International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 17, Special Issue 1, 2025

Original Article

AN RINVR SCORING EVALUATION OF ONDANSETRON, DEXAMETHASONE, AND RANITIDINE AS ANTIEMETICS IN BREAST CANCER CHEMOTHERAPY

NAJMIATUL FITRIA[1*], RONA SALSABILA RIVALDI[2], DITA PERMATASARI[3]

[1,3]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Andalas, Padang, Indonesia. [2]Faculty of Pharmacy, Universitas Andalas, Padang, Indonesia

*Corresponding author: Najmiatul Fitria; *Email: najmiatulfitria@phar.unand.ac.id

Received: 17 Sep 2024, Revised and Accepted: 20 Nov 2024

ABSTRACT

Objective: Antiemetics is used to control Chemotherapy-Induced Nausea and Vomiting (CINV) in breast cancer patients undergoing ACTH (Adriamycin, Cyclophosphamide, Docetaxel, Herceptin) chemotherapy. This study aimed to assess the effectiveness of an antiemetic regimen consisting of Ondansetron, Dexamethasone, and Ranitidine combination using (Rhodes Index Nausea Vomiting and Retching) RINVR scoring. Additionally, to evaluate the difference in CINV incidence in ACTH cycles.

Methods: A prospective cross-sectional study was conducted from March to June 2024 at Dr. M. Djamil. General Hospital Padang. The study determined the effect of antiemetic administration at the measurement time of 12 h, 24 h, 48 h, 72 h, and 96 h after chemotherapy. There were 30 respondents who met the inclusion criteria in this study. The instrument RINVR (Rhodes Index Nausea Vomiting and Retching) measured the vomit and nausea incidence.

Results: There were differences in the incidence of emesis between ACH dan TH cycles at measurement times of 12 h, 48 h, and 72 h (p-value<0.05). The effect of antiemetic administration showed significant results in the 48 h ACH cycle, which indicates that the higher the cycle, the lower the RINVR score.

Conclusion: The administration of antiemetics was notably effective at the 48 h mark in the ACH cycle, demonstrating a correlation between higher chemotherapy cycles and lower RINVR scores. These findings highlight the importance of tailored antiemetic strategies to improve patients' comfort and treatment outcomes.

Keywords: Breast cancer, ACTH chemotherapy, Antiemetic, Nausea and vomiting

DOI: https://dx.doi.org/10.22159/ijap.2025.v17s1.15 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Breast cancer is one of the most commonly diagnosed cancers in the world, surpassing lung cancer. Based on GLOBOCAN data for 2020, there are an estimated 2.3 million new cases, representing 11.7% of all cancer cases. The disease ranks as the fifth leading cause of cancer death worldwide, with a death toll of 685,000 [1, 2]. In Indonesia, breast cancer ranks first in the number of cancers and is one of the first causes of death caused by cancer. Based on GLOBOCAN data in 2020, there were 16.6% new cases of breast cancer from the total number of cancer patients in Indonesia reached 68,858 out of a total of 396,914 patients with cancer [2, 3]. Breast cancer treatment can be done with chemotherapy to destroy and stop the growth of cancer cells, which can be given singly and in combination [4–7]. The chemotherapy regimen given to patients depends on the behavior of cancer cells, such as HER2 expression [8–10]. HER2-positive patients are recommended to use chemotherapy drugs from the anthracycline and/or taxane class and combined with Herceptin/Trastuzumab [11, 12]. The combination that can be used is ACTH [13, 14].

Despite its ability to kill cancer cells, chemotherapy can take its toll on patients. Chemotherapy-induced nausea and vomiting (CINV) is one of the most debilitating side effects of cancer treatment and affects up to 40% of patients [15–17]. Many antiemetic agents with different mechanisms of action have been developed for CINV, usually given as prophylactic drugs [18–20].

In a previous study by looking at CINV that occurred in patients who received four antiemetic regimens, three antiemetic regimens, two antiemetic regimens, and monotherapy, the results showed that the incidence of CINV was relatively high despite receiving antiemetics with different regimens [21, 22]. In addition, another study in breast cancer patients using the RINVR instrument found the highest incidence of nausea and vomiting at 60 h [23, 24]. The RINVR (Rhodes Index of Nausea, Vomiting, and Retching) scoring system provides a reliable, validated, and standardized tool for quantifying the severity of nausea and vomiting, enabling consistent assessment across clinical settings and improving the evaluation of antiemetic treatment efficacy. Based on this background, the aim of this study was conducted that only focused on ACTH chemotherapy regimens in breast cancer at Dr. M. Djamil Central General Hospital Padang. This study was conducted to see the difference in the incidence of emesis in ACH and TH cycles in breast cancer patients at Dr. M. Djamil Central General Hospital Padang and determine the effect of three combinations of antiemetic (Ondasentron, Dexamethasone, and Ranitidine) administration at 12 h, 24 h, 48 h, 72 h, and 96 h using the RINVR instrument.

MATERIALS AND METHODS

Research design and target population

This study was quantitative, with prospective data collection using a follow-up design. The study was conducted by telephone interview at five measurement times, at 12 h, 24 h, 48 h, 72 h, and 96 h after chemotherapy. The study was carried out in the One Day Care chemotherapy room of Dr. M. Djamil Central General Hospital Padang-research time during March to June 2024. The sample were breast cancer patients who met the inclusion criteria. Data samples were taken non-randomly using purposive sampling techniques, which met the inclusion criteria to be sampled in this study. The sociodemographic data collection form included age, education, occupation, income, and chemotherapy cycle. Establishing well-defined and inclusive inclusion criteria is imperative to minimize bias associated with non-random purposive sampling, particularly in the collection of sociodemographic data.

Inclusion and exclusion criteria

The inclusion criteria in this study were breast cancer patients in the One Day Care chemotherapy room of Dr. M. Djamil Central General Hospital Padang from March to June 2024, receiving antiemetic therapy (Ondansetron, Dexamethasone, and Ranitidine), patients of

female gender, patients who had been undergone surgery and interviews conducted every 24 h, 48 h, 72 h, and 96 h after chemotherapy. Meanwhile, patients with metastases, male gender, and non-surgical patients were excluded from this study. Thirty respondents met the inclusion criteria.

Research instrument

The instrument used was the RINVR questionnaire, popularized by Rhodes [24, 25]. This instrument has been tested for validity and reliability [24]. RINVR is used to assess the incidence of nausea and vomiting experienced by patients after chemotherapy. RINVR uses an assessment score of 0 (no nausea and vomiting), 1-8 (mild nausea and vomiting), 9-16 (moderate nausea and vomiting), 17-24 (severe nausea and vomiting), and 25-32 (severe nausea and vomiting) [23]. The RINVR comprises eight questions that assess the severity, frequency, and distress caused by nausea, vomiting, and retching, offering a comprehensive and standardized evaluation for both clinical and research purposes [24].

Data analysis

Sociodemographic data in this study will be analyzed descriptively. The data were analyzed using the Kruskal-Wallis test to see the difference in the incidence of nausea and vomiting experienced by patients in the ACH cycle and TH cycle. The Kruskal-Wallis test was used instead of ANOVA because the dataset did not meet the assumptions of normality and homogeneity of variances required for ANOVA, as indicated by normality test using Saphiro-Wilk ($p<0.05$). Ondansetron acts by blocking serotonin-mediated nausea and vomiting through 5-HT3 receptors (acute phase), dexamethasone enhances antiemetic efficacy by suppressing inflammation and prostaglandin pathways (acute and delayed phases), while ranitidine protects gastric mucosa by inhibiting histamine-2 receptors, preventing chemotherapy-induced gastrointestinal complications. Linear regression analysis was conducted to see the difference in scores at each measurement time.

RESULTS

Research conducted prospectively in the One Day Care chemotherapy room of Dr. M. Djamil Central General Hospital Padang obtained 40 respondents who met the inclusion criteria. However, only 30 patients picked up the phone, so the sample in this study was 30 respondents. The sociodemographic profile can be seen in table 1.

Table 1: Sociodemographic characteristics

No.	Sociodemographic characteristics		n	%
1.	Age	Early adulthood (26-35 y old)	4	13.3
		Late adulthood (36-45 y old)	6	20
		Early elderly (46-55 y old)	16	53.3
		Late elderly (>55 y old)	4	13.3
2.	Educational attainment	Low education (not in school/elementary school)	4	13.3
		Secondary education (junior high school/senior high school)	17	56.7
		Higher education (Diploma/Bachelor's degree)	9	30
3.	Occupation	Housewife	22	73.3
		Teacher	4	13.3
		Nurse	1	3.3
		Retired	1	3.3
		Farmer	1	3.3
		Self-employed	1	3.3
4.	Income	No income	22	73.3
		Have income	8	26.7

Analyzed using Descriptive Analysis (Data analyzed based on a sample size of 30 respondents who met the inclusion criteria)

The table 1 above describes the sociodemographic characteristics grouped by age, latest education, occupation, and income. From 30 respondents of breast cancer patients, it was found that most patients were in the early elderly with an age range of 46-55 y at 53.3%. In the characteristics of education level, it was found that most breast cancer patients belonged to the middle education category (junior high school/high school) at 56.7%. The next characteristics are occupation and income. From the data above, 73.3% of breast cancer patients are housewives.

Table 2 presents the incidence of emesis in both the ACH (Adriamycin, Cyclophosphamide, Herceptin) and DH (Docetaxel, Herceptin) groups. This table compares nausea and vomiting episodes measured using RINVR scores over several time points (12, 24, 48, 72, and 96 h) post-chemotherapy.

There is a difference in the incidence of emesis in ACH and TH cycles in table 2. This difference is seen at the measurement time of 12 h, 48 h, and 72 h after chemotherapy. The ACH cycle, which is highly emetogenic, indicates that more than 90% of patients given this chemotherapy agent will experience nausea and vomiting. Meanwhile, the TH cycle, which is moderately emetogenic, indicates that about 30-90% of patients given this chemotherapy will experience nausea and vomiting [26]. This results indicated that the incidence of emesis should differ at each measurement time between ACH and TH cycles due to the difference in emetogenic levels between these cycles [21, 22].

Table 2: Differences in the incidence of emesis in ACH and TH cycles

RINVR			
Measurement time	**ACH**	**TH**	**p-Value***
	Mean±SD	**Mean±SD**	
12 h	3.6±4.478	0.58±1.742	0.022
24 h	1.18±2.089	0.42±1.835	0.117
48 h	5.64±4.388	1.26±3.462	0.001
72 h	3.64±5.104	0.84±3.023	0.029
96 h	4.00±5.138	1.32±2.829	0.111

*Analysed using kruskal wallis (Data analyzed based on a sample size of 30 respondents who met the inclusion criteria)

The antiemetic used in this study was a combination of Ondansetron, Dexamethasone, and Ranitidine. According to the literature, chemotherapeutic agents with high emetogenicity need to be given a 3-drug antiemetic regimen, which are Ondansetron, Dexamethasone, and Aprepitant [27]. However, aprepitant is not included in the National Formulary drug list, so this drug is not used in the hospital [28].

Table 3 presents a regression analysis examining the relationship between chemotherapy regimens and the severity of nausea and vomiting over time, as measured by RINVR scores.

Table 3: Effect of antiemetic administration at each measurement time

Chemotherapy	Measurement time	R^2	Sig
ACH	12 h	0.33	0.508
	24 h	0.001	0.485
	48 h	0.046	0.036
	72 h	0.175	0.921
	96 h	0.010	0.198
TH	12 h	0.003	0.991
	24 h	0.007	0.624
	48 h	0.092	0.314
	72 h	0.030	0.604
	96 h	0.085	0.377

Analysed using: linear regression (Data analyzed based on a sample size of 30 respondents who met the inclusion criteria)

The R^2 values indicate the proportion of variance in emesis explained by the chemotherapy regimens at different time points, while the significance values (Sig) reveal the statistical relevance of these relationships. The p-values of ACH and TH cycles at measurement times of 12 h, 24 h, 48 h, 72 h, and 96 h were obtained. The result is significant if the sig value is<0.05. Notably, at the 48 h mark, the ACH regimen significantly correlates with emesis severity (R^2 = 0.046, Sig = 0.036), whereas the TH regimen does not demonstrate any statistically significant relationships across all measured intervals. The findings suggest that the combination of Ondansetron, Dexamethasone, and Ranitidine may not provide uniform control of emesis across all time points for both chemotherapy regimens. This underscores the potential need to explore alternative or additional antiemetic strategies tailored to specific chemotherapy protocols or individual patient profiles. The low R^2 values indicate the limited explanatory power of the tested variables, highlighting that other factors, such as genetic predisposition, previous chemotherapy experience, or anxiety levels, may significantly influence emesis control. Notably, the significant finding at 48 h for the ACH group warrants further investigation to determine why the antiemetic regimen demonstrates greater effectiveness at this specific time point. Conversely, the absence of significant findings for the TH group suggests the need to examine whether this chemotherapy regimen requires a different antiemetic approach. Overall, the results imply that a one-size-fits-all antiemetic protocol may not be optimal. Instead, stratified approaches based on chemotherapy regimens or individual patient factors should be considered to enhance the effectiveness of emesis management.

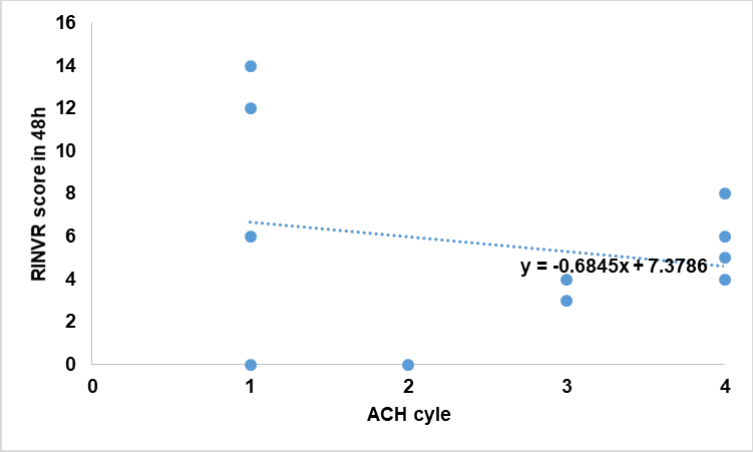

Fig. 1: ACH cycle 48 h

Fig. 1 shows a decreasing graph in the ACH cycle with a measurement time of 48 h. This indicates that in these cycles and hours, the more the cycle increases, the RINVR score decreases. The scatter plot with a trendline illustrates the relationship between the number of Adriamycin, Cyclophosphamide, and Herceptin (ACH) chemotherapy cycles and the RINVR (Rhodes Index of Nausea, Vomiting, and Retching) scores measured 48 h after chemotherapy. The x-axis shows the number of ACH cycles, ranging from 1 to 4, while the y-axis represents the RINVR scores, which reflect the severity of nausea and vomiting experienced by patients.

The trendline equation, y = 7.38-0.68x, indicates that the average RINVR score decreases by 0.68 units for each additional ACH chemotherapy cycle. However, the R^2 value of 0.046 suggests that only 4.6% of the variability in RINVR scores is explained by the number of cycles, indicating a weak correlation between these two variables.

DISCUSSION

The chemotherapy regimen used in this study is a combination of ACTH (Adriamycin Cyclophosphamide+Docetaxel Herceptin), which is used for breast cancer patients with HER2 positive. In this management, ACTH chemotherapy is given as many as eight cycles with an interval of 3 w. In cycles 1-4, the drugs given are Adriamycin Cyclophosphamide and Herceptin, while in cycles 5-8, Docetaxel and

Herceptin are given [29]. To address the significant variability in RINVR scores among patients undergoing the same treatment, it is essential to consider sociodemographic factors that may contribute to this variability. Age is a key factor, as different age groups-such as early adulthood, late adulthood, early elderly, and late elderly-may, respond differently to chemotherapy due to variations in metabolic rates, immune system function, and overall health status [24]. By considering these sociodemographic factors, the study can offer a more nuanced understanding of the variability in chemotherapy outcomes, highlighting the need for personalized approaches to manage chemotherapy-induced nausea and vomiting.

The incidence of CINV in patients depends on the emetogenicity of the chemotherapy drugs. The emetogenic level of cancer drugs is divided into four levels: high, medium, low, and minimal [23]. Adriamycin and Cyclophosphamide chemotherapy each have different emetogenic levels based on dose. Still, the MASCC/ESMO and NCCN literature explains that any chemotherapy regimen containing Anthracycline and Cyclophosphamide falls into the high emetogenic category [30]. Thus, cycles 1-4 of this regimen are highly emetogenic. In cycles 5-8, the chemotherapeutic agents used are Docetaxel and Herceptin. Docetaxel is at a low emetogenic level (level 2), while Herceptin is at a minimal level (level 1). According to the literature, adding one or more agents from level 2 can increase the emetogenicity of the combination by one level greater than the most emetogenic agent in the regimen [5]. Based on algorithm on Dipiro, Docetaxel and Herceptin agents moved up 1 level to level 3, which is a moderate level [14].

The combination of two highly emetogenic drugs (Adriamycin and Cyclophosphamide) amplifies the risk and severity of CINV, making ACH more challenging to manage in terms of nausea and vomiting compared to the TH regimen, whereas Docetaxel's emetogenic potential is lower [11]. The presence of Adriamycin and Cyclophosphamide in the ACH regimen is the primary reason why patients undergoing this treatment tend to experience worse nausea and vomiting than those on the TH regimen [12]. Adriamycin and Cyclophosphamide combination therapy can cause various gastrointestinal disturbances, including nausea, vomiting, decreased appetite, and hyperacidity [31].

CINV that occurs in the first 24 h after chemotherapy is called the acute phase, while that happens after 24 h is the delayed phase [30, 32]. Table 3 shows the average incidence of nausea and vomiting at five measurement times of ACH and TH chemotherapy. The average of all measurements showed mild nausea and vomiting. In the ACH cycle, the highest average nausea and vomiting was at the 48 h measurement time, the delayed phase, and the lowest at the 24 h, the acute phase. The results align with research conducted by Naito, Y. *et al.* (2020) by measuring the incidence of nausea and vomiting in chemotherapy agents with high emetogenic and moderate emetogenic [33]. The same results were obtained, which were nausea and vomiting. In high or moderate emetogenic agents, the highest occurred in the delayed phase [14].

Ondansetron is an antiemetic of the 5-HT3 RA class. It works by inhibiting serotonin receptors, usually in the acute phase [16, 27]. In addition to Ondansetron, patients are also given Dexamethasone. This drug can provide a booster effect for other antiemetics, which can increase antiemetic effectiveness [34–36]. According to NCCN and several studies, dexamethasone can cause dyspepsia, so it is necessary to give Histamine H2 antagonist Ranitidine [37,38].

Despite the slight downward trend in nausea and vomiting severity with more ACH cycles, the low R^2 value implies that other factors likely influence the variability in RINVR scores. Additionally, the data points highlight considerable variability in nausea and vomiting severity for the same number of cycles, reinforcing that factors beyond the number of cycles contribute to the observed outcomes. These results are in line with research conducted by Smit *et al.* in 2019, where from the results of her study, there was a relationship between the chemotherapy cycle and the incidence of nausea and vomiting; the more the chemotherapy cycle increases, the more the occurrence of nausea and vomiting decreases [39, 40].

The study demonstrates several strengths in assessing Chemotherapy-Induced Nausea and Vomiting (CINV). It comprehensively evaluates CINV across different chemotherapy cycles and emetogenic levels, including both acute and delayed phases. Additionally, the study evaluates the effectiveness of antiemetic treatments, and its findings align with existing research, which enhances the credibility of the results. However, the study also has notable weaknesses. There is significant variability in nausea and vomiting severity among patients, suggesting that factors beyond the number of chemotherapy cycles may influence outcomes. The study's cross-sectional design limits the ability to draw conclusions about causality or changes over time, and sampling issues, such as some patients being unwilling or unavailable for interviews, may affect the representativeness and completeness of the data. The next challenges include addressing the variability in CINV severity and evaluating antiemetic treatments' long-term effectiveness and side effects. Future research could benefit from a longitudinal design to better understand the dynamics of CINV over multiple cycles and to refine management strategies. Additionally, future research should address these gaps by including a more diverse cohort encompassing both genders and patients with various cancer stages, investigating newer and more effective antiemetic combinations tailored to chemotherapy regimens, and incorporating quality-of-life assessments to provide a holistic evaluation of interventions, thereby enhancing the clinical relevance and applicability of findings to improve patient care.

CONCLUSION

The study evaluates the effectiveness of Ondansetron, Dexamethasone, and Ranitidine in controlling CINV, using RINVR scoring to assess the severity of symptoms. While Ondansetron and Dexamethasone effectively manage nausea and vomiting, the variability in patient responses indicates that individual factors may influence treatment efficacy. The study suggests that while these antiemetic agents are crucial for controlling CINV, there remains a need for personalized treatment strategies to address the diverse responses among patients. Overall, this research provides valuable insights into the comparative effectiveness of antiemetic therapies in breast cancer chemotherapy and highlights the importance of tailored treatment approaches to optimize nausea and vomiting control. Future studies should continue to explore factors affecting individual responses to enhance the management of CINV in cancer patients.

ACKNOWLEDGMENT

The authors acknowledged the Dr. M. Djamil Central General Hospital Padang staff for their valuable support on this study, which provided access to conduct the study in the chemotherapy room.

FUNDING

The authors confirm that they did not receive any funding, grants, or favors while creating this manuscript.

AUTHORS CONTRIBUTIONS

The contributions to this study were distributed equally among the team members to ensure a comprehensive and collaborative effort. NF led the conception and design of the study, providing the foundational framework and research objectives. The acquisition of data was meticulously carried out by RSR and DP, who were instrumental in collecting and organizing the data necessary for the analysis. The drafting of the manuscript was a collaborative effort, with RSR and NF jointly developing the text, integrating the findings, and refining the content to ensure clarity and scientific rigor.

CONFLICT OF INTERESTS

The author(s) have disclosed no relevant financial or non-financial interests.

REFERENCES

1. Organization WH, WHO. Breast Cancer; 2023.
2. Sung HH, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. doi: 10.3322/caac.21660, PMID 33538338.

3. Nindrea RD, Aryandono T, Lazuardi L, Dwiprahasto I. Family history of breast cancer and breast cancer risk between Malays ethnicity in Malaysia and Indonesia: a meta-analysis. Iran J Public Health. 2019;48(2):198-205. doi: 10.18502/ijph.v48i2.814, PMID 31205873.
4. Trayes KP, Cokenakes SE. Breast cancer treatment. Am Fam Physician. 2021;104(2):171-8. PMID 34383430.
5. Smolarz B, Nowak AZ, Romanowicz H. Breast cancer-epidemiology, classification, pathogenesis and treatment (review of literature). Cancers (Basel). 2022;14(10):2569. doi: 10.3390/cancers14102569, PMID 35626173.
6. Divya G, Kumar JK, Praven A, Smitha P. Lakhs mi R. A study to assess knowledge, attitude and practice on breast cancer among women in Government General Hospital. Asian J Pharm Clin Res. 2021;14(2):60-5.
7. Bhosale RR, Janugade BU, Chavan DD, Thorat VM. Current perspectives on applications of nanoparticles for cancer management. Int J Pharm Pharm Sci. 2023;15(11):1-10. doi: 10.22159/ijpps.2023v15i11.49319.
8. Desriani A, Azamris SS, Ghaissani SS, Kinanti SR, Warisman MA, Fitria N. Design and characterization of a SYBR Green I-based melting curve method for investigation of HER2I655V polymorphism in breast cancer. J Genet Eng Biotechnol. 2021;19(1):6. doi: 10.1186/s43141-020-00108-9, PMID 33428029.
9. Jang BS, Han W, Kim IA. Tumor mutation burden, immune checkpoint crosstalk and radiosensitivity in single-cell RNA sequencing data of breast cancer. Radiother Oncol. 2020;142:202-9. doi: 10.1016/j.radonc.2019.11.003, PMID 31767471.
10. Desriani D, Azamris A, Rustamadji P, Abna IM, Ibadurrahman I, Fuad AM. Sensitive detection of PIK3CA exon 20 H1047R breast cancer based on low-cost intercalary dye SYBR green i real-time qPCR assay. Sains Malays. 2024;53(11):3683-93. doi: 10.17576/jsm-2024-5311-12.
11. Pusztai L, Yau C, Wolf DM, Han HS, Du L, Wallace AM. Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. Ann Oncol of F J Eur Soc Med Oncol. 2022;32(5):1277-92.
12. Xu B, Li W, Zhang Q, Shao Z, Li Q, Wang X. Pertuzumab, trastuzumab, and docetaxel for Chinese patients with previously untreated HER2-positive locally recurrent or metastatic breast cancer (puffin): a phase III, randomized, double-blind, placebo-controlled study. Breast Cancer Res Treat. 2020;182(3):689-97. doi: 10.1007/s10549-020-05728-w, PMID 32564260.
13. Lin YY, Gao HF, Yang X, Zhu T, Zheng XX, Ji F. Neoadjuvant therapy in triple-negative breast cancer: a systematic review and network meta-analysis. Breast. 2022;66:126-35. doi: 10.1016/j.breast.2022.08.006, PMID 36265208.
14. Dipiro J, Yee G, Posey M, Haines S, Nolin T, Ellingrod V Annals of Pharmacotherapy. Pharmacotherapy: a pathophysiologic approach. 11th ed. 11th ed. McGraw-Hill Companies Incorporated; 2020.
15. Yeo W, Lau TK, Li L, Lai KT, Pang E, Cheung M. A randomized study of olanzapine-containing versus standard antiemetic regimens for the prevention of chemotherapy-induced nausea and vomiting in Chinese breast cancer patients. Breast. 2020;50:30-8. doi: 10.1016/j.breast.2020.01.005, PMID 31978815.
16. Uchida E, Lei MM, Roeland E, Lou U. Evaluating the incidence of chemotherapy-induced nausea and vomiting in patients with B-cell lymphoma receiving dose-adjusted EPOCH and rituximab. J Oncol Pharm Pract. 2022;28(1):119-26. doi: 10.1177/1078155220985919, PMID 33435826.
17. Fitria N, Wulansari S, Sari YO. Potential interactions analysis of antihypertensive drugs used in geriatric. Int J App Pharm. 2023;15 Special Issue 1:29-33. doi: 10.22159/ijap.2023.v15s1.47503.
18. Nawa Nishigaki M, Kobayashi R, Suzuki A, Hirose C, Matsuoka R, Mori R. Control of nausea and vomiting in patients receiving anthracycline/cyclophosphamide chemotherapy for breast cancer. Anticancer Res. 2018;38(2):877-84. doi: 10.21873/anticanres.12297, PMID 29374715.
19. Al-Salloum HF, Al-Harbi HE, Abdelazeem A. Effectiveness of antiemetic in reducing chemotherapy-induced nausea and vomiting in adult patients; An oncology center experience. J Oncol Pharm Pract. 2023;29(6):1317-25. doi: 10.1177/10781552221118634, PMID 36518002.
20. Fitria N, Lailaturrahmi L, Sukma A. The effect of consuming fermented milk containing probiotics during pregnancy the effect of consuming fermented milk containing probiotics during pregnancy. IOP Conf Ser Earth Environ Sci. 2024;1341(1):1-7.
21. Fleming MK, Carr A, Li J, Lundberg JD, Rogers KA. Antiemetic medication efficacy during EPOCH and R-EPOCH treatment. J Oncol Pharm Pract. 2021;27(7):1691-8. doi: 10.1177/1078155220967722, PMID 33092500.
22. Yeo W, Chan VT, Li L, Lau TK, Lai KT, Pang E. Dataset on chemotherapy-induced nausea and vomiting (CINV) and quality of life (QOL) during multiple chemotherapy cycles among a Chinese breast cancer patient population who were randomized to antiemetic regimens with or without olanzapine. Data Brief. 2020;30:105421. doi: 10.1016/j.dib.2020.105421, PMID 32215313.
23. Shinn HK, Lee MH, Moon SY, Hwang SI, Lee CS, Lim HK. Post-operative nausea and vomiting after gynecologic laparoscopic surgery: comparison between propofol and sevoflurane. Korean J Anesthesiol. 2011;60(1):36-40. doi: 10.4097/kjae.2011.60.1.36, PMID 21359079.
24. Nelwati N, Noviyani D. The effect of diaphragmatic breathing on nausea, vomiting and functional status among breast cancer patients undergoing chemotherapy. Eur J Oncol Nurs. 2024;70:102548. doi: 10.1016/j.ejon.2024.102548, PMID 38513453.
25. Rhodes VA, McDaniel RW. The index of nausea, vomiting, and retching: a new format of the lndex of nausea and vomiting. Oncol Nurs Forum. 1999;26(5):889-94. PMID 10382187.
26. Gupta K, Walton R, Kataria SP. Chemotherapy-induced nausea and vomiting: pathogenesis, recommendations, and new trends. Cancer Treat Res Commun. 2021;26:100278. doi: 10.1016/j.ctarc.2020.100278, PMID 33360668.
27. Song Z, Wang H, Zhang H, Zhao K, Zhang M, Yang F. Efficacy and safety of triple therapy with aprepitant, ondansetron, and prednisone for preventing nausea and vomiting induced by R-CEOP or CEOP chemotherapy regimen for non-Hodgkin lymphoma: a phase 2 open-label, randomized comparative trial. Leuk Lymphoma. 2017;58(4):816-21. doi: 10.1080/10428194.2016.1213838, PMID 27545191.
28. Majem M, de las Penas R, Virizuela JA, Cabezon Gutierrez L, Cruz P, Lopez Castro R. SEOM clinical guideline update for the prevention of chemotherapy-induced nausea and vomiting (2021). Clin Transl Oncol. 2022;24(4):712-23. doi: 10.1007/s12094-022-02802-1.
29. Kementerian Kesehatan RI. Pedoman nasional pelayanan Kedokteran tata Laksana kanker payudara. Jakarta. Kementerian Kesehatan Republik Indonesia; 2019.
30. Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol. 2016;27 Suppl 5:v119-33. doi: 10.1093/annonc/mdw270, PMID 27664248.
31. Jamali J, Dayo A, Adeel A, Qureshi Y, Khan T, Begum S. A survey on gastrointestinal adverse drug reactions of doxorubicin and cyclophosphamide combination therapy. J Pak Med Assoc. 2018;68(6):926-8. PMID 30325912.
32. Uchida M, Nakamura T, Makihara Y, Suetsugu K, Ikesue H, Mori Y. Comparison of antiemetic effects of granisetron and palonosetron in patients receiving Bendamustine-based chemotherapy. Pharmazie. 2018;73(5):304-8. doi: 10.1691/ph.2018.7948, PMID 29724299.
33. Naito Y, Kai Y, Ishikawa T, Fujita T, Uehara K, Doihara H. Chemotherapy-induced nausea and vomiting in patients with breast cancer: a prospective cohort study. Breast Cancer. 2020;27(1):122-8. doi: 10.1007/s12282-019-01001-1, PMID 31407150.
34. Thibeault C, Bardtke L, Vanshylla K, di Cristanziano V, Eberhardt KA, Stubbemann P. Short- and long-term T cell and antibody

responses following dexamethasone treatment in COVID-19. JCI Insight. 2023;8(8):e166711. doi: 10.1172/jci.insight.166711, PMID 36881474.

35. Watanabe D, Iihara H, Fujii H, Makiyama A, Nishida S, Suzuki A. One-day versus three-day dexamethasone with NK1RA for patients receiving carboplatin and moderate emetogenic chemotherapy: a network meta-analysis. Oncologist. 2022;27(6):e524-32. doi: 10.1093/oncolo/oyac060, PMID 35427418.
36. Celio L, Bonizzoni E, Montani E, Aapro M. Efficacy of the dexamethasone-sparing triplet regimen for preventing cisplatin-induced emesis: a combined analysis. Future Oncol. 2022;18(30):3389-97. doi: 10.2217/fon-2022-0330, PMID 36017782.
37. Tashiro T, Takeuchi Y, Sakurai Y, Arai M, Shibata M, Tazaki S. Comparative study of a proton pump inhibitor with a histamine H2 receptor antagonist in Japanese patients with functional dyspepsia. Showa Univ J Med Sci. 2018;30(1):43-52. doi: 10.15369/sujms.30.43.
38. Cox JM, van Doorn L, Malmberg R, Oomen-de Hoop E, Bosch TM, van den Bemt PM. The added value of H2 antagonists in premedication regimens during paclitaxel treatment. Br J Cancer. 2021;124(10):1647-52. doi: 10.1038/s41416-021-01313-0, PMID 33762718.
39. Smit T, Van Eeden RI, Rapoport BL. High incidence of nausea during initial and repeated courses if intravenous chemotherapy in patients receiving guideline consistent antiemetic prophylaxis: a prospective, observational, real-world study. Ann Oncol. 2019;30. doi: 10.1093/annonc/mdz265.015.
40. Smit T, Kotze I, du Plessis J. The incidence of nausea in the absence of vomiting in patients receiving intravenous chemotherapy. Ann Palliat Med. 2021;10(3):2679-86. doi: 10.21037/apm-19-453, PMID 33549001.