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RESEARCH ARTICLE

The efficacy of combining ondansetron with dexamethasone in delayed chemotherapy-induced nausea and vomiting

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Abstract

Background: Chemotherapy is the primary recourse for patients with cancer that cannot be treated using local surgery or radiotherapy. Its practical application often leads to adverse effects, including nausea and vomiting. **Objective:** This study determined the efficacy of oral ondansetron and oral dexamethasone as an antiemetic regimen among patients covered by the National Health Insurance. **Methods:** This cross-sectional study, conducted at one of the largest hospitals in South Kalimantan, Indonesia, involved 114 chemotherapy patients who received a combination antiemetic regimen of ondansetron and dexamethasone. Data on the incidence of delayed nausea and vomiting after chemotherapy were collected using the Index Nausea Vomiting and Retching (INVR) questionnaire from March to May 2023. **Results:** A cohort of 114 individuals were enrolled in the present investigation, with 57.02% and 42.98% of the participants receiving non-anthracycline and anthracycline-based treatment protocols, respectively. The results showed that only 1.84% of patients did not experience chemotherapy-related adverse events, 13.16% experienced mild symptoms, 21.84% had moderate symptoms, 55.26% faced severe symptoms, and 7.89% suffered from intense symptoms of nausea and vomiting. **Conclusion:** The antiemetic regimen covered by Badan Penyelenggara Jaminan Sosial (BPJS) (Social Insurance Administration Organization) consisting of a combination of ondansetron and dexamethasone has moderate effectiveness in preventing chemotherapy-induced delayed nausea and vomiting.

Introduction

Cancer is a noncommunicable ailment marked by unregulated cell proliferation. In 2019, data from the Ministry of Health of the Republic of Indonesia showed that the prevalence of cancer cases among the Indonesian population increased between 2013 and 2018 (Ministry of Health of the Republic of Indonesia, 2019). Worldwide, there will be approximately 19.3 million newly diagnosed cases of cancer in 2020. By 2040, that number is expected to increase to 28.4 million (Sung *et al.*, 2021).

Chemotherapy is the primary treatment for cancer patients who do not undergo local surgery or radiotherapy (Khairani *et al.*, 2019). The proportion of chemotherapy in cancer management in Indonesia is quite large, which is 24.9% (Ministry of Health of the Republic of Indonesia, 2019). Chemotherapy generally involves a combination of two or more cytotoxic drugs that often result in side effects for patients. Among

these, chemotherapy-induced nausea and vomiting (CINV) emerged as a prevalent and burdensome adverse event, with potential consequences such as dehydration, weight loss, metabolic disruption, chemotherapy delays or stoppage, and a general decline in quality of life (Khairani *et al*., 2019).

CINV occurs because chemotherapy tends to damage the mucosa of the gastrointestinal tract by increasing the level of gastrin hormone and reducing gastric emptying, resulting in gastric distension (Grunberg, 2012). Based on the phase that occurs, CINV is divided into three categories. Acute CINV commences one to two hours after chemotherapy and reaches its peak intensity within the first four to six hours (Tsubata *et al*., 2019). Delayed CINV is characterised by its appearance occurring 24 hours after treatment, with the highest level of severity observed between 48 and 72 hours. Subsequently, it gradually subsides for two to three days (Manson & Routledge PA, 2012). Breakthrough CINV occurs in patients who have experienced significant CINV during a prior chemotherapy cycle (Baburaj *et al*., 2017).

A factor that potentially increases the frequency of CINV is the emetogenic level of the chemotherapy drugs used (Gupta *et al.*, 2021). Individuals undergoing chemotherapy commonly receive adjunctive medications known as antiemetics to prevent nausea and vomiting effectively. These medications are specifically designed to prevent and reduce the effects of nausea and vomiting that accompany chemotherapy sessions. The National Comprehensive Cancer Network (NCCN) has produced extensive guidelines on the use of antiemetic drugs. The guidelines mentioned above propose an active approach that encompasses the use of a combination of antiemetic drugs targeting the 5-hydroxytryptamine-3 (5-HT3) receptor antagonist, neurokinin-1 receptor antagonists, and corticosteroids for those who receive chemotherapy with a high likelihood of inducing nausea and vomiting. Meanwhile, for individuals undergoing chemotherapy with moderately emetogenic potential, the recommended antiemetic regimen includes 5-HT3 receptor antagonists combined with corticosteroids (Berger *et al*., 2017).

Although several guidelines on managing CINV are published and updated regularly by cancer organisations, they are not fully implemented in clinical practice (Moradian & Howell, 2015). In Indonesia, patients with National Health Insurance (BPJS) use the 5HT3 antagonist group, namely ondansetron, combined with dexamethasone. This study evaluated the efficacy of oral ondansetron and dexamethasone as a post-chemotherapy antiemetic regimen for patients enrolled in the Badan Penyelenggara Jaminan Sosial (BPJS) programme. It was conducted in one of the largest hospitals in South Kalimantan, Indonesia, aiming to provide valuable insights into the practical outcomes of this treatment method.

Methods

Design

Conducted in one of the largest hospitals in South Kalimantan, Indonesia, this study employed a cross-sectional design, with data collection slated from March to May 2023. The main goal of this study is to investigate the occurrence of post-chemotherapy delayed nausea and vomiting in patients. Data for this investigation were collected using the INVR-Rhodes questionnaire. The inclusion criteria included participants who were cancer patients without metastases and were in the age range of ≥ 18 to 55 years. Additionally, they must have received chemotherapy involving anthracycline-based or non-anthracycline-based regimens. Patients who suffered from gastroenteritis, individuals uncontactable within 24 hours post-chemotherapy and those who declined participation were excluded from the study. The study designated individuals who unfortunately passed away before completing a full chemotherapy cycle as meeting the dropout criteria.

Data collection

Each participant in the study was administered a post-chemotherapy antiemetic regimen. This regimen included taking one tablet of ondansetron 8 mg twice and dexamethasone 0.5 mg three times a day. The efficacy of the combination was based on the INVR (Index of Nausea, Vomiting, and Retching) questionnaire. The INVR is an 8-item, 5-point Likert-type self-report pencil and paper instrument that measures the patient's perceived a) Duration of nausea; b) Frequency of nausea; c) Distress from nausea; d) Frequency of vomiting; e) Amount of vomiting; f) Distress from vomiting; g) Frequency of dry heaves; and h) Distress from dry heaves. Total scores for nausea, vomiting, dry heaves, and subscale scores for each can be derived from the INVR (Rhodes & McDaniel, 1999).

This questionnaire assessed nausea and vomiting experienced for five days or 120 hours following chemotherapy. It was completed twice a day at 12-hour intervals. The effectiveness of antiemetic therapy in managing post-chemotherapy nausea and vomiting was determined using parameters categorised into five severity levels, namely:

a. No nausea and vomiting (INVR score = 0)

b. Mild nausea and vomiting (INVR score = 1 to 8)
c. Moderate nausea and vomiting (INVR score = 9 to 16)
d. Severe nausea and vomiting (INVR score = 17 to 24)
e. Poor nausea and vomiting (INVR score = 25 to 32)

Data analysis

Data on delayed nausea and vomiting after chemotherapy were collected and analysed using descriptive statistics.

Ethical clearance

The Research Ethics Commission approved this study at Ulin General Hospital, Banjarmasin, Indonesia, under reference number 246/XII-Reg-Riset/RSUDU/22.

Results

This study involved 114 patients; the majority were 41 to 60 years old. The female gender mostly dominated the participants. In terms of chemotherapy, 57.02% and 42.98% of patients received non-anthracycline-based and anthracycline-based regimens, as shown in Table I.

Table I: Patient demographics (n = 114)

Characteristics	Patients n (%)
Gender	
Male	12 (9.45)
Female	102 (80.31)
Age (years)	
18-40	25 (21.93)
41-60	82 (71.93)
>60	7 (6.14)
Site of primary malignancy	
Breast	57 (50.00)
Gynaecological	41 (35.96)
Lung	5 (4.39)
Lymph	9 (7.89)
Gestational Trophoblastic Disease	1 (0.88)
Sinonasal	1 (0.88)
Chemotherapy regimen	
Anthracycline-based	49 (42.98)
Non-anthracycline-based	65 (57.02)

Nausea and vomiting scores were assessed for 120 hours from the first to the fifth-day post-chemotherapy. This evaluation was carried out every 12 hours or 10 times by completing the patient questionnaire. Of the 114 study participants, 112 (98.25%) experienced nausea and vomiting after their chemotherapy sessions. Table II showed that, on average, only 1.75% of patients did not experience nausea and vomiting as a side effect of chemotherapy. Furthermore, 13.16%, 21.93%, 55.26%, and 7.89% encountered mild, moderate, severe, and extremely intense symptoms, respectively.

Table II: Type of delayed nausea and vomiting (n=114)

Category	Hour measurement										Average (%)
	12	24	36	48	60	72	84	96	108	120	
No nausea and vomiting	2	1	3	0	6	1	1	2	4	1	2 (1.75)
Mild nausea and vomiting	15	25	27	18	16	21	14	10	3	1	15 (13.16)
Moderate nausea and vomiting	25	32	30	29	30	17	19	21	24	22	25 (21.93)
Severe nausea and vomiting	63	49	41	53	54	71	73	73	77	76	63 (55.26)
Bad nausea and vomiting	9	7	13	14	8	4	7	8	6	14	9 (7.89)

Discussion

Most chemotherapy patients experience nausea and vomiting, although they are given antiemetic drugs to prevent this (Dranitsaris *et al*., 2017). In this study, the antiemetic regimen used to prevent nausea and vomiting after chemotherapy (delayed phase) was a combination of ondansetron and dexamethasone tablets. Ondansetron, a selective 5HT3 serotonin antagonist, effectively and competitively prevents nausea and vomiting related to postoperative recovery, chemotherapy, and radiotherapy. Its action involves blocking receptors in the gastrointestinal tract and the post-trauma area (Dipiro *et al*., 2017). Despite being

anticipated, monitoring and addressing the side effects of nausea and vomiting after chemotherapy is important.

Based on research, an average of more than 50% papers report severe nausea and vomiting after receiving ondansetron and dexamethasone. This may occur because the antiemetics covered by BPJS in Indonesia do not comply with the guidelines issued by the oncology consensus. The National Comprehensive Cancer Network (NCCN) has produced extensive guidelines on the use of antiemetic drugs. The guidelines propose an active approach that encompasses the use of a combination of antiemetic drugs targeting the 5-hydroxytryptamine-3 (5-HT3) receptor antagonist, neurokinin-1 receptor antagonists, and corticosteroids for those who receive chemotherapy with a high likelihood of inducing nausea and vomiting. Meanwhile, for individuals undergoing chemotherapy with a moderately emetogenic potential, the recommended antiemetic regimen includes 5-HT3 receptor antagonists combined with corticosteroids (Berger *et al*., 2017).

While numerous studies have focused on the management of acute CINV, addressing the challenges of delayed CINV remains an ongoing knowledge gap. There is the fact that the number of patients requiring rescue antiemetics in the late period was twice as high as the number observed in the early phase. CINV is significant for patients and healthcare professionals due to its potential to lead to severe outcomes such as termination of treatment and hesitancy. These complications can, in turn, extend the treatment duration, escalate financial burdens, and intensify stress on the patient, ultimately compromising their quality of life (Vaid *et al*., 2020). There is an imperative for further investigation to optimise CINV management. This encompasses refining prophylactic methods and identifying individuals susceptible to CINV and those who tend to develop the condition despite preventive measures.

Non-compliance with established standards for managing CINV is an important issue (Escobar *et al*., 2015). Despite written guidelines from numerous consensus groups, many patients do not receive the appropriate antiemetic therapy (Roila *et al*., 2016; Berger *et al*., 2017; Hesketh *et al*., 2017). This non-compliance extends to practices like not prescribing NK1 receptor antagonists (Aapro *et al*., 2012). Improved adherence to these guidelines reduces CINV occurrences (Aapro *et al*., 2012; Gilmore *et al*., 2014). A study conducted by Chan (2012) found that patients who adhered to antiemetic medication were 1.6 times more likely to control symptoms completely, including the absence of nausea and vomiting when combined with additional therapy during the delayed phase. This finding was supported by an odds ratio (OR) of 1.74, with a 95% confidence interval (CI) ranging from 1.01 to 3.01 and a *p*-value of 0.048. Pharmacists need appropriate communication skills about treatment to optimise therapeutic goals. Further research is needed to explore the role of multidisciplinary interventions in effectively managing CINV events, particularly in the delayed phase.

Conclusion

Combination of ondansetron with dexamethasone treatment was only moderately effective in controlling delayed chemotherapy-induced nausea and vomiting.

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References

Aapro, M., Molassiotis, A., Dicato, M., Peláez, I., Rodríguez-Lescure, Á., Pastorelli, D., & Roila, F. (2012). The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). *Annals of Oncology,* **23**(8), 1986–1992. https://doi.org/10.1093/annonc/mds021

Baburaj, G., Abraham, A. M., George, L., Shetty, V., Thempalangad, R. M., Rajesh, K. S., & Bharath Raj, K. C. (2017). A study on utilization and evaluation of antiemetics in chemotherapy-induced nausea and vomiting. Indian *Journal of Medical and Paediatric Oncology,* **38**(3), 334–339. https://doi.org/10.4103%2Fijmpo.ijmpo_116_17

Berger, M. J., Ettinger, D. S., Aston, J., Barbour, S., Bergsbaken, J., Bierman, P. J., & Hughes, M. (2017). NCCN guidelines insights: Antiemesis, Version 2.2017. *Journal of the National Comprehensive Cancer Network,* **15**(7), 883–893. https://doi.org/10.6004/jnccn.2017.0117

Dipiro, C. V., Schwinghammer, T. L., Dipiro, J. T., & Wells, B. G. (2017). *Pharmacotherapy handbook, Tenth Edition*: McGraw-Hill Education.

Dranitsaris, G., Molassiotis, A., Clemons, M., Roeland, E., Schwartzberg, L., Dielenseger, P., Jordan, K., Young A., & Aapro, M. (2017). The development of a prediction tool to identify cancer patients at high risk for chemotherapy-induced nausea and vomiting. *Annals of Oncology,* **28**(6), 1260–1267. https://doi.org/10.1093/annonc/mdx100

Escobar, Y., Cajaraville, G., Virizuela, J. A., Álvarez, R., Muñoz, A., Olariaga, O., & Tornamira, M. V. (2015). Incidence of chemotherapy-induced nausea and vomiting with moderately emetogenic chemotherapy: ADVICE (Actual Data of Vomiting Incidence by Chemotherapy Evaluation) study. *Support Care in Cancer,* **23**(9), 2833–2840. https://doi.org/10.1007%2Fs00520-015-2809-3

Gilmore, J. W., Peacock, N. W., Gu, A., Szabo, S., Rammage, M., Sharpe, J., & Burke, T. A. (2014). Antiemetic guideline consistency and incidence of chemotherapy-induced nausea and vomiting in US community oncology practice: INSPIRE Study. *Journal of Oncology Practice,* **10**(1), 68–74. https://doi.org/10.1200/jop.2012.000816

Grunberg, S. (2012). Patient-centered management of chemotherapy-induced nausea and vomiting. *Cancer Control,* **19**(2), 10–15. https://doi.org/10.1177/107327481201902s03

Gupta, K., Walton, R., & Kataria, S. P. (2021). Chemotherapy-induced nausea and vomiting: pathogenesis, recommendations, and new trends. *Cancer Treatment and Research Communications,* **26**, 100278. https://doi.org/10.1016/j.ctarc.2020.100278

Hesketh, P. J., Kris, M. G., Basch, E., Bohlke, K., Barbour, S. Y., Clark-Snow, R. A., & Lyman, G. H. (2017). Antiemetics: American society of clinical oncology clinical practice guideline update. *Journal of Clinical Oncology,* **35**(28), 3240–3261. https://doi.org/10.1200/jco.2017.74.4789

Khairani, S., Keban, S. A., & Afrianty, M. (2019). Evaluation of drug side effects chemotherapy on quality of life (QOL) breast cancer patients at hospital X in Jakarta. *Jurnal Ilmu Kefarmasian Indonesia*, **17**(1), 9–13. https://doi.org/10.35814/jifi.v17i1.705

Ministry of Health of the Republic of Indonesia. (2019). Hasil utama RISKESDAS 2018. Badan Penelitian dan Pengembangan Kesehatan Kemenkes RI.

Moradian, S., & Howell, D. (2015). Prevention and management of chemotherapy-induced nausea and vomiting. *International Journal of Palliative Nursing,* **21**(5), 216–224. https://doi.org/10.12968/ijpn.2015.21.5.216

Rhodes, V. A., & McDaniel, R. W. (1999). The index of nausea, vomiting, and retching: A new format of the index of nausea and vomiting. *Oncology Nursing Forum*, **26**(5), 889–894. PMID: 10382187

Roila, F., Molassiotis, A., Herrstedt, J., Aapro, M., Gralla, R. J., Bruera, E., & van der Wetering, M. (2016). 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. *Annals of Oncology,* **27**(5), v119–v133. https://doi.org/10.1093/annonc/mdw270

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians,* **71**(3), 209–249. https://doi.org/10.3322/caac.21660

Todd, A., Brierley-Jones, L., Husband, A., Williamson, S., Sarai, I., & Ling, J. (2013). Be clear on cancer: Pharmacy students' views of communicating with cancer patients. *Pharmacy Education*, **13**(0). https://pharmacyeducation.fip.org/pharmacyeducation/article/view/256

Tsubata, Y., Nakao, M., Amano, Y., Hotta, T., Hamaguchi, M., Okimoto, T., & Isobe, T. (2019). Translational and randomized study of 5-HT3 receptor antagonists for evaluation of chemotherapy-induced nausea and vomiting related biomarkers. *International Journal of Medical Investigation,* **66**(3.4), 269–274. https://doi.org/10.2152/jmi.66.269

Vaid, A. K., Gupta, S., Doval, D. C., Agarwal, S., Nag, S., Patil, P., & Barkate, H. (2020). Expert consensus on effective management of chemotherapy-induced nausea and vomiting: an Indian perspective. *Frontiers in Oncology,* **10**, 400. https://doi.org/10.3389/fonc.2020.00400