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Brief communication (Original)

Feasibility of withholding dexamethasone premedication for hypersensitivity reactions associated with paclitaxel administration

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Background: Premedication with dexamethasone is crucial to prevent hypersensitivity reactions (HSR) associated with administration of taxanes. However, high dose and prolonged exposure to dexamethasone may cause adverse effects.

Objectives: To determine the incidence of HSR in patients with early breast cancer who did or did not receive dexamethasone prophylaxis for weekly paclitaxel infusions.

Methods: We retrospectively reviewed the records of a cohort of patients with early breast cancer who received paclitaxel weekly from January 2012 through March 2015 at King Chulalongkorn Memorial Hospital. All patients received a standard premedication protocol including dexamethasone before their first paclitaxel infusion. Dexamethasone was omitted in later cycles in some patients at the discretion of the attending physician. Data concerning the baseline characteristics of the patient, details of the premedication protocol, including dose and schedule of dexamethasone, and HSR events were collected in this observational study.

Results: Data were drawn from 86 breast cancer patients (median age 52.6 years) treated with a total of 984 cycles of paclitaxel chemotherapy. No patient had any history of allergy or HSR to taxanes. Dexamethasone was omitted in 617 later cycles. Six patients had grade II–III HSR (7.0%), which occurred mostly during the first 6 cycles (5/6, 83.3%). The incidence of HRS was 3/367 cycles (0.82%) with dexamethasone premedication ($P = 0.99$) and 5/617 (0.81%) without.

Conclusions: Withholding dexamethasone premedication for paclitaxel chemotherapy was feasible, and did not result in a higher incidence of HSR. However, an optimal schedule for dexamethasone warrants investigation in a prospective manner.

Keywords: Dexamethasone premedication, infusion hypersensitivity reaction, paclitaxel

Premedication with dexamethasone, an antagonist of histamine-1 (H1) and histamine-2 (H2) receptors, is a crucial part of the prevention of hypersensitivity reactions (HSRs) associated with administration of taxanes. Although studies of the excipient Cremophor EL (Kolliphor EL) have contributed important knowledge to the mechanism of the paclitaxel HSR, the exact mechanism remains uncertain. Several risk factors, such as menopausal status, high body mass index (BMI), and history of allergy or asthma, have been demonstrated, and might play a role in the development of the HRS to paclitaxel [1]. However, no strong risk factors have been reported to play essential roles in the paclitaxel HSR. Even with the standard premedication, grade I–II and the more severe grade III–IV HSR still develop in 40% and 2%–4% of patients, respectively, paclitaxel is administered every 3 weeks [2-3]. With the recent use of weekly paclitaxel administration in the treatment of adjuvant breast cancer, HSR grade III or higher have been reported in less than 3% of patients [4].

During weekly paclitaxel administration, patients may be exposed to high and prolonged doses of dexamethasone prophylaxis, which may cause notable adverse effects such as weight gain, insomnia, and

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hyperglycemia. Therefore, many physicians may prefer to reduce or withhold dexamethasone premedication in patients who have not experienced HSR to a previous infusion. Previous prospective single-arm studies reported that reducing or withholding dexamethasone was feasible and did not result in an increase in the incidence of HSR [5-7]. Based on the experience at our institute, withholding dexamethasone has been prescribed for patients who did not experience infusion HSR or other significant adverse reactions. Thus, our study aims to evaluate the incidence of infusion HSR in patients with early breast cancer who received dexamethasone premedication during treatment with weekly paclitaxel chemotherapy and those who did not receive dexamethasone premedication.

Patients and methods

Patients

The institutional review board (IRB) of the Faculty of Medicine, Chulalongkorn University approved this retrospective observational study (Certificate of approval No. 600/2015, IRB No. 327/58). The records of a cohort of patients with early breast cancer who received the adjuvant paclitaxel weekly as a single agent, or in combination with trastuzumab from January 2012 through March 2015 at the King Chulalongkorn Memorial Hospital were reviewed. Patients who received at least 6 cycles of weekly paclitaxel administration were also included in our study. Patients who received daily doses of systemic corticosteroid for any reason, patients who received 3 weekly paclitaxel administrations, and patients who received albumin-bound paclitaxel or docetaxel were excluded.

Treatment

All patients received a standard dose of the adjuvant paclitaxel weekly, 80 mg/m^2. Some patients received standard loading doses of 4 mg/m^2 and then 2 mg/m^2 of trastuzumab during weekly paclitaxel administration. All patients received a standard premedication protocol before the first paclitaxel infusion. This standard premedication protocol included dexamethasone 5–20 mg intravenously (iv), oral diphenhydramine 25 mg, and parenteral ranitidine 50 mg, administered at least 30 min before the start of paclitaxel administration. Dexamethasone was omitted in later cycles at the physician's discretion in some patients who did not experience previous infusion hypersensitivity reactions (HSR).

Statistical analysis

Data concerning the incidence of HSR were collected after reviewing medical records and nurse record forms. Patients who received additional doses of H1 receptor antagonists (diphenhydramine or chlorpheniramine), H2 receptor antagonists (ranitidine), dexamethasone, or epinephrine during weekly paclitaxel infusion were also defined to have HSR. Baseline patient characteristics, such as age, menopausal status, BMI, and history of allergy or asthma, and tumor characteristics, such as pathology reports, tumor grade, and TNM staging, were recorded. Details of the premedication protocol, including the dose and schedule of dexamethasone, were also noted. Categorical patient and tumor characteristics were defined using frequencies and percentages, whereas age and body mass index were described using the mean and standard deviation (SD). Patients were categorized into 1 of 2 groups according to their HSR; HSR or no HSR. Patient characteristics, including age, menopausal status, BMI, and history of allergy or asthma were tabulated and compared between the groups using a Fisher exact test. Additionally, in all 984 cycles of paclitaxel administration, the incidence of infusion HSR in cycles with and without dexamethasone premedication were compared using a Fisher exact test.

Results

From January 2012 to March 2015, data from 86 early breast cancer patients who received weekly adjuvant paclitaxel as a single agent or in combination with trastuzumab at the King Chulalongkorn Memorial Hospital were retrospectively reviewed. No patient had any history of HSR associated with taxane exposure. Their median age was 52.6 (range 33–78) years. Approximately 24% were premenopausal. Only 11% of patients in the present study had a BMI greater than 30 kg/m^2. Approximately 70% received weekly paclitaxel as single agent, while approximately 30% received weekly paclitaxel in combination with trastuzumab administration. Approximately 85% of the patients (73 cases) received all 12 cycles of paclitaxel administration, while another 13 women received paclitaxel for at least 6 cycles. Approximately 94% had invasive ductal carcinoma and 97% had stage II–III disease. All but 3 patients received paclitaxel as part of their adjuvant systemic therapy (97%). Other baseline characteristics are listed in **Table 1**.

Table 1. Baseline characteristics of patients and tumors

Baseline characteristic	Breast cancer patients (n = 86)
Age (y) (mean ± SD)	52.6 ± 9.8 (range 33–78)
Body weight (kg) (mean ± SD)	58.8 ± 10.4
Body mass index (kg/m^2) (mean ± SD)	24.5 ± 4.2
Adjuvant/neoadjuvant chemotherapy regimen (number; %)	
Paclitaxel	61 (70%)
Paclitaxel + Trastuzumab	25 (30%)
Received paclitaxel cycle (number; %)	
12 cycles	73 (85%)
>6 cycles	13 (15%)
Menopausal status	
Premenopausal	21 (24%)
Postmenopausal	65 (76%)
Underlying disease	
No allergy/asthma	83 (97%)
Allergy/asthma	3 (4%)
Pathology (number; %)	
Infiltrating ductal carcinoma	81 (94%)
Non infiltrating ductal carcinoma	4 (5%)
Unknown	1 (1%)
Infiltrating ductal carcinoma grading (number; %)	
Grade I	3 (4%)
Grade II	48 (56%)
Grade III	29 (34%)
Unknown	6 (7%)
Staging (number; %)	
Stage I	3 (4%)
Stage II	33 (38%)
Stage III	50 (58%)
Physician preferences (number; %)	
Medical oncology clinic	72 (84%)
Radiation oncology clinic	13 (15%)
Surgical oncology clinic	1 (1%)

There were 8 episodes of grade II–III HSR reported in 6 patients (7%), which occurred mostly during the first six cycles (5/6, 83%). One patient exhibited HSR grade II during the 8th cycle of paclitaxel administration. Additionally, we noticed a higher proportion of premenopausal patients in the group with HSR group than the group without HSR (50% vs. 22.5%, P = 0.15). The baseline characteristics of patients in the group with HSR and the group without HSR are shown in **Table 2**.

Two of the 6 women who reported a history of paclitaxel hypersensitivity developed a HSR grade IIIII after dexamethasone premedication was withheld in either the 2nd cycle (one patient), or the 4th or 5th cycles (one patient). Another 2 women received dexamethasone premedication in the 1st cycle (one patient) and the 5th and 6th cycles (one patient), but they still exhibited HSR grade II–III. All pertinent information from the 6 women with a HSR is shown in **Table 3**.

Table 2. Patient characteristics based on incidence of hypersensitivity reaction (HSR) vs no HSR

Patient characteristic	Total (n=86)	No HSR (n=80)	HSR (n=6)	*P*
Age (y; mean)	52.62	53	46.50	0.12
Body weight (kg; mean)	58.77	59	55.97	0.49
Body mass index (kg/m^2; mean)	24.46	25	23.46	0.54
Body mass index				
<25 (kg/m^2; mean)	53	49 (61%)	4 (67%)	
25–30 (kg/m^2; mean)	23	21 (26%)	2 (33%)	0.87
>30 (kg/m^2; mean)	10	10(13%)	0 (0%)	>0.999
Menopausal status				0.15
Premenopausal	21	18 (22.5%)	3 (50%)	
Postmenopausal	65	62 (77.5%)	3 (50%)	
Underlying disease				
No allergy/asthma	83	77 (96%)	6 (100%)	
Allergy/asthma	3	3 (4%)	0 (0%)	>0.999

Table 3. Hypersensitivity reaction (HSR) in 6 patients after weekly paclitaxel administration

Age (y)	Paclitaxel cycle in which HSR (cycle) developed	Premedication with dexamethasone (dose, mg)	Signs and symptoms of HSR	Note**
33	1st	10 mg	Flushing	After HSR in the 1st cycle, she received dexamethasone 10 mg premedication in all other cycles
54	2nd	0 mg	Sweating, abdominal and back pain	In the 1st cycle, she received 10 mg dexamethasone; it was withheld in the 2nd cycle
43	4th	0 mg	Flushing premedication	No history of dexamethasone
49	8th	0 mg	Back pain	No history of dexamethasone premedication in 1st, 2nd, 4th, 5th, 6th, and 7th cycles. However, she received dexamethasone 5 mg iv in the 3rd cycle
56	4th and 5th	0 mg and 0 mg	Flushing	In the 1st cycle, received 10 mg dexamethasone; it was withheld in the 2nd, 3rd, 4th, and 5th cycles
44	5th and 6th	10 mg and 20 mg	Flushing	Received dexamethasone premedication 10–20 mg iv in all cycles

All 6 women with HSR were retreated with paclitaxel after stopping the infusion and H1-receptor and H2-receptor antagonists were added without another HSR. Of the 6 women, 4 were successfully retreated with paclitaxel in later cycles without further HSR.

Of all 984 cycles of paclitaxel administration, dexamethasone was omitted in 617 later cycles (62.7%). There were 5 episodes of HSR in 617 cycles (0.81%) of paclitaxel administration without dexamethasone premedication, and 3 in 367 (0.82%) with dexamethasone premedication. There was no

significant difference in HSR between the patients who received dexamethasone premedication and those that did not ($P = 0.99$).

In the 80 patients who did not report HSR after paclitaxel infusion, various dexamethasone premedication schedules were noted. In 49% of patients who did not experience previous infusion HSR, dexamethasone was omitted in cycles 2–3. All dexamethasone premedication schedules are shown in **Figure 1**.

Discussions

Here we report grade II–III HSR in 7% of patients with early breast cancer after weekly paclitaxel infusion, which occurred mostly during the first 6 cycles (83.3%) The present study showed a higher proportion of premenopausal women in the group with HSR than the group with no HSR (50% vs 23%, $P = 0.15$). Dexamethasone premedication was omitted in 62.7% of subsequent cycles of paclitaxel administration. Considering 984 cycles of paclitaxel administration, there was no statistically significant difference in HSR between the patients who received dexamethasone premedication and those that did not ($P = 0.99$).

Prolonging paclitaxel infusion and using a premedication protocol are promising strategies in preventing HSR. Although all practical strategies were applied in this study, grade III HSR occurred in approximately 40% of patients. Several risk factors, such as menopausal status, high BMI, history of hypersensitivity, and respiratory dysfunction, are recognized to predict the incidence of paclitaxel HSR in a subgroup of patients with gynecological cancers [1, 8]. Sendo et al. reported 4 risk factors associated with HSR: history of mild dermal reactions in previous courses, presence of respiratory dysfunction, body mass index >25, and postmenopausal status at the time of ovariectomy. These authors concluded that the marked depletion of estrogen may be related to a change in sensitivity to paclitaxel by affecting vascular endothelial function, resulting in the enhancement of the HSR to paclitaxel [1]. Conversely, Piovano et al. reported that postmenopausal women showed a protective effect for HSR, but a history of systemic hypersensitivity was associated with higher HSR [8]. Like Piovano et al., we found an insignificantly higher proportion of women with premenopausal status in the group with HSR than in the group with no HSR (50% vs 23%, $P = 0.15$). Additionally, no significant

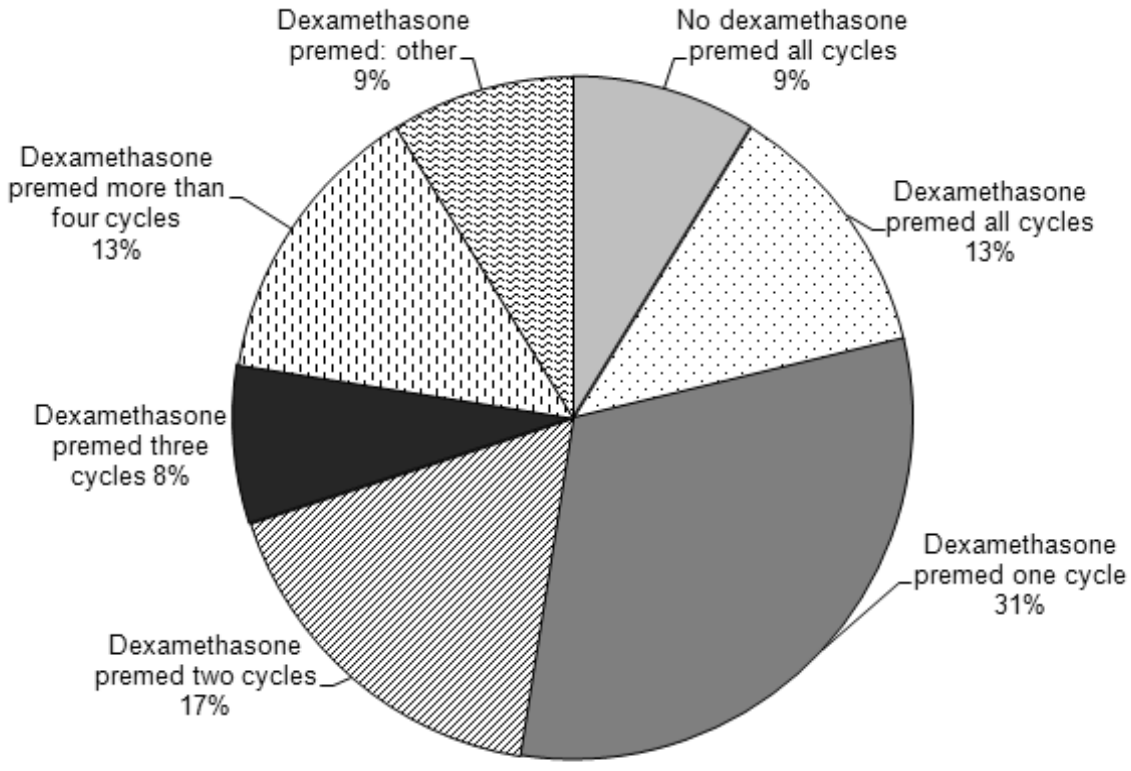

Figure 1. Dexamethasone premedication (premed) schedules in patients with no hypersensitivity reaction (n = 80)

difference in the proportion of women with high BMI between the group with HSR and the group with no HSR was shown in the present study. Because of these inconsistencies, the estrogen level and the risk of HSR to paclitaxel requires extensive exploration in a larger prospective cohort study before forming conclusions concerning the role of estrogen in the risk of developing HSR to paclitaxel.

Reducing or withholding dexamethasone premedication has been investigated in several previous studies with pronounced outcomes. One previous study from Köppler et al. reported that reducing dexamethasone to 10 mg iv before paclitaxel infusion was feasible and safe in 132 patients with various cancers including breast and ovarian cancer who were treated with a 3 week and/or a weekly schedule [5]. Recently, Berger et al. evaluated 70 women with breast cancer and found that none of the 55 patients whose premedication was withheld for all subsequent cycles required treatment for HSR [6]. These authors concluded that stopping premedication was reasonable and might be considered as an alternative option in patients without an increased risk of HSR. Berger et al. [7] also evaluated 234 patients with breast cancer whose dexamethasone premedication was discontinued after none experienced HSR after the first 2 doses of paclitaxel-based chemotherapy. They showed that most of the patients did not report an infusion reaction, and only 2 patients required rescue medication. This large prospective study confirmed that the discontinuation of paclitaxel premedication in patients who did not experience a previous infusion HSR was not correlated with an increased incidence of HSR. The present study showed that dexamethasone could be omitted after 2–3 cycles in 49% of 80 patients who did not report HSR after early cycles of paclitaxel infusion. We found that withholding dexamethasone premedication in Thai women with breast cancer was feasible and safe, without the need for any extra rescue premedication.

Additionally, the long-term use of dexamethasone may have several negative impacts, such as cushingoid symptoms, weight gain, hyperglycemia, hypertension, acne, dyspepsia, edema, anxiety, insomnia, depression, and infection. Reducing, tapering, or withholding dexamethasone premedication strategies may minimize the adverse effects of steroid use. However, our retrospective study could not determine whether the women who received steroid premedication experienced such unfavorable reactions, and further prospective studies are warranted to identify these unacceptable consequences. Preclinical studies found that dexamethasone rendered cancer cells resistant to paclitaxel infusion. Sui M et al. found that premedication with dexamethasone affected the cytotoxic effects of paclitaxel on morphological abnormalities and apoptosis in cells [9]. Hou et al. described that premedication with dexamethasone reduced the inhibitory effect of paclitaxel on tumor growth in mice with ovarian carcinoma xenografts compared with mice treated with paclitaxel alone [10]. Therefore, withholding the dexamethasone protocol should be widespread not only in patients at high risk of steroid-induced side effects, but also in patients in whom excellent outcomes are a priority.

Our retrospective observational study has several limitations. First, even though we included only women with early breast cancer who received more than 6 cycles of weekly paclitaxel chemotherapy, the number of women in this study is small, and this might have affected the reported incidence of HSR. Second, the HSR to paclitaxel was determined by the retrospective review of medical records, and minor reactions may not have been reported. Finally, the adverse effects of steroid use were not identified in this study; thus, further large prospective studies are warranted to validate all comprehensive outcomes.

Conclusion

Withholding premedication with dexamethasone in patients who do not experience hypersensitivity reactions during first few weeks of weekly paclitaxel administration is feasible, and appears to yield a similar incidence of HSR. However, a prospective study to identify the optimal schedule of premedication with dexamethasone for use with the widespread paclitaxel chemotherapy adjuvant regimen is warranted.

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Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

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