EJGO European Journal of Gynaecological Oncology

The effect of aprepitant and dexamethasone combination on paclitaxel-induced hypersensitivity reaction

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Summary

Purpose of investigation: Dexamethasone (DEX) is often administered to prevent paclitaxel (PTX)-induced hypersensitivity reactions (HSR). The DEX dose is reduced when administered in combination with aprepitant (APR). However, the influence of that dose reduction on PTX-induced HSR has not been thoroughly studied. The present authors aimed to investigate the effects of the combined administration of APR and DEX on PTX-induced HSR. *Materials and Methods*: Fifty-one patients who received a three-week PTX regimen in combination with APR and DEX were retrospectively analysed. The authors compared the dose of DEX with the incidence of HSR and other toxicities. *Results*: Patients were stratified into two groups depending on the DEX dose, > 20 mg (group D, 33 patients), and < 12 mg (group reD, 26 patients). The incidence of HSR in Groups D and reD were 51.5% (17/33) and 53.8% (14/26), respectively. The frequencies of other toxicities between the groups were comparable. *Conclusion*: The findings suggest that although a reduction in DEX dose is possible when APR is co-administered, this does not affect the PTX-induced HSR. However, adverse effect should be closely monitored.

Key words: Paclitaxel; Hypersensitivity reactions; Aprepitant; Dexamethasone.

Introduction

Paclitaxel (PTX) is a commonly used anticancer agent for the treatment of various solid tumors, including breast, ovarian, peritoneal, gastric, and non-small-cell lung cancers [1-3]. The administration of PTX is complicated by hypersensitivity reactions (HSRs), the causes of which are not fully understood yet. HSRs include bronchospasm, dyspnea, hypotension/hypertension, shortness of breath, chest pain/tightness, flushing, wheezing, anxiety, and urticaria [4], The identification of HSRs has led to mandatory premedication with 20 mg dexamethasone (DEX) and histamine-1 and -2 receptor antagonists prior to PTX infusion to prevent PTX-induced HSRs [5].

Aprepitant (APR) is a neurokinin-1 (NK1) receptor antagonist developed as a treatment for both acute and delayed chemotherapy-induced nausea and vomiting (CINV) [6]. For CINV management, it is recommended that APR be used in combination with a serotonin antagonist and DEX to prevent nausea/vomiting induced by highly and moderately emetogenic cancer chemotherapy [7, 8]. According to McCrea *et al.*, APR inhibits CYP3A4, a member of the cytochrome P450 superfamily, thereby inhibiting the metabolism of DEX, a substrate of CYP3A4 [9]. The authors found that the area under the concentration-time curve (AUC) of DEX was increased approximately two-fold after administration APR at a dose of 125 mg on day1 and at a dose of 80 mg on days 2 and 5 in healthy adults [9], suggesting that co-administration of APR can increase the effective body exposure to DEX. In addition, a population pharmacokinetics analysis conducted in Japan demonstrated that clearance of DEX decreased by 47.5% if given in combination with APR at a dose of 125 mg on day 1 compared with DEX administration alone [10]. A recent study further validated dose adjustment of DEX when used in combination with APR and determined that the plasma pharmacokinetics of APR are similar in Japanese and non-Japanese patients [11]. Thus, the dose of DEX must be reduced when administered in combination with APR. However, there are few reports investigating the influence of that dose reduction on PTX-induced HSRs. The purpose of this study was to evaluate the effect of co-treatment with APR and DEX on PTX-induced HSRs.

Materials and Methods

Patients

From March 2010 to December 2012, 91 patients received chemotherapy consisting of a combination of PTX, APR, and DEX at Osaka University Hospital. Among these patients, those who received a three-week PTX regimen (n = 51) were selected for this study. The medical records of these patients were reviewed

Revised manuscript accepted for publication September 16, 2015

and the data were collected. This is retrospective observational study report utilizing an electronic medical record system. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Osaka University Hospital.

Evaluation of PTX-induced HSRs

The authors first stratified the patients into two groups based on the DEX dose used for premedication: group D (>20 mg) and group reD (<12 mg). They then compared the frequencies of PTX-induced HSRs according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (Allergic reaction, Anaphylaxis) between the two groups. During the follow-up, patients who received an increased or decreased dose of DEX were added to the number of group D and group reD. The data of these patients were added to both groups prior to performing the analysis.

Evaluation of DEX-induced hyperglycemia

To evaluate DEX-induced hyperglycemia potentially caused by the increased body exposure to DEX when combined with APR, the authors calculated the blood glucose levels of patients with type 2 diabetes before and 7.5 hours after DEX administration.

Statistical analysis

The differences in the mean values between the two groups were assessed using a Fisher's exact test. *P* values less than 0.05 were considered significant.

Results

Patient characteristics

The authors reviewed the medical records of 51 patients who received a three-week regimen of PTX combined with APR and DEX. Patients' characteristics are outlined in Table 1, including sex, average age (range), primary tumor site, chemotherapy regimen, and average dose of PTX. The majority of patients enrolled in this study (39/51) had corpus uteri cancer, for which a three-week PTX regimen is frequently employed. The majority of patients received a combination regimen of epirubicin and carboplatin (TAC regimen, 42/51). Table 2 lists the doses of DEX used for premedication. Patients received either 4 mg (one patient), 6 mg (three patients), 12 mg (22 patients), 20 mg (32 patients) or 32 mg (one patient) and were stratified into two groups, group D (> 20 mg) and group reD (< 12 mg), depending on the DEX dose received. During the follow-up, eight patients were found to have an increased or decreased dose of DEX. The data of these eight patients were added to both groups prior to performing the analysis.

HSR according to DEX dose

The frequencies of the development of HSRs and other toxicities during chemotherapy are outlined in Tables 3 and 4, respectively. The incidence of HSRs was 51.5% (17/33) and 53.8% (14/26) in groups D and reD, respectively, and included the following (group D/group reD): angioedema (1/1), bradycardia (0/0), chest pain (0/1), dyspnea (0/1), flush (8/8), hypotension (3/2), sweating (4/1) and tachycardia (1/0). The difference in HSR frequency between groups D and reD did not differ significantly. Only two patients (belonging to Group D) developed grades 3 and 4 HSR (hypotension). These patients were treated using cardiopulmonary resuscitation (CPR) and administration of anti-allergic agents and subsequent PTX administration was discontinued. Other toxicities that were evaluated include (group D /group reD): digestive symptoms (3/2), dizziness (9/5), drying (0/1), edema (2/5), fatigue (23/14), hoarseness (1/1), hypertension (1/2), insomnia (2/2), itching (3/2), numbness (21/15), pain (26/14), rash (6/3), sleepiness (16/11), swelling of gums (1/1), and taste disorders (2/3). Fatigue, numbness, and pain occurred at the highest frequency and were considered adverse effects of PTX use. Similar to HSRs, the difference in the frequency of other toxicities between the two DEX dosage groups was not statistically significant.

Table 1. — *Clinical characteristics of patients receiving a three-week paclitaxel regimen (n=51)*

	No of patients	Percent (%)
Sex		
Male	3	5.9
Female	48	94.1
Average age, years (range)	61 (42-70)	
Primary tumor site		
Corpus uteri	39	76.5
Lung	4	7.8
Ovarian	1	2.0
Vaginal	1	2.0
Unknown	6	11.8
Concurrent regimen		
TAC	42	82.4
TC	1	7.8
Other	8	15.7
Average dose of PTX (range)	235.6 (200-370)	

Abbreviations: TAC: paclitaxel, epirubicin and carboplatin; TC: paclitaxel and carboplatin; PTX: paclitaxel.

Table 2. — *Dose of dexamethasone used for premedication.*

	Number
Dose of DEX	
Group reD	26
4 mg	1 (1*)
6 mg	3
12 mg	22 (7*)
Group D	33
20 mg	32 (7*)
36 mg	1 (1*)

*Increased or decreased DEX dose during the follow-up.
Abbreviations: DEX: dexamethasone; Group reD, reduced DEX dose group; Group D, high DEX dose group.

Table 3. — *Frequency of hypersensitivity reactions during chemotherapy.*

Hyper sensitivity reactions	Group D (%)	Group reD (%)	*p* value
Angioedema	1 (3.0)	1 (3.9)	
Bradycardia	0	0	
Chest pain	0	1 (3.9)	
Dyspnea	0	1 (3.9)	
Flush	8 (24.2)	8 (30.8)	
Hypotension	3* (9.1)	2 (7.7)	
Sweating	4 (12.1)	1 (3.9)	
Tachycardia	1 (3.0)	0	
Total	17(51.5)	14 (53.8)	0.796

Abbreviations: Group reD, reduced DEX dose group; Group D: high DEX dose group; *: Grade 3 (1 patient) and Grade 4 (1 patient) events as determined by the CTCAE.

Table 4. — *Frequency of other toxicities during chemotherapy.*

Other toxicities	Group D (%)	Group reD (%)	*p* value
Digestive symptom	3 (9.1)	2 (7.7)	
Dizziness	9 (27.3)	5 (19.2)	
Drying	0	1 (3.9)	
Edema	2 (6.1)	5 (19.2)	
Fatigue	23 (69.7)	14 (53.8)	
Hoarseness	1 (3.0)	1 (3.9)	
Hypertension	1 (3.0)	2 (7.7)	
Insomnia	2 (6.1)	2 (7.7)	
Itching	3 (9.1)	2 (7.7)	
Numbness	21 (63.6)	15 (57.7)	
Pain	26 (78.8)	14 (53.8)	
Rash	6 (18.2)	3 (11.5)	
Sleepiness	16 (48.5)	11 (42.3)	
Swelling of gums	1 (3.0)	1 (3.9)	
Taste disorder	2 (6.1)	3 (11.5)	
Total	116	81	0.936

Group reD: reduced DEX dose group; Group D: high DEX dose group.

Evaluation of DEX-induced hyperglycemia

Five patients with type 2 diabetes were enrolled in this study. All five patients self-monitored their blood glucose. To evaluate the effect of DEX on blood glucose, the authors calculated the change in blood glucose levels before and 7.5 hours after DEX administration. They found that blood glucose levels increased 2.29-fold and 2.54-fold following DEX administration in groups D and reD, respectively (Figure 1). However, the increases in blood glucose levels were transient and did not differ significantly between the two groups.

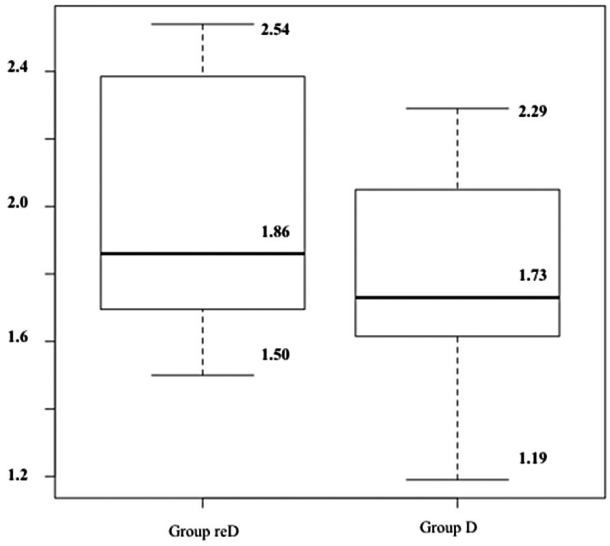

Figure 1. — Ratio of blood glucose levels before and 7.5 hours after DEX administration in type 2 diabetic patients (n = 5). DEX: dexamethazone; Group reD, reduced DEX dose group; Group D, high DEX dose group.

Discussion

The frequency of severe PTX- induced HSRs was 18% in an American phase I clinical trial [12]. Another study reported that of 450 patients, 44 (9.8%) experienced a total of 71 episodes of clinically relevant PTX-associated HSRs [13]. Based on these findings, patients in a clinical trial in Japan were premedicated with histamine H1 and H2 receptor antagonists and corticosteroids prior to PTX administration in an effort to reduce the occurrence of HSRs [5]. This premedication resulted in a decrease in HSRs such that they became a rare event [5]. HSRs are manifested as various symptoms, including skin, cardiovascular, respiratory, digestive system, psychiatric, and nervous system symptoms. Skin symptoms are relatively frequent, but are often either localized and mild or absent. If untreated, moderate symptoms can become severe, developing into systemic reactions. The most intense and immediate HSR is anaphylaxis. Although its frequency is low and unpredictable, it is important to quickly perform CPR and administer shock medication in the event of its occurrence.

Generally, immediate HSRs appear to involve immunoglobulin E. Delayed reactions might be caused by other mechanisms, such as activation of the complement cascade [14]. Although the molecular mechanisms of PTX-induced HSRs have not been elucidated, several mechanisms have been postulated. For example, an immunoglobulin E-mediated mast-cell degranulation by PTX or its solubilizing agent, cremophor EL [4], a non-immunoglobulin E-mediated idiosyncratic mast-cell degranulation by PTX or cremophor EL [15], and complement activation [16] have all been reported. Alternatively, cremophor EL has been reported to activate histamine release [17]. The incidence of HSRs is high with the use of certain

anticancer agents including taxanes (PTX, docetaxel) and platinum drugs (cisplatin, carboplatin, oxaliplatin). Other drugs, including L-asparaginase, cytarabine, bleomycin, and monoclonal antibodies have an even higher reported HSR incidence [18].

In this study, the authors investigated the dose of DEX used prior to PTX in combination with APR. They evaluated the following DEX doses: > 20 mg (group D) and < 12 mg (group reD). There was no significant difference between the two groups in the frequency of PTX-induced HSRs. Additionally, to evaluate DEX-induced hyperglycemia in patients with type 2 diabetes, they monitored blood glucose levels in groups D and reD and found no significant difference between the two groups.

In conclusion, the present retrospective investigation suggested that reducing the dose of DEX is feasible in cases co-administered with APR, although the adverse effects should be carefully monitored in these cases. There was no difference in the development of hyperglycemia among the patients with type 2 diabetes between the high and low DEX dose groups. However, Brunello *et al.* reported that hyperglycemia during chemotherapy for hematologic and solid tumors correlates with increased toxicity [19]. As this study included a low number of patients with type 2 diabetes (five patients), it is essential to carefully monitor DEX-induced hyperglycemia. At present, the authors cannot confirm that the AUC of DEX in all patients increased by about two-fold, when APR was co-administered. Hence, focus should be on preventing the occurrence of PTX-induced HSRs, as the present authors believe that the DEX dose should be reduced only when steroid-induced disease is concerned. These findings require replication and confirmation in a larger prospective trial.

Acknowledgements

The authors thank Ms. Satoko Yamaue and Ms. Chie Konishi for data collection. This study was supported by the Department of Pharmacy, Osaka University Hospital of Japan.

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