Incidence of Hypersensitivity Reactions from Paclitaxel

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Background: *Paclitaxel has been used widely for various solid tumors such as ovarian, lung and breast cancers. Patients treated with paclitaxel often experience mild to moderate hypersensitivity reactions (HSR) which usually occur at the first or second dose of paclitaxel. Giving premedication regimens consisting of corticosteroid, H_1 and H_2 antagonists can reduce the incidence of HSR from paclitaxel, but even when premedication is used, HSR can still occur.*

Objective: *To find the incidence of hypersensitivity reactions (HSR) from paclitaxel, including characteristics and severity of paclitaxel-associated hypersensitivity reaction and the effects of premedication regimens used in preventing HSR.*

Material and Method: *Data of patients who received paclitaxel between January 2014 and December 2015 at Rajavithi Hospital were collected from hospital computer databases, pharmacy databases and chemotherapy unit. Patients who received antidotes for paclitaxel HSR were confirmed as having paclitaxel-induced HSR by medical record review. Reports of HSR from adverse drug reactions and risk management units were also included. The severity of HSR was determined in accordance with NCI CTCAE v4.03. All grade 1 or 2 types were classified as mild-moderate HSR, while severe HSR was defined as grade ≥3.*

Results: *A total of 1,132 patients received paclitaxel 5,152 times, and 48 patients (4.24%) 70 times were found to have HSR resulting from the use of paclitaxel. The severity was mostly grade 2 (55 times). Only one patient had grade 4 and did not continue paclitaxel. The first episode of HSR occurred most frequently at the first (17 patients) and second (26 patients) cycle. Premedication used in this study was divided into 2 groups: Group 1, premedication (oral dexamethasone) was given 6 to 24 hours before paclitaxel; and Group 2, premedication (iv dexamethasone) was given 30 minutes before paclitaxel. In the HSR group, HSR occurred 29.17% (14 from 48 patients, 20 times) in group 1 and 70.83% (34 from 48 patients, 50 times) in group 2. Agricultural patients had a higher incidence of HSR (OR 2.55, 95% CI: 1.20 to 5.43). Lung (14 from 187) and cervical (9 from 141) cancer patients had a higher risk of HSR than other cancer sufferers.*

Conclusion: *The incidence of HSR found in the present research was similar to the results of previous studies in relation to severe HSR. Agricultural workers had a higher risk of HSR, while a premedication regimen of oral dexamethasone 6 to 24 hour before paclitaxel resulted in a lower incidence of HSR. However, the HSR found in both groups was not severe and most patients were able to continue taking paclitaxel.*

Keywords: *Hypersensitivity reactions, Paclitaxel, Premedication*

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Paclitaxel is a taxane drug class. It is a tubulin-stabilizing chemotherapeutic agent which was originally extracted from the bark of Pacific yew tree (*Taxus brevifolia*)[1]. In later years, paclitaxel precursors were able to be transformed via a semisynthetic process into paclitaxel from different *Taxus* species[2]. Due to its hydrophobic properties, paclitaxel must be emulsified in a vehicle consisting of 50% polyoxyethylated castor oil (Cremophor EL) and 50% ethanol[3].

Paclitaxel has been used widely in various solid tumors such as ovarian, lung, and breast cancers[4]. Patients treated with paclitaxel often experience mild to moderate hypersensitivity reactions (HSR)[5,6]. Cremophor EL has been mooted as one of the causes of HSR[7]. In previous studies, the incidence of paclitaxel-induced HSR was 2% to 63%[8-14]. It usually occurs at the first or second dose of paclitaxel. Giving premedication regimens consisting of corticosteroid, H_1 and H_2 antagonists can reduce the incidence of HSR resulting from taking paclitaxel[1]. However this premedication cannot prevent all incidences of HSR.

The aims of the present study were to find the incidence, characteristics and severity of paclitaxel-associated hypersensitivity reaction and the results of premedication regimens used in preventing HSR.

Material and Method

This observational study was conducted

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among all patients who received paclitaxel between January 2014 and December 2015 at Rajavithi Hospital. Data were collected from hospital databases from the computer, pharmacy and chemotherapy units. Patients who received antidotes for paclitaxel HSR were confirmed HSR by review of their medical records. Reports of HSR resulting from adverse drug reactions and risk management units were also included. The severity of HSR was determined in accordance with NCI CTCAE v4.03. A reaction was considered as mild-moderate (grade 1 to 2) if the patient experienced flushing, rash, fever, dyspnea, and mild hypotension or hypertension. Symptoms such as severe hypotension, bronchospasm, angioedema, and anaphylaxis, requiring therapeutic intervention, were classified as severe HSR (grade 3 to 4). The protocol of this research was reviewed and approved by the Ethics Committee of Rajavithi Hospital (No. 081/2559).

Statistical analysis was performed using SPSS17. Baseline characteristics were described using frequency and percentages for categorical data and mean, standard deviation, median and range for numerical data. Comparisons between groups were performed using Chi-square test or Fisher exact test for categorical variables and Student t-test or Mann Whitney U-test for continuous variables, as appropriate. A value of $p<0.05$ was considered statistically significant.

Results

A total of 1,132 patients received paclitaxel 5,152 times. 48 patients (70 times) were found to have HSR as a result of taking paclitaxel (4.24%). Among patients who experienced HSR, 35 patients had a single episode and 13 patients had repeated episodes. Lung cancer (14 from 187) and cervical cancer (9 from 141) had higher HSR than other cancers when compared to the non-HSR group (Fig. 1).

The severity of HSR mostly was NCI CTCAE grade 2 (55 times). Only one patient had grade 4 (anaphylaxis) and did not continue paclitaxel (Fig. 2). The first episode of HSR occurred most frequently at the first (17 patients) and second (26 patients) cycle. The frequent signs and symptoms of paclitaxel-associated HSR were characterized by dyspnea, flushing, and hypertension (Fig. 3). Baseline characteristics of the HSR and non-HSR groups are shown in Table 1. There were no significant differences between groups relative to demographics, doses of paclitaxel, allergy history or underlying disease. There was a significant difference between agricultural and non-agricultural workers with the odds of HSR in agricultural workers being higher than those in other types of employment (OR 2.55, 95% CI: 1.20 to 5.43), and these figures were statistically significant (p = 0.031).

Premedication used in this study was divided

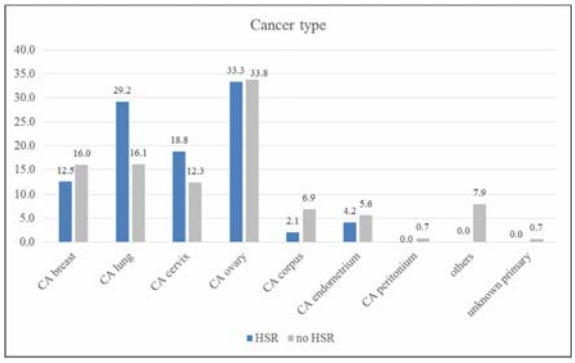

Fig. 1 Cancer type in patients who received paclitaxel.

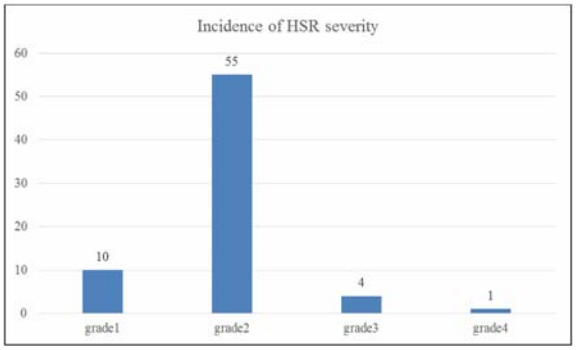

Fig. 2 Incidence of HSR severity.

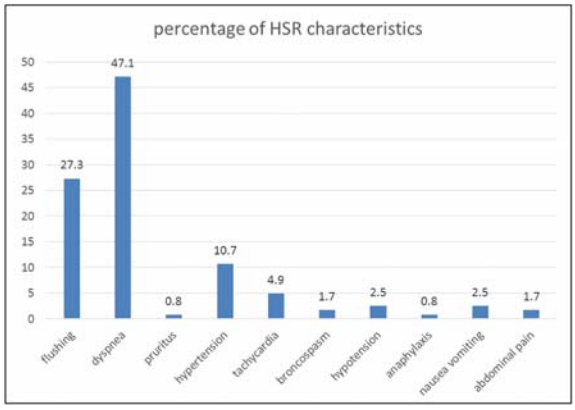

Fig. 3 Clinical characteristics of paclitaxel-associated HSR.

into 2 groups. In Group 1, premedication (oral dexamethasone) was given 6-24 hour before paclitaxel while in Group 2, premedication (iv dexamethasone) was given 30 minutes before paclitaxel. With regard to treatment cycles, in cycle 2 there was a significant difference between the two premedication groups (*p*-value 0.041) with group 1 having less HSR than group 2 (OR 2.09, 95% CI: 1.02 to 4.30). For cycle 1 although not statistically significant, there was a tendency of higher HSR in group 2 premedication (OR 3.38, 95% CI: 0.96 to 11.82). Percentage of HSR from paclitaxel with two different premedication (cycle 1 and 2) was shown in Fig. 4. In HSR group, HSR occurred 29.17% (14 from 48 patients, 20 times) in group 1 premedication and 70.83% (34 from 48 patients, 50 times) in group 2 premedication.

Discussion

The wide use of paclitaxel in many solid tumors can increase the incidence of HSR. Since premedication consists of dexamethasone, H_1 and H_2 antagonists have been used, and some studies have shown a dramatic reduction in the incidence of paclitaxel-associated HSR with up to 10% for all severity levels and approximately 1% for severe HSR[15,16]. In the present study, the incidence of HSR was 4.24% per

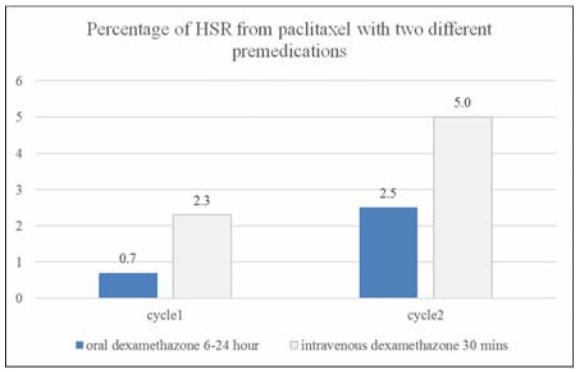

Fig. 4 Percentage of HSR from paclitaxel with two different premedications.

Table 1. patient characteristics

	hypersensitivity reactions		*p*-value
	Yes (n = 48)	No (n = 1084)	
Age (year)	53.77±10.76	56.06±11.49	0.177
Height (cm)	155.36±7.10	155.86±7.89	0.670
Body weight (kg)	54.68±10.52	55.9±10.95	0.450
BMI (kg/m^2)	23.23±3.60	23.147±6.03	0.937
Serum creatinine (mg/dl)	0.71±0.19	0.96±3.53	0.630
Paclitaxel dosage (mg)	267.54±29.14	267.41±37.19	0.981
Gender			0.918
Male	7 (4.1)	164 (95.9)	
Female	41 (4.3)	920 (95.7)	
Marital status			0.269
Married	30 (4.8)	598 (95.2)	
Divorced	3 (1.9)	156 (98.1)	
Single	15 (4.4)	328 (95.6)	
Allergy history			0.177
Yes	9 (6.4)	132 (93.6)	
No	39 (3.9)	952 (96.1)	
Career			0.031*
Agriculture	9 (9.1)	90 (90.9)	
Non-agriculture	39 (3.80)	994 (96.2)	
Underlying diseases			0.137
Yes	26 (5.3)	460 (94.7)	
No	22 (3.5)	615 (96.5)	

Values are represented as n (%), mean ± SD
* = significance at *p*-value <0.05

two years (all grade) and the incidence of severe HSR (grade 3 or 4) was less than 1% (n = 5), which is consistent with the findings of the research by Berger MJ et al, Aoyama T et al and Zidan J et al (4 to 6%)[3,14,17]. In contrast, other studies have reported higher incidences of HSR of up to 34%[6, 8-10,18].

Previous studies have reported signs and symptoms of HSR such as dyspnea, flushing, hypertension, skin rash, tachycardia, and bronchospasm[2,3,5], and this is in keeping with the results of the current study. Paclitaxel-associated HSR was found to occur frequently at the first or second treatment and within the first few minutes of paclitaxel administration[4], and this study also had concurrent findings.

Premedication regimens in the present study showed that the incidence of oral dexamethasone given 6 to 24 hour before paclitaxel induced less HSR than intravenous dexamethasone given 30 minutes before paclitaxel, with statistical significance in cycle 2 administrations. These findings were similar to those of a study by Kwon JS et al[6]. In contrast, previous studies have reported that oral dexamethasone given 6 to 24 hour before paclitaxel and intravenous dexamethasone given 30 minutes before paclitaxel had similar incidences of HSR[5,18]. The higher dose of dexamethasone in the 6 to 24 hour premedication may account for the increase in side effects[5]. There were positive and negative aspects to the premedication in both groups; however, the side effects in the 6 to 24 hour premedication group were mild and the severity of HSR in the 30 minutes premedication group was just mild to moderate and almost all patients were able to continue paclitaxel treatment. Agriculture workers had a higher incidence of HSR than people in other occupations of up to 2.5 times. These may lead to taking good care of these patients in the period of first 1 hour of infusion. On the other hand, many factors were identified as predictive factors for HSR: younger age, history of allergy, presence of respiratory dysfunction, obesity (BMI >25) and surgical menopause from ovariectomy[9,14].

Conclusion

The incidence of HSR found in the present study was similar to the results of previous studies in terms of severe HSR. Agricultural employees had a higher risk of HSR than people in other lines of work, and premedication regimens using oral dexamethasone 6 to 24 hour before paclitaxel resulted in less HSR. However, HSR was not severe in either group, and most patients were able to continue using paclitaxel.

What is already known in this topic?

The incidence of HSR from paclitaxel varied from 2 to 63%, it usually occurred at the first or second dose of paclitaxel. Premedication consisting of dexamethasone, H_1 and H_2 antagonists dramatically reduced the incidence of paclitaxel-induced HSR.

What this study adds?

This study found that agricultural workers and lung cancer patients had higher risks of HSR.

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Potential conflict of interest

None.

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