Characteristics of immediate hypersensitivity reaction to paclitaxel-based chemotherapy in gynecologic cancer patients

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Abstract

Background: Immediate hypersensitivity reactions (IHRs) are commonly found in patients receiving paclitaxel. Effects of paclitaxel vary because of variable co-therapy or re-challenge with paclitaxel.

Objective: Our objective was to investigate the incidence, patterns, and risk factors for paclitaxel-related IHRs and management of IHRs in gynecologic malignancy patients.

Methods: This retrospective study was performed in gynecologic cancer patients receiving paclitaxel-based regimens at Siriraj hospital from January 2012 to December 2017.

Results: 416 subjects were included and received ranitidine 50 mg, dexamethasone 20 mg, ondansetron 16 mg intravenously and diphenhydramine 50 mg orally 30 minutes before starting chemotherapy. The incidence of IHRs was 17.79%. IHRs occurring on first exposure to paclitaxel was 81.1% and occurred within 30 minutes after starting paclitaxel. The most commonly found presentation of IHRs were skin reactions (86.5%). In multivariate analysis, age < 54.5 years, stage of cancer ≥ 2, and leukocyte cell count < 7.735×10^9/L were significantly associated with IHRs. Seventy-two out of 74 patients that recovered from IHRs were reintroduced paclitaxel. Forty-seven patients (97.92%) of 48 patients with mild reactions were successfully reintroduced to paclitaxel after treatment with chlorpheniramine or other interventions.

Conclusion: The incidence of paclitaxel-related IHRs was about one in five. Skin reactions were the most commonly occurring reactions. Younger age, stage of cancer ≥ 2, and leukocytes < 7.735×10^9/L were significant risk factors for IHRs. Patients with IHRs recovered without the use of dexamethasone and antihistamines before the reintroduction of paclitaxel.

Key words: adverse drug reactions, malignancy, paclitaxel, risk factors, hypersensitivity

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Introduction

Paclitaxel is a member of the taxane class of antineoplastic agents, first described in 1971.[1] Paclitaxel is an integral part of chemotherapeutic regimens that are widely used in various types of cancers, such as gynecologic, breast, and lung cancers.[2-4] There are many adverse drug reactions to paclitaxel such as neutropenia, peripheral neuropathy, arrhythmias, alopecia, mucositis, nausea, vomiting, diarrhea, arthralgias, myalgias and hypersensitivity reactions (HSRs).[1]

HSRs are commonly found in patients receiving paclitaxel. The severity of paclitaxel-related HSRs can be classified as mild, severe, or lethal.[5] Paclitaxel-related HSRs usually occur within the first few minutes of starting administration, especially on the first or the second exposure. The symptoms of HSRs can vary from flushing to cutaneous reactions to life-threatening reactions.[1,2,6] Paclitaxel-related HSRs can be enhanced by cremophor EL (polyoxyethylated castor oil) which is a surfactant for increasing solubility.[4-7] The incidence of HSRs related to paclitaxel varies. In some studies, up to 30% of patients treated with paclitaxel suffered from HSRs.[2] Premedications given prior to paclitaxel therapy can reduce the incidence of HSRs by 10%.[2,3] Sendo et al.[8] and Aoyama et al.[9] investigated risk factors associated with HSRs to paclitaxel and reintroduction of paclitaxel. They demonstrated that postmenopausal status at the time of oophorectomy, history of mild hypersensitivity during the first course, respiratory dysfunction, obesity, age, and premedication were HSR-related risk factors.

There have been few studies related to paclitaxel-induced hypersensitivity syndrome. Moreover, the clinical progression of HSRs varies because of co-treatment with others agent, re-challenge with paclitaxel, or desensitization.[10] We aimed to investigate the incidence, patterns, and risk factors for immediate hypersensitivity reactions (IHRs) to paclitaxel in patients treated for gynecologic malignancies and to study the safety of reintroducing paclitaxel among such patients. In our study, IHRs refer to HRSs occurring within 1 hour after paclitaxel administration.

Methods

Participants

In this study, we investigated the incidence of paclitaxel-related IHRs, pattern of IHRs, risk factors, and reintroduction of paclitaxel. The inclusion criteria for study participants were diagnosis with gynecologic malignancy and administration of paclitaxel-based chemotherapy between January 2012 and December 2017. Subjects that developed HSRs more than one hour after starting paclitaxel administration or had incomplete medical records were excluded.

The study was approved by the Siriraj Institutional Review Board of Human Research Protection Unit at Siriraj Hospital (Approval code: Si 001/2019; start date: January 02, 2019; expiry date: January 01, 2020). The requirement for informed consent was waived because of the retrospective nature of the analysis. All 416 participants received ranitidine 50 mg intravenous (IV) injection, dexamethasone (DEX) 20 mg IV injection, ondansetron 16 mg IV injection and diphenhydramine 50 mg orally 30 minutes before starting chemotherapy. Paclitaxel was administered intravenously over 3 hours with a stepwise titration schedule.

Definitions

IHRs specific to paclitaxel are defined as those that occur within one hour after paclitaxel administration.[11] Re-challenge is the reintroduction of paclitaxel after the first episode of IHRs by decreased 50% of infusion rate at IHRs.[12] Desensitization is the induction of a temporary state of clinical tolerance for paclitaxel, causing a decrease in IHRs. Desensitization protocol were based on the progressive dose of paclitaxel starting at concentration 0.1%, 1%, 10% and 88.9%, at 1-hour interval.[11] Anaphylaxis is a serious, life-threatening and might cause death. In this study, the IHRs patients can be defined as anaphylaxis by using world allergy organization guidelines for the assessment and management of anaphylaxis.[13] The severity of IHRs was graded using the National Comprehensive Cancer Network (NCCN)

Table 1. The National Comprehensive Cancer Network (NCCN) 2.2018, the Common Terminology Criteria for Adverse Events (CTCAE) 4.03 and CTCAE 5.0

NCCN 2.2018	CTCAE 4.03	CTCAE 5.0
Mild: hot flushing, rash, pruritus, pain in chest/abdomen/pelvis/back	Grade 1: transient flushing or rash, drug fever < 38 °C; intervention not indicated	Grade 1: systemic intervention not indicated
Severe: shortness of breath, changes blood pressure requiring treatment, dyspnea, nausea, vomiting pain in chest/abdomen/pelvis/back, feeling something wrong	Grade 2: intervention or infusion interruption indicated; responds promptly to symptomatic treatment; prophylactic medications indicated for ≤ 24 hours	Grade 2: oral intervention indicated
Life-threatening: anaphylaxis, generalize hives, respiratory compromise, severe hypotension, nausea, vomiting pain in chest/abdomen/pelvis/back, feeling something wrong	Grade 3: prolonged; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Grade 3: bronchospasm hospitalization indicated for clinical sequelae; intravenous intervention indicated
	Grade 4: life-threatening consequences; urgent intervention indicated	Grade 4: life-threatening consequences; urgent intervention indicated
	Grade 5: death	Grade 5: death

NCCN, National Comprehensive Cancer Network; CTCAE, Common Terminology Criteria for Adverse Events.

guidelines Version 2.2018,[14] the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 and CTCAE Version 5.0, which are shown in **Table 1**.

Data collections

The number of patients who received paclitaxel and developed IHRs divided by the total number of patients receiving paclitaxel defined the fraction of paclitaxel-induced IHRs. All participants were reviewed for age, body mass index (BMI), cancer type, stage of cancer, history of allergy to medication, history of asthma, menopausal status, ovariectomy, white blood cell count, and absolute eosinophil count for risk factor analysis. Onset of IHRs, clinical presentation and severity data were collected for describing the pattern of IHRs. After the IHRs patients received paclitaxel re-challenge. If the patients had no symptoms after re-challenge, the patient success to re-challenge. To assess the success rate of paclitaxel re-challenge after a first episode of IHRs, we calculated the success rate of re-challenge by dividing the number of patients who succeeded to re-challenge by the number of patients who underwent paclitaxel re-challenge. The success rate of paclitaxel desensitization was not examined because there were a few patients who underwent desensitization. This was the limitation of this study to prove a success of desensitization protocol.

Statistical analysis

Descriptive statistics were presented for patient characteristics, incidence of IHRs, the pattern of IHRs and the reintroduction of paclitaxel. Receiver-operator characteristics (ROC) were used to identify the cut off values for some variables. The correlation of IHR risk factors were analyzed by Chi-square or Fisher's exact tests. All significant variables in the univariate analysis were further evaluated in multivariate analysis by logistic regression. Statistical analyses were carried out using R version 3.6.2 at $\alpha = 0.05$ for statistical significance.

Results

Patient characteristics

During the six-year study period, there were 416 gynecologic cancer patients who received paclitaxel-based chemotherapy. Their mean age (±SD) was 56.37 (±10.68) years. The median BMI, leukocyte count, and absolute eosinophil count were 23.81 kg/m², 7.700×10^9/L and 0.120×10^9/L, respectively. Most of the patients (89.1%) received paclitaxel plus carboplatin as their first-line chemotherapy regimen because about 80% of them were diagnosed with ovarian and uterine cancer. Disease status of enrolled participants was stage I in 122 patients (29.8%) and stage III in 152 patients (37.2%). Participants with a history of allergy and asthma comprised 87 patients (20.9%) and 10 patients (2.4%), respectively. Menopausal status was recorded before receiving chemotherapy, and 273 of 416 patients (65.6%) were menopausal (**Table 2**).

Table 2. Baseline characteristics.

Characteristics	All patients N = 416 (±SD/%/range)	IHRs patients N = 74 (±SD/%/range)
Age, mean ± SD	56.37 (±10.68)	53.10 (±10.79)
Body mass index, median (range)	23.81 (13-48.6)	23.18 (13.8-43.4)
Cancer type, n (%)		
Ovarian cancer	228 (54.8)	39 (52.7)
Uterine cancer	120 (28.8)	24 (32.4)
Cervical cancer	60 (14.4)	10 (13.5)
Two primary cancer (Ovarian cancer + Endometrium cancer)	7 (1.7)	1 (1.4)
Vulvar cancer	1 (0.2)	-
Stage of cancer, n (%)		
I	122 (29.8)	15 (20.3)
II	57 (13.9)	18 (24.3)
III	152 (37.2)	27 (36.5)
IV	78 (19.1)	14 (18.9)
History of allergy (medication, environmental factors, foods, contrast media), n (%)		
Yes	87 (20.9)	15 (20.3)
No	329 (79.1)	59 (79.7)
Asthma, n (%)		
Yes	10 (2.4)	1 (1.4)
No	406 (97.6)	73 (98.6)
Postmenopausal, n (%)		
Yes	273 (65.6)	41 (55.4)
No	93 (22.4)	25 (33.8)
Unknown	50 (12)	8 (10.8)
Regimen, n (%)		
Paclitaxel/carboplatin	367 (89.1)	64 (86.5)
Paclitaxel/cisplatin	36 (8.7)	10 (13.5)
Paclitaxel single agent	4 (1.0)	-
Paclitaxel/ifosfamide	3 (0.7)	-
Paclitaxel/carboplatin/ Bevacizumab	2 (0.5)	-
White blood cell, median (range)	7.700 (2.900-30.80)	7.180 (3.200-30.80)
Absolute eosinophils count, median (range)	0.120 (0-3.184)	0.121 (0-1.072)

Incidence and pattern of paclitaxel-related immediate hypersensitivity reactions

Paclitaxel-related IHRs occurred in 74 out of 416 patients (17.79%). Among these cases, 60 patients (81.1%) developed IHRs during the first cycle of paclitaxel-based chemotherapy, and the others developed IHRs during the second chemotherapy cycle. Thirty-two of 74 patients (47.8%) had an onset of IHRs within the first 5 minutes after starting paclitaxel administration, while the remaining patients had IHRs that occurred within the first thirty minutes. The most common severities were grade 2 (86.5%), grade 3 (86.5%) and mild reactions (64.9%) according to CTCAE Version 4.03, CTCAE Version 5.0 and NCCN Version 2.2018 guidelines, respectively. The most common initial clinical presentations of IHRs included skin reactions (86.5%), chest pain (74.3%), cardiovascular reaction (39.2%), and abdominal pain (1.4%). Seven patients (9.5%) out of 74 developed anaphylaxis within the first 10 minutes of paclitaxel administration. There were no IHR-related deaths (**Table 3**).

Table 3. Initial Clinical manifestations of paclitaxel immediate hypersensitivity reactions.

	N = 74 (%)
Chemotherapy cycles with first IHRs	
Cycle 1	60 (81.1%)
Cycle 2	14 (18.9%)
Onset of IHRs	
≤ 5 minutes	35 (47.3)
6-10 minutes	24 (32.4)
11-15 minutes	12 (16.2)
16-30 minutes	3 (4.1)
Severity grading by CTCAE version 4.03	
1	1 (1.4)
2	64 (86.5)
3	6 (8.1)
4	3 (4.1)
5	-

Table 3. (Continued)

	N = 74 (%)
Severity grading by CTCAE version 5.0	
1	5 (6.8)
2	2 (2.7)
3	64 (86.5)
4	3 (4.1)
5	-
Severity grading by NCCN version 2.2018	
Mild	48 (64.9)
Severe	19 (25.7)
Life-threatening	7 (9.5)
Clinical manifestation	
Skin	64 (86.5)
Flushing	55 (85.9)
Pruritus	5 (7.8)
Maculopapular rash	4 (6.3)
Angioedema	2 (2.7)
Gastrointestinal tract (nausea, vomiting, discomfort)	10 (13.5)
Pain (chest, abdominal, back, headache)	59 (79.7)
Cardiovascular (hypotension, hypertension, tachycardia)	29 (39.2)
Anaphylaxis	7 (9.5)

IHRs, immediate hypersensitivity reactions; NCCN, National Comprehensive Cancer Network; CTCAE, Common Terminology Criteria for Adverse Events.

Risk factors

ROC curve analysis used to determine cut off values of some variables. The sensitivity and specificity of the following variable cutoffs: age < 54.5 years, white blood cell count < 7.735×10^9/L, and absolute eosinophils count ≥ 0.615×10^9/L were 39.2% and 39.8%, 33.8% and 46.9%, and 84.9% and 20.2%, respectively. Univariate analysis demonstrated that age < 54.5 years, stage of cancer ≥ 2, white blood cell < 7.735×10^9/L, and postmenopausal status were significant variables correlating with paclitaxel-related IHRs. In multivariate analysis, age < 54.5 years, stage of cancer ≥ 2, and white blood cell count < 7.735×10^9/L remained significant independent risk factors of IHRs with odds ratios of 2.400 (95% confidence interval CI: 1.104–5.217, $P = 0.027$); 2.596 (95%CI: 1.302–5.177; $P = 0.007$), and 2.326 (95%CI: 1.305–4.145; $P = 0.004$), respectively (**Table 4**).

Table 4. Univariate logistic regression analysis and multivariate logistic regression analysis for risk factors of paclitaxel immediate hypersensitivity reactions.

Factors	Univariate			Multivariate		
	Odds ratio	95% Confidence interval	*P* value	Odds ratio	95% Confidence interval	*P* value
Age < 54.5 years	2.350	1.405–3.932	0.001*	2.400	1.104–5.217	0.027*
Obesity (BMI > 25 kg/m²)	0.841	0.498–1.422	0.519	-	-	-
Ovarian cancer	0.902	0.545–1.493	0.688	-	-	-
Stage of cancer ≥ 2	1.846	1.001–3.402	0.049*	2.596	1.302–5.177	0.007*
History of drug allergy	0.953	0.511–1.779	0.881	-	-	-
Asthma	0.507	0.063–4.063	0.522	-	-	-
Postmenopausal	0.481	0.273–0.847	0.011*	0.817	0.362–1.848	0.628
White blood cell < 7.735 × 10⁹/L	2.22	1.311–3.765	0.003*	2.326	1.305-4.145	0.004*
Absolute eosinophils count ≥ 0.615 × 10⁹/L	1.008	0.213–4.765	0.992	-	-	-

BMI, body mass index.

Supportive treatment and management of immediate hypersensitivity reactions

All seventy-four patients who developed IHRs were managed with the immediate termination of paclitaxel infusion and immediately received chlorpheniramine maleate (CPM), CPM plus DEX, or other interventions depending on the severity of reaction. Seventy-two of 74 patients (97.3%) recovered from their reaction, they received the remaining volume of paclitaxel with a 50% reduction of administration rate (**Figure 1**). Grades of severity, according to NCCN, were mild reactions, severe reactions, and life-threatening reactions, which occurred in 48 patients (64.86%), 19 patients (25.68%) and 7 patients (9.46%), respectively. Forty-seven (97.92%) of 48 patients with mild reactions were successfully re-challenge to paclitaxel after CPM IV or other interventions. Only one patient failed re-challenge after CPM plus DEX. All patients with severe reactions were successfully re-challenged with the remaining paclitaxel after receiving CPM plus DEX or other interventions. The benefits of DEX-containing IHR treatment were analyzed; however, the results did not show a statistically significant difference between DEX-containing regimens and non-DEX-containing regimens. Only one patient was discontinued from paclitaxel and switched to a new regimen without paclitaxel (carboplatin monotherapy) because of a life-threatening reaction (hypotension and wheezing due to bronchospasm). This patient received only carboplatin and achieved to complete remission at the end of carboplatin monotherapy. The remaining patient experienced hypotension and reduction of oxygen saturation. Paclitaxel infusion was also discontinued in this patient, who then underwent desensitization because of the need to use paclitaxel. Desensitization protocol was developed by administering 0.1%, 1%, 10% and 88.9% of paclitaxel concentration
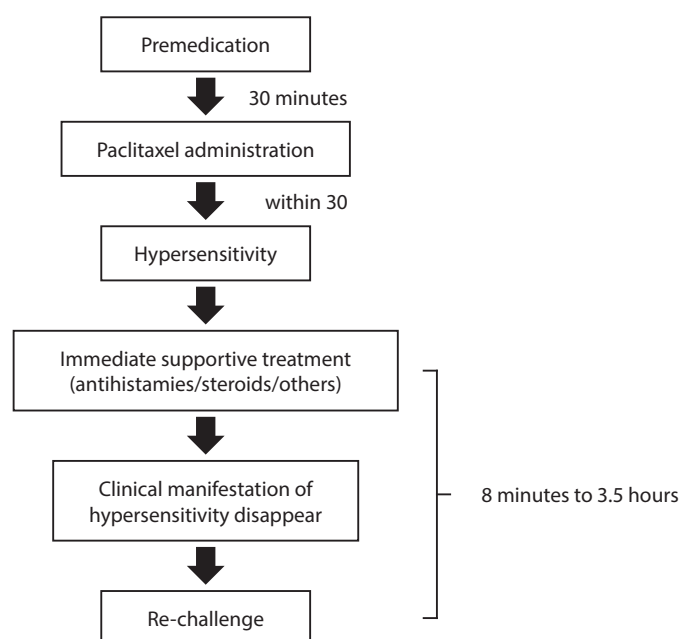

Figure 1. Timeline of the premedication regimen to re-challenge.

via intravenous infusion for 1 hour, 1 hour, 1 hour and 3 hours, respectively. However, one patient who underwent desensitization failed (**Table 5**). This patient had IHRs after administration of 0.1% paclitaxel only 6 minutes. In life-threatening group, Two of 7 patients (28.6%) had age < 54.5 years. Six of 7 patients (85.7%) had stage of cancer ≥ 2. Five of 7 patients (71.4%) had white blood cell < 7.735 × 10⁹/L. One patients who failed desensitization had age < 54.5 years.

Table 5. Supportive treatment and management of immediate hypersensitivity reactions.

Severity grading by NCCN	Intervention after IHRs	Re-challenge		Discontinuation	Desensitization
		Success n (%)	Failure n (%)		
Total (74 patients; 100%)	Any treatment	71 (95.95)	1 (1.35)	1 (1.35)	1 (1.35)
Mild (48 patients; 64.86%)	Chlorpheniramine maleate 10 mg intravenous	9 (18.75)	-	-	-
	Chlorpheniramine maleate 10 mg intravenous + Dexamethasone 20 mg intravenous	26 (54.16)	1 (2.09)	-	-
	Others	12 (25)	-	-	-
Severe (19 patients; 25.68%)	Chlorpheniramine maleate 10 mg intravenous + Dexamethasone 20 mg intravenous	17 (89.50)	-	-	-
	Others	2 (10.50)	-	-	-
Life-threatening (7 patients; 9.46%)	No	1 (14.30)	-	-	-
	Chlorpheniramine maleate 10 mg intravenous	1 (14.30)	-	-	-
	Chlorpheniramine maleate 10 mg intravenous + Dexamethasone 20 mg intravenous	3 (42.80)	-	1 (14.30)	-
	Chlorpheniramine maleate 10 mg intravenous + Ranitidine 50 mg + Dexamethasone 20 mg intravenous + Oxygen + NSS + Salbutamol nebulizer + Epinephrine	-	-	-	1 (14.30) Fail to desensitize

IHRs, immediate hypersensitivity reactions; NCCN, national comprehensive cancer network; NSS, 0.9% sodium chloride.

Discussion

Paclitaxel-based chemotherapy is the mainstay of treatment for gynecologic cancer. In a previous study by Weiss et al., 13.29% of enrolled patients who did not receive premedication got HSRs, while 8.3% of patients who received premedication developed HSRs.[15] Markman et al., Sendo et al., Piovano et al., Ratanajarusiri et al., and Aoyama et al. reported that the incidence of paclitaxel-related HSRs in patient receiving premedication was approximately 10%.[7,8,16,17] In the present study, 17.79% of subjects had HSRs, and all subjects received premedication.[7-9,16,17] This result is higher than that of the previous study. Variation in premedication may have caused this difference considering that our study protocol did not use dexamethasone at 12 hours and 6 hours before paclitaxel administration, unlike that in other studies.[6,8,9] All subjects in this present study received premedication 30 minutes before paclitaxel administration (short-regimen), while some studies used DEX 20 mg 12 hours or 6 hours infusions before paclitaxel administration (long-regimen).[6,8,9] Kwon et al. compared the benefit of short-regimen versus long-regimen premedication. Short-regimen premedication showed a higher rate of HSRs (17.3%) than long-regimen premedication did (7.5%).[18] Kwon's result was comparable to the results of the current study.

In this study, IHRs manifested during the first or second exposure to paclitaxel and always occurred within the first 5 minutes of administration, which is similar to observations of previous studies.[8,16] No patients died from IHRs. Most enrolled patients experienced IHRs that were mild to severe in concordance with other studies.[6,8]

In the multivariate model, age < 54.5 years, stage of cancer $\geq$ 2, and white blood cell count < 7.735 $\times$ 10^9/L exhibited significant correlations with IHRs. In patients aged < 54.5 years, HSR was increased significantly in concordance with Aoyama et al.[9] This may be explained by the inverse relationship between younger age and atopic disease as shown in Wolkewitz et al.[19] Picard et al. showed a direct relationship between atopic disease and risk of paclitaxel-related IHRs.[4] The relationship between atopic disease and paclitaxel-related IHRs was shown to be caused by reduced lymphocyte production and function in elderly patients.[20] In this study, cancer stage $\geq$ 2 was associated with significantly increased risk of IHRs possibly caused by increased pro-inflammatory cytokines, such as interleukin-2 (IL-2) and tumor necrosis factor.[21,22] IL-2 was particularly increased in patients with drug allergies.[23] Here, white blood cell count < 7.735 $\times$ 10^9/L was associated with significantly higher risk of IHRs. Surprisingly, to the best of our knowledge, no previous study has reported the relationship between white blood cell count or stage of cancer $\geq$ 2 and paclitaxel-related IHRs identified in the present study. Endogenous estrogen levels showed a direct relationship with estrogen receptor on the surface of immunoregulatory cells, which was shown to be important for enhancing antigen-presenting cell function in the development of the allergic reaction.[24] The present study's findings were in concordance with this concept. Postmenopausal status was a significant protective factor in univariate analysis, but this could not be confirmed in multivariate analysis.

Severity of symptom ranged from mild to life-threatening. These finding were similar to previous studies, except in the reporting of anaphylaxis.[6,8,16] We found anaphylaxis among patients with IHRs, but the previous studies did not. This may have been due to differences in premedication regimens and rate of paclitaxel administration between these settings. After paclitaxel-receiving patients developed IHRs, infusion of paclitaxel was discontinued and DEX, H1 antihistamine, and H2 antihistamine were given as supportive treatment according to NCCN Version 2.2018 guidelines. In previous studies, DEX, H1 antihistamine and H2 were administered as premedication before the reintroduction of the remaining volume of paclitaxel. However, our practice did not use DEX, H1 antihistamine, and H2 before reintroduction of paclitaxel because of the long half-life of the previous supportive medication. Our practice successfully re-challenged 97.91% and 100% of patients having initially had mild reactions and severe reactions, respectively.

Conclusion

In conclusion, the present study found a 17.79% incidence of paclitaxel-related IHRs, which was higher than in prior studies.[7-9,16,17] Compare to other studies used similar premedication regimen, the incidence of paclitaxel-related IHRs of our study were higher.[7] Symptoms and severity of IHRs were similar to the previous reports.[6,8,16] This study confirmed that younger age was a risk factor for paclitaxel-related IHRs. Surprisingly, new risk factors were found in this study including stage of cancer ≥ 2 and white blood cell count $< 7.735 \times 10^9$/L. Treatment for IHRs in this setting was almost completely successful. These findings inform the careful monitoring of paclitaxel-receiving patient and identify predictive risk factors for IHRs.

Acknowledgments

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