80 is believed to be the cause of immediate HSRs to docetaxel.⁹

Cabazitaxel was developed to overcome tumor drug resistance to other taxanes and just like docetaxel is prepared with polysorbate 80. It is used in the treatment of resistant metastatic prostate cancer.¹⁰

Immediate HSRs to taxanes, namely, paclitaxel and docetaxel, used to occur in about 50% of patients, usually during the first or second administration. They usually develop within minutes of starting the infusion and include symptoms such as throat tightness, flushing, hypotension, dyspnea, and chest or back pain.¹¹

Premedication with antihistamines and steroids for paclitaxel and only with steroids for docetaxel dramatically reduced the risk of HSRs to less than 10%, even if severe reactions were reported in about 1% of cases.¹²⁻¹⁶

It is generally accepted that immunopathogenesis of these reactions is caused by the surfactants used in the formulations of taxanes, by their direct activation of complement cascade or basophils and/or mast cells.^{17,18} However, in recent years, some observations, such as the positivity of skin tests in subsets of patients with immediate HSRs to taxanes or the development of severe HSRs caused by nab-paclitaxel,¹⁹ suggest that the pathogenesis of immediate HSRs to taxanes involves different mechanisms and structures, including the taxane moiety, and an IgE-mediated pathomechanism could be involved in some cases.²⁰

The role of skin tests in the diagnosis of HSRs to taxanes has not been yet well established. Some authors observed a greater percentage of positivity in patients with immediate reactions to taxanes, but other reports did not confirm these data.²¹⁻²⁴

Therefore, in an effort to better clarify the role of skin tests in the allergological workup of patients with reactions to taxanes, the European Network of Drug Allergy, one of European Academy of Allergy and Clinical Immunology's interest groups, conducted a prospective multicenter study to evaluate and analyze the results of skin tests in these types of patients. Secondary aims were the safety of desensitization and graded challenge with the culprit drugs of HSRs and research into factors eventually correlated with the results of tests or predictors of HSRs.

METHODS

The study was approved by ethics committees of all the interested centers. Patients older than 18 years with a documented taxane-induced immediate HSR and who were capable of giving informed consent were recruited in the July 2015 to July 2017 period. Immediate HSRs were defined as an adverse reaction with onset during the infusion or within 1 hour from its completion and with features suggestive of mast cell/basophil degranulation. The severity of immediate HSRs was graded according to the Brown classification²⁵ (Table I). Patients with severe cutaneous adverse drug reactions (eg, desquamative/blistering skin reactions) were advised to avoid all taxanes.

Skin tests were conducted as follows: For a positive control, a prick test with a solution of histamine hydrochloride (10 mg/mL) was used, whereas for the negative control a physiological saline solution was used. Prick tests were then carried out with a solution of taxanes at a concentration of 6 mg/mL for paclitaxel and 1 mg/mL for docetaxel. In the case of a negative result in the prick test, an intradermal test with 0.03 mL of paclitaxel with a concentration of 0.06 mg/mL and 0.03 mL of docetaxel with a concentration of 0.01 mg/mL was performed. Each test was read 15, 20, and 30 minutes after administration. According to the recommendations of the European Academy of Allergy and Clinical Immunology, the prick test result was considered positive when the cutaneous response was a wheal of at least 3 mm with surrounding flare, whereas the intradermal test result was considered positive with a wheal of at least 5 mm with surrounding flare. The subjects were then observed again in the following days (24 and 72 hours after the test) to establish whether there were any possible delayed reactions.²⁶ Skin tests were carried out at least 2 weeks after the HSR to minimize the possibility of a false-negative result, as previously described.²¹ In addition, skin tests were performed in 30 subjects exposed to taxanes without HSRs as control group.

In a second phase, if alternative antineoplastic agents were not available, the culprit drug was administered as follows:

For patients with grade 1 HSRs and negative skin test results, a graded challenge was performed, whereas in the case of grade 2 or 3 HSRs and/or positive skin test results, patients underwent a desensitization schedule.

For the graded challenge, the drug was administered at 10 mL/h for the first hour. If tolerated, the rest of the drug was administered according to manufacturer's instructions.

For desensitization, the drug was injected according to the classical 12-step procedure.²⁷

TABLE I. Severity grading system of immediate HSRs

Grade	Severity	Description
I	Mild	Symptoms are limited to the skin (eg, flushing) or involve a single organ/system and are mild (eg, mild back pain)
II	Moderate	Symptoms involve at least 2 organs/systems (eg, flushing and dyspnea), but there is no significant decrease in blood pressure or oxygen saturation
III	Severe	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 (<92%)

TABLE II. Characteristics of patients with HSRs

Variable	HSR to paclitaxel	HSR to docetaxel	OR	95% CI OR	χ^2	P value
Age (y), mean $\pm$ SD	55.2 $\pm$ 11.4	59.8 $\pm$ 10.4				
Sex, n (%)						
Male	5 (7.9)	5 (23.8)	3.625	0.933-14.089	3.784	.052
Female	58 (92.1)	16 (76.2)				
Cancer site, n (%)						
Breast	33 (52.4)	13 (61.9)				
Endometrium	9 (14.3)	1 (4.8)				
Ovary	12 (19.0)	1 (4.8)				
Prostate	0 (0.0)	2 (9.5)				
Lung	3 (4.8)	4 (19.0)				
Peritoneum	1 (1.6)	0 (0.0)				
Kaposi's sarcoma	1 (1.6)	0 (0.0)				
Bladder	1 (1.6)	0 (0.0)				
Testis	1 (1.6)	0 (0.0)				
Esophagus	1 (1.6)	0 (0.0)				
Colon	1 (1.6)	0 (0.0)				
Atopy, n (%)						
Yes	23 (36.5)	4 (19.0)	2.444	0.733-8.145	2.201	.138
No	40 (63.5)	17 (81.0)				
Resected, n (%)						
Yes	46 (73.0)	17 (81.0)	0.637	0.187-2.163	0.529	.467
No	17 (27.0)	4 (19.0)				
Metastatic, n (%)						
Yes	46 (73.0)	14 (66.7)	1.353	0.467-3.922	0.311	.577
No	17 (27.0)	7 (33.3)				
Drug allergy, n (%)						
Yes	16 (25.4)	5 (23.8)	1.089	0.344-3.452	0.021	.844
No	47 (74.6)	16 (76.2)				
Cutaneous reaction, n (%)						
Yes	40 (63.5)	15 (71.4)	0.696	0.237-2.042	0.439	.508
No	23 (36.5)	6 (28.6)				
Cardiovascular reaction, n (%)						
Yes	29 (46.0)	8 (38.1)	1.386	0.505-3.807	0.403	.526
No	34 (54.0)	13 (61.9)				
Respiratory reaction, n (%)						
Yes	35 (55.6)	10 (47.6)	1.375	0.511-3.701	0.399	.528
No	28 (44.4)	11 (52.4)				
Other reactions, n (%)						
Epigastralgia	4 (20.0)	1 (20.0)			1.250	.535
Back pain	12 (60.0)	4 (80.0)				
Nausea	4 (20.0)	0 (0.0)				

OR, Odds ratio.

TABLE III. Number of exposures to taxanes at time of reaction

Taxane	n	%	Cumulative %
Paclitaxel			
1	35	55.6	55.6
2	20	31.7	87.3
3	1	1.6	88.9
4	5	7.9	96.8
6	1	1.6	98.4
10	1	1.6	100.0
Total	63	100	
Docetaxel			
1	7	33.3	33.3
2	9	42.9	76.2
3	3	14.3	90.5
4	2	9.5	100.0
Total	21	100	

Statistical analysis

Comparisons were made for categorical variables by using nonparametric tests. A *P* value of less than .05 was considered significant.

Multivariate analysis with dichotomous variables was performed by using binary logistic regression. Statistical analysis was performed with IBM SPSS statistical software (Chicago, III, version 25).

RESULTS

Eighty-four patients with immediate HSRs to paclitaxel and docetaxel from 8 different centers were enrolled in the July 2015 to July 2017 period (Table II). Sixty-three had reactions associated with paclitaxel, 21 with docetaxel. Median age was 57 years; most patients were female (74 [88.1%]) especially in the group exposed to paclitaxel (58 [92.1%]), whereas in the patients with HSRs to docetaxel there were 16 females (76.2%). The most involved neoplasm was breast cancer (46 [54.8%]), followed by ovarian (13 [15.5%]) and endometrium (10 [11.9%]) cancer; the antineoplastic agents were administered in an adjuvant setting in 24 cases (60 in metastatic stage). A history of atopy (allergic rhinitis, allergic conjunctivitis, allergic asthma, atopic dermatitis, or food allergy) was detected in 27 cases (32%), with prevalence in the paclitaxel group being 23 [36.5%] with respect to the docetaxel group (4 [19%]). HSRs developed in correspondence of first infusion and second infusion in 71 (84.5%) cases, during third, fourth, or sixth administration in other 12 cases, whereas, surprisingly, 1 woman reacted at the tenth infusion of paclitaxel (Table III). All the patients experienced only 1 HSR, of which 58 (69%) were grade 2 or 3, 46 with paclitaxel (73.0%) and 12 with docetaxel (57.1%) (Table IV). The modality of presentation of HSRs was similar in the 2 groups of patients (Figure 1).

Prick test results were negative in all patients, whereas intradermal test results were positive in 14 patients (16.7%), 10 with paclitaxel (15.9%) and 4 with docetaxel (19%). The characteristics of these patients are reported in Table V. Patients with grade 1 or 2 immediate HSRs were significantly less likely to have positive skin test results (ST+) than patients with an immediate grade 3 HSR (10.7 vs 28.6%; $\chi^2(1) = 4286$; *P* = .038; odds ratio, 0.300; 95% CI, 0.092-0.975).

TABLE IV. Relationship between type of taxane and grade of reactions*

		Taxane		
Grade		Paclitaxel	Docetaxel	Total
1				
Count		17	9	26
% within taxane		27.0%	42.9%	31.0%
2				
Count		23	7	30
% within taxane		36.5%	33.3%	35.7%
3				
Count		23	5	28
% within taxane		36.5%	23.8%	33.3%
Total				
Count		63	21	84
% within taxane		100.0%	100.0%	100.0%

* $\chi^2(2) = 2.088$; *P* = .352.

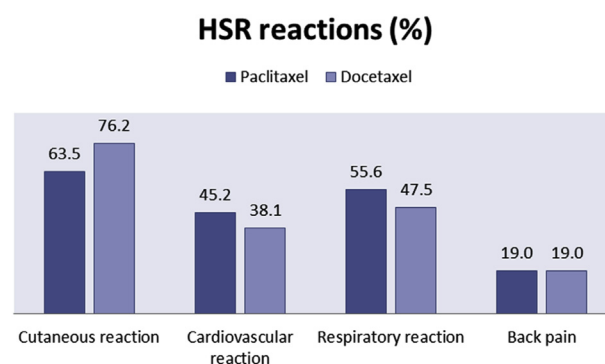


FIGURE 1. Type of HSR (%).

Immediate HSRs experienced by patients with ST+ were more frequently characterized by cutaneous symptoms compared with those with negative skin test results (ST-) (23.6% vs 3.4%; $\chi^2(1) = 5572$; *P* = .018; odds ratio, 8.667; 95% CI, 1.073-70.028). However, we did not observe a significant predictor of HSRs in the 84 patients analyzed (Table VI). Regarding the control group, skin testing was performed in 30 subjects exposed to taxanes without HSRs (Table VII) and results were negative in all cases. Two-sided 95% score CIs for sensitivity and specificity was (8.7%-24.6%) and (100.0%-100.0%), respectively (Table VIII).

Graded challenge was performed in 16 patients with grade 1 HSRs and ST-, whereas 58 patients with grade 2 or 3 reactions and/or ST+ underwent desensitization. The latter was safe and well tolerated and permitted the administration of the planned schedule of chemotherapy in all patients, for a total of 252 procedures. We observed minor adverse effects in 30 patients and only in 2 cases of treatment with paclitaxel desensitization did grade 2 reactions develop during the ninth step of the procedure but resolved quickly after we stopped the procedure temporarily, followed by infusions of steroids and antihistamines. One of these 2 patients presented a grade 3 HSR and ST-, whereas the other subject had a grade 2 HSR with positive intradermal test

TABLE V. Characteristic of patients with respect to outcome of intradermal test

Variable	Positive	Negative	OR	95% CI OR	χ^2	P value
Age (y), mean $\pm$ SD	58.9 $\pm$ 10.0	55.8 $\pm$ 11.5				
Sex, n (%)						
Female	12 (85.7)	62 (88.6)	0.774	0.146-4.105	0.091	.763
Male	2 (14.3)	8 (11.4)				
Cancer site, n (%)						
Breast	7 (50.0)	39 (55.7)				
Endometrium	1 (7.1)	9 (12.9)				
Ovary	1 (7.1)	12 (17.1)				
Prostate	1 (7.1)	1 (1.4)				
Lung	2 (14.3)	5 (7.1)				
Peritoneum	1 (7.1)	0 (0.0)				
Kaposi's sarcoma	0 (0.0)	1 (1.4)				
Bladder	1 (7.1)	0 (0.0)				
Testis	0 (0.0)	1 (1.4)				
Esophagus	0 (0.0)	1 (1.4)				
Colon	0 (0.0)	1 (1.4)				
Atopy,* n (%)						
Yes	5 (35.7)	22 (31.4)	1.212	0.364-4.041	0.098	.754
No	9 (64.3)	48 (68.6)				
Resected, n (%)						
Yes	9 (64.3)	54 (77.1)	0.533	0.156-1.820	1.029	.310
No	5 (35.7)	16 (22.9)				
Metastatic, n (%)						
Yes	11 (78.6)	49 (70.0)	1.571	0.397-6.216	0.420	.517
No	3 (21.4)	21 (30.0)				
Drug allergy, n (%)						
Yes	2 (14.3)	19 (27.1)	447	0.092-2.187	1.029	.310
No	12 (85.7)	51 (72.9)				
Cutaneous reaction, n (%)						
Yes	13 (92.6)	42 (60.0)	8.667	1.073- 70.028	5.572	.018
No	1 (7.1)	28 (40.0)				
Cardiovascular reaction, n (%)						
Yes	8 (57.1)	29 (41.4)	1.885	0.591-6.016	1.169	.280
No	6 (42.9)	41 (58.6)				
Respiratory reaction, n (%)						
Yes	10 (71.4)	35 (50.0)	2.500	0.716-8.731	2.154	.142
No	4 (28.6)	35 (50.0)				
Other reactions, n (%)						
Epigastralgia	1 (16.7)	4 (21.1)			0.055	.973
Back pain	4 (66.7)	12 (63.2)				
Nausea	1 (16.7)	3 (15.8)				
Grade level, n (%)						
Grade 1-2	6 (42.9)	50 (71.4)	0.300	0.092-0.975	4.286	.038
Grade 3	8 (51.7)	20 (28.6)				
Taxane, n (%)						
Paclitaxel	10 (71.4)	53 (75.7)	0.802	0.223-2.889	0.114	.735
Docetaxel	4 (28.6)	17 (24.3)				
Desensitization, n (%)						
Paclitaxel	12 (85.7)	46 (65.7)	3.130	0.647-15.141	2.184	.139
Docetaxel	2 (14.3)	24 (34.3)				
Graded challenge, n (%)						
Yes	0 (0.0)	16 (22.9)	1.259	1.116-1.421	3.953	.047
No	14 (100.0)	54 (77.1)				

OR, Odds ratio.

*In the general population, atopy prevalence is 20%; in our sample, it is 32%.

TABLE VI. Logistic regression predicting likelihood of positive outcome of intradermal test

Variable	B	SE	Wald	df	P value	OR	95% CI OR
Age	−0.025	0.029	0.789	1	.374	0.975	0.922-1.031
Sex	−0.214	0.998	0.046	1	.830	0.807	0.114-5.709
Breast cancer	−0.112	0.686	0.027	1	.870	0.894	0.233-3.428
Atopy	−0.234	0.640	0.134	1	.714	0.791	0.226-2.772
Resected	0.724	0.750	0.932	1	.334	2.062	0.474-8.963
Metastatic	−0.375	0.729	0.265	1	.607	0.687	0.164-2.870
Constant	3.155	2.058	2.350	1	.125	23.443	

OR, Odds ratio.

result. Graded challenge was well tolerated in all patients and permitted the correct administration of chemotherapy.

Regarding the remaining 10 patients, oncologists replaced taxanes with other antineoplastic drugs in 5 cases; 3 subjects stopped the therapy because of progression of disease and the other 2 refused the desensitization procedure.

DISCUSSION

Taxanes are antineoplastic agents introduced into clinical practice in 1980 for the treatment of a number of cancers, namely, gynecological malignancies and breast, lung, prostate, and gastric cancer.³ The class of taxanes includes the first synthesized drug, paclitaxel, solvent-free nab-paclitaxel, docetaxel, and cabazitaxel. Paclitaxel and docetaxel provoke HSRs in about 50% of cases, usually during the first or second dose, when administered without a premedication based on antihistamines and steroids. This preventive procedure determines a dramatic decrease in immediate reactions, which, however, can be observed in around 1% of cases despite premedication.² In this prospective multicenter study of patients with immediate HSRs to paclitaxel or docetaxel, we performed prick and intradermal tests with these drugs with the aim of evaluating the real role of skin testing in the diagnosis of HSRs to taxanes. Secondary aims were to research factors eventually correlated with the results of tests or predictors of HSRs and the safety of desensitization or graded challenge with the culprit drug.

A total of 84 patients were evaluated and to our knowledge this represents the largest group of patients in which the role of skin testing in the diagnosis of HSRs to taxanes was analyzed. In their historic article, Weiss et al²³ first performed skin tests in patients with HSRs to paclitaxel; the results were negative. This observation had been confirmed by the negative results obtained by Messaad et al²⁸ and Bursztejn et al,²⁹ even if in very small groups of patients. In addition, most of the authors hypothesized that the immunopathogenetic mechanism of HSRs involves a solubilizer added to the drug formulation, such as cremophor or polysorbate, which induces direct complement activation and a direct effect on basophils with histamine release. For these 2 reasons no author performed skin tests on patients with suspected immediate HSRs to paclitaxel or docetaxel for several years. Something changed when, more recently, Prieto Garcia and Pineda de La Losa³⁰ obtained a positive intradermal test result with paclitaxel with a concentration of 0.001 mg/mL in a patient who developed a severe immediate HSR during the second infusion of the drug. The result of the same test was negative in 15 controls. Subsequently, other authors conducted skin tests on patients with suspected HSRs. Gastaminza et al²²

TABLE VII. Characteristics of control group

Variable	Value
Age (y), mean ± SD	60.2 ± 10.7
Sex, n (%)	
Male	14 (53.3)
Female	16 (46.7)
Cancer site, n (%)	
Breast	13 (43.3)
Endometrium	1 (3.3)
Ovary	1 (3.3)
Prostate	1 (3.3)
Lung	7 (23.3)
Bladder	1 (3.3)
Testis	1 (3.3)
Esophagus	1 (3.3)
Colon	4 (13.3)
Atopy,* n (%)	
Yes	7 (23.3)
No	23 (76.7)
Resected, n (%)	
Yes	24 (80.0)
No	6 (20.0)
Metastatic, n (%)	
Yes	6 (20.0)
No	24 (80.0)

*In the general population, atopy prevalence is 20%; in our sample, it is 23.3%.

obtained a positive intradermal test result with docetaxel with a concentration of 0.04 mg/mL, administered on 2 patients with immediate reactions to this taxane.

In another study, Madrigal-Burgaleta et al²⁴ described 2 positive results for intradermal tests with paclitaxel with a concentration of 0.06 mg/mL that were performed on 9 patients.

However, in the largest cohort of patients treated for taxane-induced HSRs reported in literature, Picard et al²¹ performed skin tests on 145 patients; 105 had positive results, 91 (71%) with paclitaxel and 8 (89%) with docetaxel. In their study, the authors used the results of skin tests and the severity of HSR for the management of patients, which allowed a significant number of subjects to resume regular infusion of the culprit drug.

In our study, the positivity of skin tests, namely, the intradermal test, was evidenced in 14 patients (16.7%), 10 with paclitaxel (15.9%) and 4 with docetaxel (19%); grade 3 reactions and cutaneous symptoms during HSRs correlated with these

TABLE VIII. Diagnostic test outcome

Measure	Value	95% CI	
		Lower	Upper
Sensitivity	0.1667	0.0870	0.2464
Specificity	1.0000	1.0000	1.0000
False-positive rate	0.0000	0.0000	0.0000
False-negative rate	0.8333	0.7536	0.9064

results, confirming the report of Picard et al. There are some explanations regarding the difference in the prevalence of positive skin test results between our study and the Picard et al study.

First of all, there are differences in the population examined. In fact skin test positivity correlates with severity of reactions and with skin manifestations during the immediate HSR and our cohort of patients had less immediate severe reactions (90% vs 69%) and cutaneous reactions (80% vs 65.5%) with respect to the group described by Picard et al. Another possible reason could be the different vegetation in Europe and the United States. Vanhaelen et al³¹ detected specific antipaclitaxel IgG in subjects who had never been exposed to the drug but who reside in an area where the pollen from *Taxus baccata*, the plant from which paclitaxel is derived, is widespread. Persistent sensitization with these pollens leads to the development of specific antibodies and could explain why most reactions to the taxanes occur during the first administration of the drug. The study of Picard et al was conducted in a high concentration area of *Taxus baccata* and *Taxus brevifolia* (from which docetaxel is derived), whereas in southern Europe, where most of the analyzed subjects live, these 2 plants, especially *brevifolia*, are less common. This fact could, at least partially, explain the less frequency of ST positivity in our patients.

The comparison of the 2 different populations (ST+ and ST-) regarding age, sex, type and stage of tumor, atopy, personal history of drug allergy, and respiratory, gastrointestinal, and cardiovascular involvement did not reveal significant differences. However, cutaneous involvement and severity of HSRs to taxanes were significantly more frequent in patients with ST+. These results, which confirm Picard et al's observations, highlighted 2 predictive factors that seem very useful for the subsequent treatment of patients with HSRs. The subgroup of subjects with severe reactions involving the skin must receive an alternative drug or, where this is not possible, they should receive taxane very carefully, preferably with a desensitization procedure by experienced health personnel.

In our study, ST specificity was very high, whereas sensitivity was low; this situation is similar to the results obtained with most drugs²⁶ and should be interpreted together with the clinical histories.

In addition, in our population, graded challenge and desensitization confirmed their safety. In particular, graded challenge performed in grade 1 HSRs and/or ST- was perfectly tolerated in all subjects and represents a criterion standard for this population. Desensitization was safely administered in all but 2 patients, one with grade 2 reactions and ST+, the other with grade 3 reaction and ST-. The number of subjects is low but confirms that patients with these characteristics are at increased risk of reactions upon taxane reintroduction.

This study had some limitations. First, not all the patients with HSRs to taxanes were evaluated by allergists, because some

of them were treated by oncologists; thus, these patients only partially represent and reflect the entire, nontolerant taxane population. Second, almost all patients were enrolled in southern Europe and this could represent a bias because environment may modify patients' reactivity and, consequently, skin test results. Third, we did not distinguish whether HSRs were provoked by the brand or generic formulations; in this regard, a recent article has demonstrated that the incidences of HSRs were similar with generic and original paclitaxel but significantly different with generic and original docetaxel.³² Finally, we did not measure tryptase levels after HSRs, and the lack of these data could determine an incorrect interpretation of some reactions, especially in case of ST-.

In conclusion, skin tests for taxanes are useful and must be performed in the allergological workup of subjects with HSRs to this class of chemotherapeutic drugs, especially in cases of severe reactions with cutaneous involvement. In fact, this subset of patients probably presents IgE-mediated reactions even if further studies are imperative to better highlight immunopathomechanisms of these reactions.

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