RESEARCH ARTICLE

Editorial Process: Submission:08/13/2024 Acceptance:12/14/2024

Efficacy of Omitting H2 Antagonists versus Famotidine in Taxane Hypersensitivity Reactions Prophylaxis: A Randomized, Prospective, Open-Label, Controlled Trial

Chaichana Chantharakhit*, Tanarat Ruchakorn, Pathra Theeratrakul, Buraphat Pengnoraphat

Abstract

Objective: This study aims to evaluate the efficacy of premedication protocols in preventing immediate hypersensitivity reactions (HSRs) to taxane chemotherapy by comparing protocols that omit H2 antagonists with those that include famotidine. **Methods:** This was an open-label, single-center, randomized clinical trial. Randomization was 1:1 to two groups. The experimental arm omitted H2 antagonists from the premedication protocol, while the control arm included famotidine. The efficacy of the premedication protocol for preventing HSRs in the experimental group was compared with that of the control group using a multilevel regression analysis with a random intercept and random effect model. **Results:** Between September 2022 and December 2023, 150 patients enrolled. The group without H2 antagonists had 331 cycles, averaging 3.15 per patient. The famotidine group had 327 cycles, averaging 3.39 per patient. The total number of cycles was not significantly different (p = 0.951). There were six HSRs (1.81%) in the group without H2 antagonists and five (1.53%) in the famotidine group. The HSRs risk difference between groups was 0.28% (95% CI -0.02 to 0.02, p = 1.000). A multilevel regression analysis with a random intercept and effect model compared the efficacy of premedication protocols for preventing HSRs between the experimental and control groups. The risk ratio for HSRs in the group without H2 antagonists was 1.00, which was not statistically significant compared to the famotidine group (95% CI 0.98 to 1.04, p = 0.528). **Conclusion:** The clinical trial demonstrated that omitting the H2 antagonists premedication protocol for taxane chemotherapy is as effective in preventing HSRs as using famotidine. These findings suggest that this protocol can be implemented in clinical practice.

Keywords: Taxane- Hypersensitivity reactions (HSRs)- Premedication- Omitting H2 Antagonists- Famotidine

Asian Pac J Cancer Prev, **25 (12)**, 4333-4338

Introduction

Taxane drugs, such as paclitaxel and docetaxel, are chemotherapy agents classified as anti-microtubule agents. Paclitaxel and docetaxel are used in the treatment of various types of cancer, including non-small cell lung cancer, breast cancer, ovarian cancer, endometrial cancer, esophageal cancer, and cancers of the head and neck, among others. Based on historical usage data, it has been determined that the taxane drug class, specifically paclitaxel, exhibits a high incidence of hypersensitivity reactions (HSRs) [1, 2]. Approximately 30-40% of cases exhibit mild to moderate HSRs, whereas about 1-4% of cases manifest severe reactions [3, 4]. The prevailing hypothesis is that these HSRs are attributable to Cremophor EL, a chemical solvent employed at higher concentrations in paclitaxel relative to other drugs, due to the poor solubility of paclitaxel [5, 6]. Consequently, this leads to a higher incidence of HSRs in patients treated with paclitaxel compared to those treated with other drugs [7].

There are three identified mechanisms for HSRs: IgE-mediated mast cell degranulation, non-IgE-mediated idiosyncratic mast cell degranulation, and complement activation [8, 9]. The reaction's severity relates to Cremophor EL levels, used at higher concentrations in paclitaxel due to its poor solubility. This leads to a higher incidence of hypersensitivity reactions in paclitaxel patients.

Hypersensitivity symptoms typically develop within the first 10 to 15 minutes after infusion. The standard protocol for preventing HSRs includes prolonging infusion time and using premedication drugs like dexamethasone, diphenhydramine (an H1 antagonists), and H2 antagonists such as ranitidine or famotidine. Ranitidine is commonly used in this protocol [10].

In January 2020, the US FDA announced the withdrawal

*Division of Medical Oncology, Department of Internal Medicine, Buddhasothorn Hospital, Chachoengsao, Thailand. *For Correspondence: Chaichana.MD@gmail.com*

of ranitidine from the market due to the detection of the harmful substance N-nitrosodimethylamine (NDMA). This decision led to the global withdrawal and cessation of ranitidine production, affecting its clinical use and making it unavailable. After 2020, data showed that omitting ranitidine from paclitaxel premedication protocols did not increase the risk of HSRs compared to the standard premedication protocol. Additionally, literature indicates that the evidence for using ranitidine to prevent HSRs is less clear than for steroid premedication [11, 12].

However, when ranitidine is unavailable, famotidine, another H2 antagonists, is used as a substitute in the premedication protocol. Previously, a clinical trial found that premedication without ranitidine showed no difference in preventing HSRs compared to with ranitidine [13]. Additionally, retrospective data from Hong Kong showed no difference in HSRs prevention between patients receiving ranitidine and famotidine [14].

This study aims to compare the efficacy of premedication without H2 antagonists to that of famotidine in preventing HSRs in patients undergoing taxane chemotherapy. The study is a randomized prospective open-label controlled trial to further investigate the effectiveness of HSRs prevention.

Materials and Methods

This is an open-label, single-center, randomized clinical trial conducted at a cancer tertiary care hospital in Thailand, using a prospective randomized cohort design from September 2022 to December 2023. Patients are assigned to groups using stratified blocked randomization. The control group consists of patients who received famotidine premedication. The experimental group consists of patients who did not receive H2 antagonists in premedication. Collect data on HSRs in patients during each cycle of taxane-based chemotherapy. Collect data on the following: age, gender, weight, height, type of cancer, chemotherapy regimen received with paclitaxel or docetaxel, and the number of treatment cycles. Eligible patients were aged 18 years or older and required standard treatment with a taxane regimen, including paclitaxel and docetaxel. Patients with severe HSRs to taxanes, such as bronchospasm or hypotension, were excluded. Patients with severe hepatic impairment, defined as bilirubin levels more than 5 times the upper limit of normal (ULN) or AST/ALT levels more than 10 times the ULN, were also excluded. Withdrawal criteria for individual participants include severe hypersensitivity reactions to taxane, such as bronchospasm and hypotension, or the patient's request to withdraw from the study.

Ethical approval was provided by the Institutional Review Board, number BSH-IRB 014/2565. The study was registered with the Thai Registry of Clinical Trials, identification number TCTR20220913005. All participants provided written informed consent before randomization.

Randomization and masking

Eligible patients receiving taxane-based chemotherapy were randomly assigned (1:1) using stratified blocked randomization. They were divided into two groups: one receiving famotidine and the other omitting H2 antagonists in premedication. Stratified random assignment with blocked randomization was based on four strata: male, female, age < 60 years, and age ≥ 60 years. Treatment allocation was not concealed from participants or study investigators.

Premedication protocol

Protocols for premedication are arranged as follows: Dexamethasone 20 mg intravenously, Ondansetron 8 mg orally, Famotidine 20 mg orally (control group) or omitted (study group), Diphenhydramine 50 mg orally, and Chlorpheniramine 10 mg intravenously. Patients received follow-up hematology and laboratory chemistry tests at each chemotherapy visit. They were also assessed for HSRs at each chemotherapy session, according to standard clinical practice.

Outcomes

The primary endpoint was the efficacy of the prevention of HSRs between a premedication protocol without H2 antagonists and a protocol with famotidine. The severity grading system for immediate HSRs is divided into three grades: Grade 1 (Mild): Symptoms are limited to the skin (e.g., flushing) or involve a single organ/system and are mild (e.g., mild back pain). Grade 2 (Moderate): Symptoms involve at least two organs/systems (e.g., flushing and dyspnea) without significant decrease in blood pressure or oxygen saturation. Grade 3 (Severe): Symptoms involve at least two organs/systems, with a significant decrease in blood pressure (systolic <90 mm Hg and/or syncope) and/or oxygen saturation (<92%) [15].

Statistical analysis

This study investigates the efficacy of premedication in taxane chemotherapy. We hypothesize a 15% incidence of HSRs with famotidine based on the findings of Tsoi TT et al. and a 1% incidence without H2 antagonists from the study by Chantharakhit et al. [13, 14]. We used a two-sided test with an alpha of 0.05 and a power of 0.80. With a 1:1 allocation ratio, the required sample size was 72 per group.

The risk difference of HSRs was compared between the group that did not receive H2 antagonists and the group that received famotidine. The HSRs were influenced by the intervention effect and the number of chemotherapy cycles (time effect). These were repeated measures of correlated data. Therefore, The efficacy of the premedication protocol for preventing HSRs in the experimental group was compared with that of the control group using a multilevel regression analysis with a random intercept and random effect model. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using STATA version 16 (StataCorp, TX, USA).

Results

Participants were enrolled from September 2022 to December 2023. 150 patients were randomized to receive premedication without H2 antagonists or with

famotidine. 75 patients received premedication without H2 antagonists, while 75 received premedication with famotidine (see Figure 1). Two patients from the premedication without H2 antagonists group withdrew consent and did not receive the treatment. The baseline characteristics of the participants were balanced between the groups (Table 1). The end of the study was March 20, 2024. The average number of chemotherapy cycles per patient was 3.27. The premedication without H2 antagonists group had 331 cycles, averaging 3.15 per patient. The famotidine group had 327 cycles, averaging 3.39 per patient. There was no significant difference in the total number of cycles between the groups (p = 0.951). Most lung cancer patients received paclitaxel and carboplatin (49 patients, 75%), while 16 patients (25%) received docetaxel monotherapy. Most breast cancer patients received paclitaxel monotherapy (57 patients, 85%), while 10 patients (15%) received a docetaxel-based regimen, as shown in Table 2. Eleven patients (7%) discontinued treatment due to severe taxane-induced peripheral neuropathy.

In 331 cycles in the premedication without H2 antagonists group, 6 HSRs occurred (1.81%). The

Table 1. Patient Prognostic Characteristics

Characteristics	Protocol without H2 antagonists group N=73	Protocol with famotidine group N=75
Age (year)		
Mean (+SD)	55.99 (13.75)	60.45 (12.21)
Age <60 (%)	42 (57.53)	40 (53.33)
Age ≥ 60 (%)	31 (42.47)	35 (46.67)
Gender, N (%)		
Male	23 (31.51)	29 (38.67)
Female	50 (68.49)	46 (61.33)
Cancer type, N (%)		
Lung	29 (39.73)	36 (48.00)
Breast	36 (49.32)	31 (41.33)
Head and neck	3 (4.11)	2 (2.67)
Others	5 (6.85)	6 (8.00)
Chemotherapy regimen, N (%)		
Paclitaxel-based	57 (78.08)	60 (80.00)
Docetaxel-based	16 (21.92)	15 (20.00)
The number of cycles of chemotherapy (cycles)	331	327

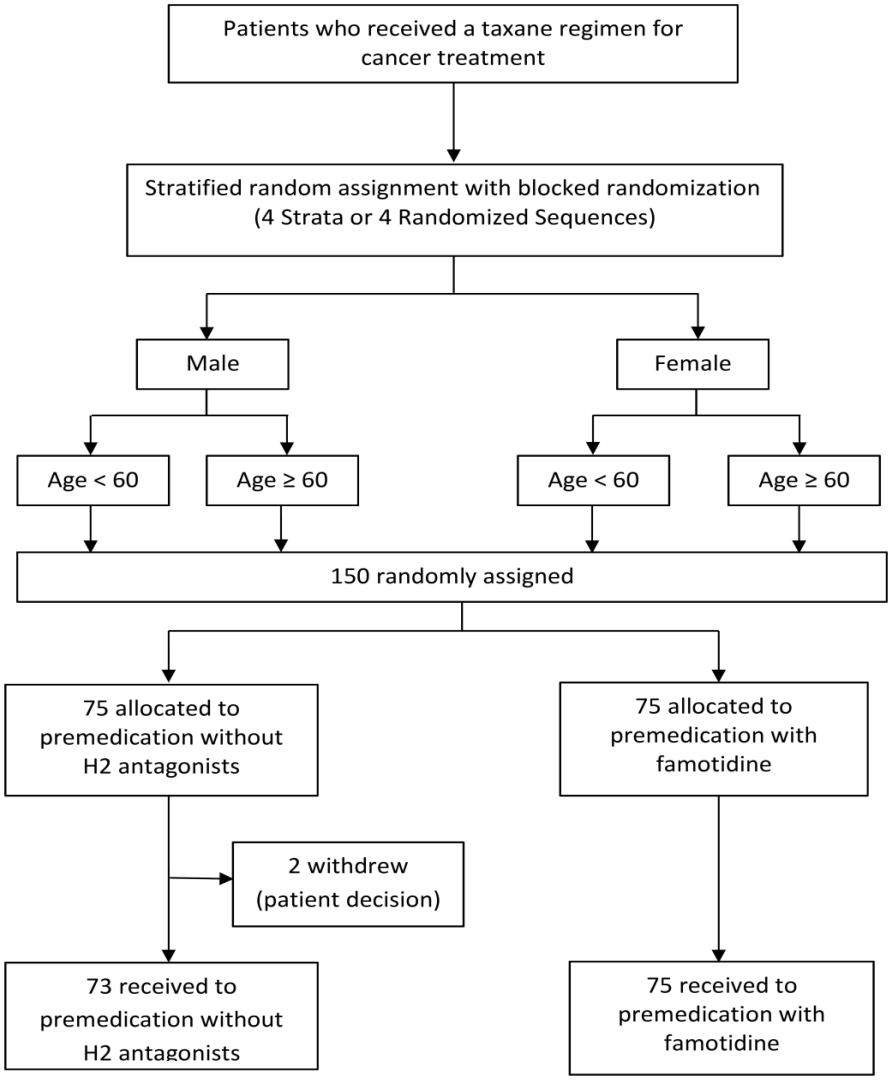

Figure 1. The CONSORT Flow Diagram

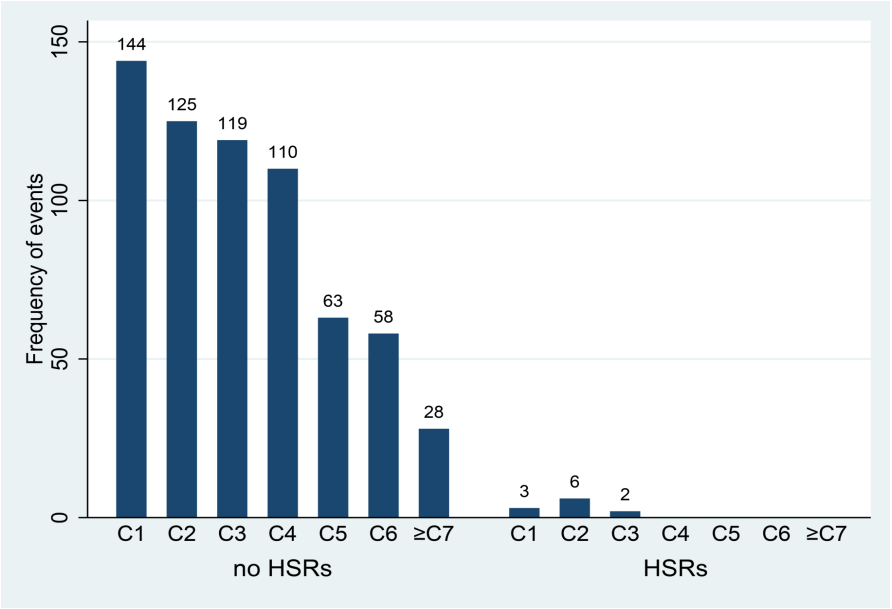

Figure 2. Comparison of Immediate Hypersensitivity Reactions (HSRs) Across Chemotherapy Cycles (C)

Table 2. The Types of Cancer and Chemotherapy Regimens

Cancer type	Paclitaxel (%)	Paclitaxel/ Carboplatin (%)	Docetaxel (%)	Docetaxel/ Cyclophosphamide (%)	Docetaxel/ Gemcitabine (%)	Total (%)
Lung	0 (0)	49 (75)	16 (25)	0 (0)	0 (0)	65 (100)
Breast	57 (85)	0 (0)	9 (13)	1 (2)	0 (0)	67 (100)
Head and neck	0 (0)	5 (100)	0 (0)	0 (0)	0 (0)	5 (100)
Others	0 (0)	6 (55)	3 (27)	0 (0)	2 (18)	11 (100)

famotidine group had 5 HSRs among 327 cycles (1.53%). Grade 3 HSRs were identified in both groups: 2 cases in the group without H2 antagonists premedication and 1 case in the famotidine group, as detailed in Table 3. HSRs can occur from the first chemotherapy session, with the highest incidence during the second cycle (6 cases, 55%) (Figure 2).

The risk difference in HSRs between the premedication without H2 antagonists and famotidine groups was 0.28%. This difference was not statistically significant (95% CI -0.02 to 0.02, p = 1.000). The efficacy of the premedication protocol for preventing HSRs in the experimental group was compared with that of the control group using a multilevel regression analysis with a random intercept and random effect model. The risk ratio for HSRs in the group without H2 antagonists was 1.00. This difference was not statistically significant compared to the famotidine group (95% CI 0.98-1.04, p = 0.528).

Discussion

The study aimed to evaluate the impact of H2 antagonists on HSRs. The findings showed no significant difference in HSRs occurrence between groups receiving premedication with or without H2 antagonists. A key strength of the study is its use of multilevel analysis. This method was selected because the data on HSRs occurrence in taxane chemotherapy patients involve repeated measurements, characteristic of repeated-measure correlation data. The effectiveness of the premedication protocol in preventing HSRs is influenced by the "time effect," including the cycle number and sequence of chemotherapy cycles. It is also influenced by the "treatment effect," or the impact of chemotherapy drugs on patients. Due to varying effects, a multilevel regression analysis with a random intercept and random effects model was used. Previous studies have not used multilevel model analysis for this data.

Based on the mechanism of ranitidine, an H2

Table 3. Immediate Hypersensitivity Reactions (HSRs) between Two Groups of Premedication Methods

Grade	Protocol without H2 antagonists group (Total cycle = 331)	Protocol with famotidine group (Total cycle = 327)
No immediate hypersensitivity reactions (HSRs)	325	322
Grade 1 (mild)	1	2
Grade 2 (moderate)	3	2
Grade 3 (severe)	2	1

antagonists that inhibits the H2 receptor, it affects the secretion of gastric acid when stimulated through IgE. Severe HSRs symptoms include bronchospasm, dyspnea, and hypotension, primarily operating through the H1 receptor pathway [16]. From this mechanism of action, a retrospective study suggests that ranitidine can be omitted from the premedication protocol.

Recent studies indicate that the benefits of premedication with ranitidine are unclear. Ranitidine has been the standard premedication for patients receiving taxane drugs. A recent study found that a premedication regimen without ranitidine is non-inferior to a regimen that includes ranitidine [17]. In the ranitidine group, 20% experienced HSRs, while in the group without ranitidine, 12% experienced HSRs. Additionally, there was no difference in HSRs of grade ≥ 3 between the groups. A retrospective review identified no significant difference in the occurrence of HSRs between patients who received ranitidine premedication and those who did not [18].

Following the unavailability of ranitidine, the British Oncology Pharmacy Association (BOPA) recommended in 2022 the withdrawal of H2 antagonists from paclitaxel premedication regimens due to evidence indicating a lack of benefit [12]. However, there remain questions regarding the use of famotidine as a substitute for ranitidine. Previous data suggests that famotidine may be a viable substitute for ranitidine [14, 19, 20]. However, the incidence of HSRs in this study was 1.81% in the group that omitted H2 antagonists and 1.53% in the group that received famotidine. This is lower than reported in previous reference studies, where the incidence was generally around 10%. For example, the study by Tsoi TT et al. reported an incidence rate of approximately 17-19% [14]. This discrepancy is likely due to variations in premedication protocols, particularly in corticosteroid use, which likely contribute to the observed differences in the incidence of HSRs. In the reference study, corticosteroids were administered as oral dexamethasone, whereas in the present study, dexamethasone was administered through intravenous injection 30 minutes prior to taxane chemotherapy. Previous studies indicate that corticosteroids are crucial in preventing HSRs [3]. These differences in corticosteroid administration may have contributed to the lower and distinct incidence pattern of HSRs observed in this study.

A key benefit of this study is that it clarifies whether H2 antagonists are still beneficial in the paclitaxel premedication regimen. The study confirms through its open-label, randomized clinical trial that omitting H2 antagonists shows no difference compared to using famotidine. The trial aimed to balance the influence of prognostic factors between the two groups. It compared the efficacy of the two premedication methods using a multilevel model, a key highlight of this research.

This study has some minor limitations despite its valuable contributions. The study was conducted in a single center. It included only patients with solid malignancies, which limits its generalizability. The control group used oral famotidine, a medication listed in the Thai National List of Essential Medicines (NLEM). Additionally, famotidine injection is not available in Thailand, so it could not be compared with all forms of famotidine. Further studies involving more diverse patient groups and multicenter settings are required. Additional research is necessary to evaluate the effectiveness of HSRs prevention and to identify predictive factors for HSRs in patients receiving taxane chemotherapy. No significant difference in HSRs occurs during premedication with or without H2 antagonists. Identifying predictive factors for HSRs is crucial for improving patient management and outcomes. Investigating prognostic factors is essential to enhance predictive accuracy and guide clinical decision-making.

In conclusion, the study demonstrated that omitting the H2 antagonists premedication protocol for taxane chemotherapy is as effective in preventing HSRs as using famotidine. Therefore, this approach can be implemented in clinical practice. However, a non-inferiority trial approach to evaluate the omission of H2 antagonists as a new treatment, compared to the standard treatment with H2 antagonists, is suggested for further study. Additionally, future research should aim to identify predictive factors for HSRs to enhance prevention strategies.

Author Contribution Statement

Chaichana Chantharakhit: Designed the study, reviewed the paper, central contact, facility contact information, collected data, analyzed data, draft manuscript preparation, edited the final version. Tanarat Ruchakorn: Site sub-investigator, collected data. Pathra Theeratrakul: Site sub-investigator, collected data. Buraphat Pengnoraphat: Site sub-investigator, collected data. All authors read and approved the final version.

Acknowledgements

The authors express their gratitude to all the team members at the Buddhasothorn Cancer Research Center for their invaluable support in the successful completion of this research project.

Study Registration

The study was registered by the Thai Registry of Clinical Trials with identification number TCTR20220913005.

Ethical Declaration

The study protocol was approved by the Institutional Review Board of Buddhasothorn Hospital number BSH-IRB 014/2565.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

References

1. Panday VRN, Huizing MT, Ten Bokkel Huinink WW, Vermorken JB, Beijnen JH. Hypersensitivity Reactions to the Taxanes Paclitaxel and Docetaxel. Clin Drug Investig. 1997;14(5):418-27.

2. Tsao LR, Young FD, Otani IM, Castells MC. Hypersensitivity Reactions to Platinum Agents and Taxanes. Clin Rev Allergy Immunol. 2022;62(3):432-48. https://doi.org/10.1007/s12016-021-08877-y.
3. Boulanger J, Boursiquot JN, Cournoyer G, Lemieux J, Masse MS, Almanric K, et al. Management of hypersensitivity to platinum- and taxane-based chemotherapy: cepo review and clinical recommendations. Curr Oncol. 2014;21(4):e630-41. https://doi.org/10.3747/co.21.1966.
4. Kloover JS, den Bakker MA, Gelderblom H, van Meerbeeck JP. Fatal outcome of a hypersensitivity reaction to paclitaxel: a critical review of premedication regimens. Br J Cancer. 2004;90(2):304-5. https://doi.org/10.1038/sj.bjc.6601303
5. Surapaneni MS, Das SK, Das NG. Designing Paclitaxel drug delivery systems aimed at improved patient outcomes: current status and challenges. ISRN Pharmacol. 2012;2012:623139. https://doi.org/10.5402/2012/623139.
6. Yang Q, Zu C, Li W, Wu W, Ge Y, Wang L, et al. Enhanced Water Solubility and Oral Bioavailability of Paclitaxel Crystal Powders through an Innovative Antisolvent Precipitation Process: Antisolvent Crystallization Using Ionic Liquids as Solvent. Pharmaceutics. 2020;12(11):1008. https://doi.org/10.3390/pharmaceutics12111008.
7. Szebeni J, Alving CR, Muggia FM. Complement Activation by Cremophor EL as a Possible Contributor to Hypersensitivity to Paclitaxel: an In Vitro Study. J Natl Cancer Inst. 1998;90(4):300-6. https://doi.org/10.1093/jnci/90.4.300.
8. Galateanu B, Pușcașu AI, Tircol SA, Tanase BC, Hudita A, Negrei C, et al. Allergy in Cancer Care: Antineoplastic Therapy-Induced Hypersensitivity Reactions. Int J Mol Sci. 2023;24(4):3886. https://doi.org/10.3390/ijms24043886
9. Mezzano V, Giavina-Bianchi P, Picard M, Caiado J, Castells M. Drug desensitization in the management of hypersensitivity reactions to monoclonal antibodies and chemotherapy. BioDrugs. 2014;28(2):133-44. https://doi.org/10.1007/s40259-013-0066-x.
10. Joerger M. Prevention and handling of acute allergic and infusion reactions in oncology. Ann Oncol. 2012;23 Suppl 10:x313-9. https://doi.org/10.1093/annonc/mds314.
11. Gelderblom H, Zwaveling J. No need for H(2)-antagonists in premedication regimens for paclitaxel infusions: less is more. Br J Cancer. 2021;124(10):1613-4. https://doi.org/10.1038/s41416-021-01316-x.
12. Foreman E, Polwart C, Walker A, Chambers P. Histamine-2 (H2) antagonists can be safely removed from standard paclitaxel premedication regimens. Br J Clin Pharmacol. 2022;88(9):4191-8. https://doi.org/10.1111/bcp.15363.
13. Chantharakhit C, Ruchakorn T, Mungkornkaew S, Amorntrakoon P, Tassanamethee S, Theeratrakul P, et al. Efficacy of Premedication Protocol without Ranitidine for Taxane Regimen: A Multicenter Non-Randomized Historical Controlled Study. Asian Pac J Cancer Prev. 2022;23(4):1331-6. https://doi.org/10.31557/APJCP.2022.23.4.1331.
14. Tsoi TT, Young WM, Cheung YT, Lam TN, Lau CY, Suen SY, et al. Hypersensitivity Reaction to Paclitaxel: A Retrospective Analysis on the Non-Inferiority of Oral Famotidine to Intravenous Ranitidine in Premedication Regimen. Research Square; 2022.
15. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004;114(2):371-6. https://doi.org/10.1016/j.jaci.2004.04.029.
16. Kou E, Zhang X, Dong B, Wang B, Zhu Y. Combination of H1 and H2 Histamine Receptor Antagonists: Current Knowledge and Perspectives of a Classic Treatment Strategy. Life (Basel). 2024;14(2). https://doi.org/10.3390/life14020164.
17. Cox JM, van Doorn L, Malmberg R, Oomen-de Hoop E, Bosch TM, van den Bemt P, et al. The added value of H(2) antagonists in premedication regimens during paclitaxel treatment. Br J Cancer. 2021;124(10):1647-52. https://doi.org/10.1038/s41416-021-01313-0.
18. Ryan M, Snoswell C, Carrington C. Is the use of ranitidine required as a pre-medication to prevent hypersensitivity reactions to paclitaxel? J Pharm Pract Res. 2022;52(1):53-8. https://doi.org/10.1002/jppr.1768.
19. Barroso A, Estevinho F, Hespanhol V, Teixeira E, Ramalho-Carvalho J, Araújo A. Management of infusion-related reactions in cancer therapy: strategies and challenges. ESMO Open. 2024;9(3):102922. https://doi.org/10.1016/j.esmoop.2024.102922.
20. Generali J, Cada DJ. Famotidine: Prevention of Paclitaxel Hypersensitivity Reactions. Hospital Pharmacy. 2001;36(7):766-70