

Hypersensitivity reactions to paclitaxel: The Mexican experience of rapid desensitization

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Abstract

Background: Taxanes adjuvant therapy is recommended in certain high risk or metastatic tumors, particularly in lung and breast cancer, but also in other types of cancer like ovarian. The incidence of severe adverse drug reactions to paclitaxel is of approximately 10%.

Objectives: Analyze type I hypersensitivity reactions to paclitaxel and their management in the Mexican population.

Method: It is a retrospective, observational and descriptive study that included type I hypersensitivity reactions to paclitaxel reported from our database. Symptoms of hypersensitivity reactions to paclitaxel were classified and skin testing was performed with a 6 mg/mL paclitaxel concentration. The desensitization procedure consisted of a 12-steps, 3-bags of 250 mL protocol with a 6–7-hour duration.

Results: A total of 60 desensitization procedures were performed and were all completed successfully. All participants in our group were female, their median age was 44.5 years.

All of our patients had hypersensitivity adverse drug reaction to paclitaxel during their first exposure and within the first 10 minutes of infusion. 63.6% of the patients had a moderate hypersensitivity reaction to paclitaxel and 36.4% had a severe reaction.

Conclusions: Paclitaxel continues to be a common use drug and has a high rate of adverse drug reactions. This is the first study of hypersensitivity to paclitaxel in a Mexican population.

Keywords

Cancer, desensitization, hypersensitivity reactions, paclitaxel

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Introduction

The World Health Organization (WHO) estimates that cancer is the leading cause of death before age 70, in more than half of the countries worldwide. Breast cancer and lung cancer are in the lead for the most common cancer diagnosed in both men and women and encompass more than 20% of the incidence and mortality for cancer.¹ A 70% increase in new cases of cancer is expected over the next 2 decades.² Taxanes adjuvant therapy is recommended in certain high risk or metastatic tumors, particularly in lung and breast cancer, but also in other types of cancer like ovarian. For breast cancer, taxanes can increase chemotherapy

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efficacy at the cost of its side effects. Regimens that include taxanes and anthracyclines can reduce mortality by one third.³

Like any other drug, paclitaxel adverse reactions can be classified as predictable (type A) and unpredictable (type B). Type B reactions account for 20 to 25% of all adverse drug reactions (ADR) and are the ones that are unrelated to the pharmacologic actions of the drug, from which hypersensitivity reaction belongs to. In general, hypersensitivity reactions are less than 10% of all ADR.⁴ After systematic use of premedication with corticosteroids and antihistamines, the incidence of ADR to paclitaxel was reduced to around 10% of patients, from which 10% are severe. Premedication reduces the intensity of the symptoms but does not protect from severe reactions.⁵ In paclitaxel hypersensitivity adverse drug reaction (HADR) the infusion duration and the administered dose do not influence the rate of reactions. Despite the rate of adverse reaction, paclitaxel is still a commonly used and relevant chemotherapeutic agent in today's medical practice.⁶

Patients with either IgE-mediated or non-IgE-mediated reaction, should be risk-stratified before re-introduction through a desensitization protocol. Patients with severe delayed-type reactions should not be re-exposed to the agent by any means, but mild delayed-type reactions could be desensitized after skin testing.⁶ Desensitization should always be considered when the offending drug is essential and when no alternatives exist.⁷

The objective of this study is a descriptive analysis of type I hypersensitivity reactions to paclitaxel and their management in the Mexican population.

Materials and methods

This study was approved by the clinical research ethics committee with approval number AL20-00007. It is a retrospective, observational and descriptive study that included type I hypersensitivity reactions to paclitaxel reported from our database from June 2018 to June 2020 involving Mexican population. The reports were reviewed for patient's age, sex, cancer diagnosis and clinical stage according to the TNM system, and description of the adverse reaction reported. Atopy was defined as the presence of allergic rhinitis, asthma, atopic dermatitis, food or drug allergy. We reviewed the files of the patients and collected the data retrospectively. Patients with incomplete data in medical records were excluded.

Immediate type I reactions were defined as adverse reactions with onset within an hour after starting the infusion and with immunological mediated clinical features, such as mast cell degranulation. Symptoms of hypersensitivity reactions to paclitaxel were classified

into cutaneous (flushing, pruritus, urticaria, angioedema, maculopapular rash), cardiovascular (chest pain, tachycardia, bradycardia, sense of impending doom, presyncope, syncope, hypertension, hypotension, diaphoresis), respiratory (sneezing, nasal congestion, dyspnea, coughing, wheezing, desaturation, throat tightness), gastrointestinal (nausea, vomiting, diarrhea, abdominal pain, bloating) and neurological/muscular (disorientation, hallucinations, vision disturbances, ringing/pounding in ears, unusual taste, back pain, numbness/weakness, chills/rigors).

We used the grading system for generalized hypersensitivity reactions as described by Brown.⁵ This includes mild reactions as those limited to the skin and subcutaneous tissues. Moderate reactions were defined as those suggesting respiratory, cardiovascular, or gastrointestinal involvement. Severe reactions were those with hypoxia, hypotension or neurological compromise, such as cyanosis, $SpO_2 \leq 92\%$, systemic blood pressure <90 mmHg, confusion, collapse, loss of consciousness or incontinence.⁸

Skin testing was performed with paclitaxel using a 6 mg/mL concentration. For intradermal skin testing, paclitaxel was diluted to a concentration of 0.06 mg/mL and 0.6 mg/mL. A positive test was defined as those with a wheal measuring at least 3 mm larger than the obtained by the negative control after 15 minutes.

Our rapid desensitization protocol was based on Brigham and Women's Hospital and Dana-Farber Cancer Institute protocols, starting from September 2018. The desensitization protocol consists of a 12-steps (Table 1) (16-steps in high-risk patients), 3-bags of 250 mL each at 1:1, 1:10 and 1:100 dilution (plus 1:1,000 in high-risk patients), doubling the rate of infusion up to 80 mL/hour until finished, which is usually around 6 to 7 hours.⁹ Patients before this date used a 6-bag desensitization protocol.

Results

A total of 11 patients were included, performing 60 desensitization procedures, of which all were completed successfully. All participants in our group were female, their median age was 44.5 years (16 to 71 years). The most common cancer site was breast and ovarian cancer, followed by cervical cancer, endometrium and larynx cancer (Table 2). Only one patient had previously received another chemotherapeutic agent, cisplatin. Systemic arterial hypertension was the most common comorbidity (45.5%), followed by type II diabetes mellitus (18.2%) and hypothyroidism (9.1%). Every hypertensive patient used angiotensin receptor blockers as monotherapy, one patient with diabetes used metformin and one patient metformin with insulin.

Table 1. Desensitization 12-step protocol for paclitaxel (300 mg).

3 Bag/12-step protocol	Volume (mL) per bag	Concentration (mg/mL) per bag	Amount (mL) of bag infused	Dose infused (mg) per bag
Solution 1	250	0.013	9.38	0.12
Solution 2	250	0.12	18.75	2.25
Solution 3	250	1.191	250	297.63

Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused (mg)	Cumulative dose (mg)
1	1	2.5	15	0.625	0.008	0.008
2	1	5	15	1.25	0.016	0.024
3	1	10	15	2.5	0.032	0.056
4	1	20	15	5	0.065	0.121
5	2	5	15	1.25	0.15	0.271
6	2	10	15	2.5	0.3	0.571
7	2	20	15	5	0.6	1.171
8	2	40	15	10	1.2	2.37
9	3	10	15	2.5	2.98	5.35
10	3	20	15	5	5.96	11.31
11	3	40	15	10	11.91	23.22
12	3	80	174.4	232.5	276.91	300 mg
Total dose: 300 mg Total time: 5.67 h						

Atopy was positive in 45.5% of our sample (Table 2), similar to other series,⁹ and 90.9% had positive skin tests. The most common allergic disease was allergic rhinitis in 36.4% while asthma was positive in 9.1%. Only one patient had a history of drug-induced hypersensitivity reactions.

All of our patients had HADR in their first exposure, despite premedication. All of the HADR to paclitaxel were within the first 10 minutes and 9 of which were within the first 5 minutes. There was no mild reaction to paclitaxel in our sample, 63.6% of the patients had a moderate hypersensitivity reaction to paclitaxel and 36.4% had a severe reaction. The only patient who had biphasic anaphylaxis had a moderate reaction and history of atopy. All patients in our sample had respiratory symptoms such as dyspnea or desaturation (Figure 1) followed by cutaneous symptoms and throat tightness, we did not have any report of fever. One of the atypical symptoms that occurred in more than half of the cases was low back pain, as reported in the literature associated with a hypersensitivity reaction secondary to taxanes.⁵

For the treatment of anaphylactic reactions to paclitaxel, patients received corticosteroids in 90.9%, 36.4% antihistamines and only 18.2% received epinephrine. Our case of biphasic anaphylaxis received only corticosteroids as treatment.

Skin testing was performed in each of our patients. Skin prick tests were negative in all of our patients, but the intradermal skin test was positive in 90.9% of our patients. A desensitization protocol was performed in

all of our sample as they did not have any contraindication. During the 60 desensitization protocols there was no immediate hypersensitivity reaction, however one non-atopic patient had a delayed reaction with urticarial vasculitis and discontinued treatment.

The desensitization protocols were performed based on risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions as published by Picard et al. with desensitization using 4, 3 and 2 bags depending on the immediate hypersensitivity reactions grade and tolerance to protocols. No challenge tests were performed in this study.

Discussion

Paclitaxel's activity against cancer is a result of its ability to stabilize microtubules, leading to cell cycle arrest and cell death. Its well-recognized potential is limited by its frequent side effects like alopecia, peripheral neuropathy, bone marrow depression and hypersensitivity reactions to the molecules itself or to its solvents.¹⁴

Paclitaxel, first extracted from the bark of the *Taxus brevifolia*, originally was isolated naturally. A few years later a semisynthetic process was discovered which allows using only the tree needles. However, in recent years it has been produced from plant cell cultures from the same tree species in bioreactors. Its alternative, docetaxel, is obtained from a semisynthetic process from the needles of the same tree and its structure is similar to paclitaxel.⁵ As these drugs are insoluble molecules, they need to be combined with solvents

Table 2. Characteristics of patients with HADR to paclitaxel.

	Our study 2020	Kendirlihan et al. ¹⁰	Pagani et al. ¹¹	Banerji et al. ¹²	Castells et al. ¹³
Characteristics	n = 11 (%)	n = 7 (%)	n = 63 (%)	n = 107 (%)	n = 28 (%)
Age					
Mean	44.5	45.3	55.2	55.7	55
Range	16-71	25-74	44-67	44-68	30-78
Sex					
Male	0(0.0)	1 (14.3)	5 (7.9)	33 (30.8)	0 (0.0)
Female	11 (100.0)	6 (85.7)	58 (92.1)	74 (69.2)	28 (100.0)
Cancer site, n (%)					
Breast	4 (36.4)	2 (28.6)	33 (52.4)	25 (23.4)	4 (14.3)
Ovarian	4 (36.4)	1 (14.3)	12 (19.0)	19 (17.8)	16 (57.1)
Endometrial	1 (9.1)	1 (14.3)	9 (14.3)	NA	3 (10.7)
Cervix	1 (9.1)	0 (0.0)	0 (0.0)	NA	0 (0.0)
Larynx	1 (9.1)	0 (0.0)	0 (0.0)	NA	0 (0.0)
Lung	0 (0.0)	1 (14.3)	3 (4.8)	34 (31.8)	0 (0.0)
Peritoneal	0 (0.0)	0 (0.0)	1 (1.6)	NA	2 (7.1)
Kaposi's sarcoma	0 (0.0)	0 (0.0)	1 (1.6)	NA	0 (0.0)
Bladder	0 (0.0)	0 (0.0)	1 (1.6)	NA	0 (0.0)
Testicular	0 (0.0)	1 (14.3)	1 (1.6)	NA	0 (0.0)
Esophagus	0 (0.0)	0 (0.0)	1 (1.6)	NA	0 (0.0)
Colon	0 (0.0)	0 (0.0)	1 (1.6)	NA	0 (0.0)
Uterine	0 (0.0)	1 (14.3)	0 (0.0)	NA	1 (3.6)
Fallopian	0 (0.0)	0 (0.0)	0 (0.0)	NA	1 (3.6)
Epithelioid hemangioendothelioma	0 (0.0)	0 (0.0)	0 (0.0)	NA	1 (3.6)
Prostate	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metastatic, n (%)					
Yes	9 (81.8)	NA	46 (73.0)	NA	NA
No	2 (18.2)	NA	17 (27.0)	NA	NA
Atopy, n (%)					
Yes	5 (45.5)	NA	23 (36.5)	22 (20.6)	NA
No	6 (54.5)	NA	40(63.5)	85 (79.4)	NA
Cutaneous reaction, n (%)					
Yes	9 (81.8)	10 (66.7) ^a	40 (63.5)	90 (84.1)	23 (82.0)
No	2 (18.2)	5 (33.3) ^a	23 (36.5)	17 (15.9)	5 (18.0)
Respiratory reaction, n (%)					
Yes	11 (100.0)	5 (33.3) ^a	35 (55.6)	57 (53.3)	12 (43.0)
No	0 (0.0)	10 (66.7) ^a	28 (44.4)	50 (46.7)	16 (57.0)
Throat tightness, n (%)					
Yes	9 (81.8)	3 (20.0) ^a	NA	36 (33.6)	7 (25.0)
No	2 (18.2)	12 (80.0) ^a	NA	71 (66.4)	21 (75.0)
Cardiovascular reaction, n (%)					
Yes	7 (63.6)	12 (80.0) ^a	29 (46.0)	45 (42.1)	21 (75.0)
No	4 (36.4)	3 (20.0) ^a	34 (54.0)	62 (57.9)	7 (25.0)
Gastrointestinal reaction, n (%)					
Yes	5 (45.5)	4 (26.7) ^a	8 (12.7)	22 (20.6)	12 (43.0)
No	6 (54.5)	11 (73.3) ^a	55 (87.3)	85 (79.4)	16 (57.0)
Neurological/muscular reaction, n (%)					
Yes	9 (81.8)	3 (20.0) ^a	12 (19.0)	83 (77.6)	11 (39.0)
No	2 (18.2)	12 (80.0) ^a	51 (81.0)	24 (22.4)	17 (61.0)
Back pain, n (%)					
Yes	6 (54.5)	2 (13.3) ^a	12 (19.0)	37 (34.6)	10 (36.0)
No	5 (45.5)	13 (86.7) ^a	51 (81.0)	70 (65.4)	18 (64.0)

NA: Not available.

^aTaxanes (n = 15): Paclitaxel (7) + Docetaxel (8).

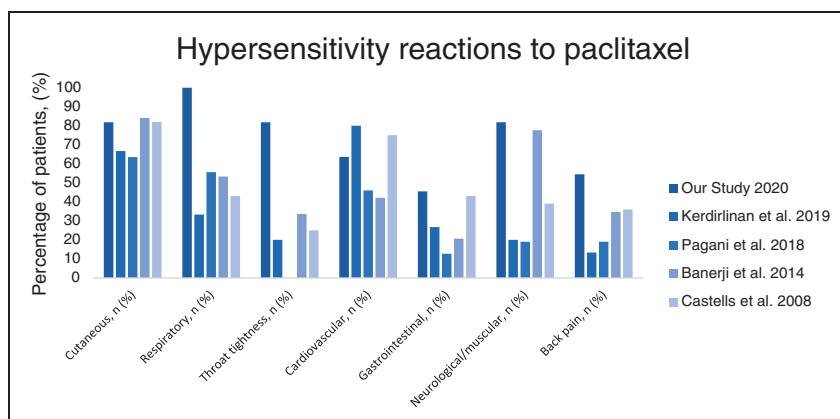


Figure 1. Immediate hypersensitivity reactions to paclitaxel.

like Cremophor-EL or polysorbate in order to be used in humans. Although both molecules are FDA approved, some studies have reported that they are not completely inert compounds and have the means to cause hypersensitive reactions in susceptible patients.¹⁵

Skin prick tests can detect an IgE-mediated pathology, they are used as the diagnosis procedure of choice to detect hypersensitivity reactions to paclitaxel but are limited by an irritant concentration that could cause a false-positive result. To date, there is no standardized dilution for skin prick testing, most of the research data use a paclitaxel concentration ranging from 6 mg/mL to 0.6 mg/mL, and intradermal skin testing is even more variable, however, 1 mg/mL seems to be the most used concentration.^{16,17} A positive result is defined as a wheal measuring 3 mm more than the negative control. This test is generally performed at least 2 weeks after the hypersensitivity reaction to minimize false-negative results.⁷ It is important to remember that positive and negative predictive values have not been established to date for skin testing. The largest series to date that evaluates taxanes, reports positive skin test in 71% of its patients.⁹ In Pagani et al, 84 patients were included with negative prick test results in all of the cases, however intradermal test results were positive in 10 patients with paclitaxel (15.9%).¹¹

Similar to the findings in our study, previous authors frequently reported cutaneous and respiratory symptoms as well as back pain, which may suggest an IgE mediated reaction. Banerji et al., reported 107 patients with taxane HSR that more commonly described facial flushing and chest or throat tightness.¹²

In Castells et al, 82% of symptoms were cutaneous¹³ and along with Pagani et al. and our study, included a higher percentage of female patients with a mean age range of 44 to 55.¹¹ Cardiovascular symptoms including hypotension and loss of consciousness are

considered moderate to severe HSR, in our study it followed after cutaneous and respiratory symptoms. Kerdirlinan et al., included 41 patients where ovarian and breast cancer were the most commonly presented, similar to our demographic population studied.¹⁰

Despite numerous studies, to date only some mechanisms are defined as able to cause HADR to paclitaxel. Because reactions to this drug are usually in the first or second administration, an IgE-mediated mechanism is not the most accepted pathway, thus still possible. Direct or indirect complement activation by pharmaceutical surfactants is responsible for some of the HADR. In one study a significant production of C3a was shown in response to these solvents. Both Cremophor-EL and polysorbate-80 have been shown to activate complement independently if the active compound was present or absent.¹⁵ Some studies attribute its capability to activate complement by the lectin pathway due to structural similarities in segments of the poloxamer and a region of D-mannose, other authors point at the alternative pathway activation triggered by calcium-sensitive pathways, enabling hydrolysis of the thioester bond in C3 by hydrophilic constituents formed from lipoproteins to form the fluid-phase C3-convertase.^{18,19} Another theory that explains why most patients react to their first dose of paclitaxel comes from its natural source. As paclitaxel is extracted from *Taxus* trees, a natural sensitization may occur by its pollen. We found no reports that directly studied sensitization by IgE to pollen from *Taxus* trees and allergy reaction by infusion of paclitaxel, but one study found anti-paclitaxel IgG in a group of Belgian atopic patients. They theorized that paclitaxel could be released from the pollen from *Taxus* or hazel trees in contact with the nasal mucosa and could induce the production of specific immunoglobulins. This IgG in serum may activate complement by its classic pathway.²⁰ The possibility of cross-reactivity

between paclitaxel and other plant components is still unknown. We only found one case report that suggests cross-reactivity of some kind, but no skin or serum test was performed to confirm the assumption and the cross-reactivity was attributed by the history of a similar reaction by hazelnut.²¹ If pollen sensitization could be possible, it should be induced by either pollen of the yew, the hazel or another member of the Taxaceae or Betulaceae family, as both are already recognized to produce a certain amount of paclitaxel. This grants an area of opportunity for future research.

This study has some limitations. First, our sample size is limited, so no risk factors could be associated, and the results may not be representative for other populations. Second, despite all hypersensitivity severity reactions were included, our sample has only moderate and severe reactions, no mild reactions to paclitaxel were presented in our sample. The most probable reason of this is because they are defined as “limited to the skin” and did not classify as anaphylaxis in the patient’s clinical setting, so the drug was probably administered just by slowing or temporally stopping the infusion and treatment with antihistamines and corticosteroids. Finally, since most patients had positive skin tests, it is not applicable to all populations.

In conclusion, although every chemotherapeutic agent has the potential to cause HADR, paclitaxel continues to be a common use drug and has a high rate of adverse drug reactions. Further prospective studies involving larger samples are needed to collect more data on this particular population of patients. Despite this, it is the first study of hypersensitivity to paclitaxel in Mexican population.

Author contributions

Rosalaura Virginia Villarreal-Gonzalez: design of the work, analysis, interpretation of data, drafting and final approval of the version. Integrity of any part of the work are appropriately investigated and resolved.

Sandra Nora Gonzalez-Diaz and Oscar Vidal-Gutierrez: design of the work, analysis, interpretation of data, drafting and final approval of the version.

Rodrigo Alejandro de la Cruz-Cruz: design of the work, analysis, interpretation of data, drafting and final approval of the version. Integrity of any part of the work are appropriately investigated and resolved.

Cindy Elizabeth de Lira-Quezada: design of the work, analysis, interpretation of data, drafting and final approval of the version. Integrity of any part of the work are appropriately investigated and resolved.

Statement of Ethics

Research was conducted ethically in accordance with the Declaration of Helsinki and informed consent was obtained by participants.

Declaration of Conflicting Interests

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