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An Overview of Antiemetic Prophylaxis for Chemotherapy-Induced Nausea and Vomiting in Head and Neck Cancer Patients at Dharmais National Cancer Hospital

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ABSTRACT

Background: Chemotherapy-induced nausea and vomiting (CINV) are frequently experienced by cancer patients. One of the antineoplastic agents with high emetogenicity is cisplatin. Cisplatin is commonly used in the treatment of head and neck cancer (HNC). Therefore, the use of prophylactic antiemetics is recommended. This study aimed to examine the use of antiemetics as prophylaxis for CINV in HNC patients.

Method: This study is a cross-sectional, using retrospective data from medical record observations at Dharmais National Cancer Hospital. Purposive sampling was used to collect data on antiemetic use between October and December of 2023. All patients with HNC who were undergoing chemotherapy and receiving antiemetics as prophylaxis during this period were included in the study and analyzed descriptively.

Results: A total of 177 chemotherapy cycles in 96 head and neck cancer patients included in this study indicated that the most commonly used prophylactic antiemetic was a combination of ondansetron and dexamethasone (83.1%). The experience of CINV occurred more frequently in the delayed phase, with nausea occurring in 64.4% and vomiting in 44.6%. The highest severity level of nausea occurred at grade 2 (50.8%), meanwhile vomiting occurred at grade 1 (55.9%).

Conclusion: The findings of this study show that the use of 5-HT3 RA (ondansetron) and dexamethasone alone is not sufficient to reduce the CINV response, thus requiring additional therapy such as D-2 RA, PPI, and H-2 Blockers.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) remains the most common side effect among cancer patients undergoing chemotherapy [1]. Among a total of 4,197 chemotherapy cycles, 2,567 cycles (61.2%) resulted in CINV occurrences [2]. A study at Dharmais Cancer Hospital reported that from January 2021 to December 2022, nausea and vomiting were the most frequent drug-related side effects, with incidence rates of 64 (11.6%) and 55 (9.9%) [3].

CINV is triggered by afferent impulses to the vomiting center. The sources of these impulses include the chemoreceptor trigger zone, the vestibular system, the vagal afferent nerves, and spinal nerves from the gastrointestinal tract, and the central nervous system [4]. The main neurotransmitter receptors involved in this signaling include serotonin (specifically the 5-hydroxytryptamine type 3, 5-HT3), neurokinin-1 (NK-1), and dopamine receptors. Acute CINV is mediated by serotonin receptors in the gastrointestinal tract. Delayed CINV is associated with substance P acting at central NK-1 receptors [5–7].

Prevention of CINV caused by highly emetogenic chemotherapy (HEC), such as cisplatin, is recommended using antiemetic prophylaxis to prevent undesirable CINV occurrences. Antiemetic prophylaxis should be started on the first day of chemotherapy and continued through

the fourth day. The recommended antiemetic prophylaxis includes NK-1 receptor antagonists (NK-1 RA), 5-HT3 receptor antagonists (5-HT3 RA), dexamethasone, and olanzapine [7–9].

NK-1 RA act on the area postrema of the fourth ventricle in the brain, commonly known as the chemoreceptor trigger zone (CTZ). 5-HT3 RA and dexamethasone affect the afferent vagal and spinal nerves of the gastrointestinal tract, as well as CTZ [4,10–12]. The antiemetic effect of olanzapine is related to its role as an antagonist of dopamine, serotonin, and histamine receptors in the vomiting center [13,14].

HNC develops from squamous cells located in the mucosal epithelium within the head and neck region [15,16]. One of the chemotherapy agents commonly used for HNC is cisplatin. Therefore, the recommended use of antiemetics should be administered to HNC patients before chemotherapy is administered to the patient [17,19]. This study aims to assess the use of prophylactic antiemetics for CINV and the resulting outcomes in HNC patients at Dharmais National Cancer Hospital.

METHODS

This study is a cross-sectional study with retrospective data obtained from medical record observations. Data collection was conducted through purposive sampling of antiemetic usage records from October to December 2023 at Dharmais National Cancer Hospital (Indonesia National Cancer Centre).

The inclusion criteria were patients over the age of 18, diagnosed with HNC, who received chemotherapy with cisplatin and antiemetic therapy as prophylaxis. The exclusion criteria were HNC patients with metastasis to the gastrointestinal tract or those undergoing radiation therapy to the gastrointestinal tract, as these conditions can cause nausea and vomiting.

Patient data on characteristics, antiemetic usage, and the occurrence of CINV will be analyzed descriptively using Microsoft Excel and presented as percentages. Patient characteristic data includes age, gender, type of malignancy, and chemotherapy regimen. Antiemetic usage data were classified according to the class of therapy. The type of malignancy is categorized based on medical diagnosis coding in medical records, referring to the ICD-10 (International Classification of Diseases, 10th Edition). Chemotherapy regimens for head and neck cancer are classified based on the chemotherapeutic agents used by the patient.

CINV occurrence data is categorized into acute CINV and delayed CINV. CINV that occurs within the first 24 hours of chemotherapy administration is called acute CINV. CINV that develops more than 24 hours after chemotherapy, peaks at 48 to 72 hours, and potentially lasts up to 1 week is called delayed CINV [5–7]. The severity assessment was categorized using NCI CTCAE V.5.0 (National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0) into five categories: grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening), and grade 5 (death related to adverse events). NCI CTCAE V.5.0 is a descriptive terminology that can be utilized for reporting Adverse Events (AEs) based on the Medical Dictionary for Regulatory Activities (MedDRA) Primary System Organ Class (SOC).

RESULTS

A total of 177 cycles of chemotherapy were performed on 96 head and neck cancer patients studied at Dharmais Cancer Hospital; there were 67 men and 29 women included in the analysis. The most common age range was 45–59, followed by 18–44 and ≥ 60 years. Among all patients, the most common type of malignancy was malignant neoplasm of the nasopharynx. Meanwhile, the chemotherapy regimen most frequently administered to patients was a combination of cisplatin, docetaxel, and 5FU, as shown in **Table 1.**

A total of 177 cycles used prophylactic antiemetics during chemotherapy, both in the acute and delayed phases. The antiemetic prophylaxis used during chemotherapy in head and neck cancer patients are shown in **Table 2**. The most commonly used antiemetic prophylaxis class is 5-HT3 RA and corticosteroids, which are used in all cycle's chemotherapy (100%). The 5-HT3 RA group that is often used is ondansetron in 177 cycles (100%), while the corticosteroid group that is often used is dexamethasone in 147 cycles (83.1%). Other commonly used antiemetic prophylaxis includes ranitidine in 94 cycles (53.1%), domperidone in 75 cycles (42.4%), metoclopramide in 59 cycles (33.3%), and omeprazole in 55 cycles (31.1%).

The majority of HNC patients included in this study experienced CINV, both in the acute and delayed phases. In the acute phase, patients experienced nausea in 103 cycles (58.2%) and vomiting in 27 cycles (15.3%). In the delayed phase, patients experienced nausea in 114 cycles (64.4%) and vomiting in 79 cycles (44.6%), as shown in **Figure 1**.

The severity levels of CINV occurrences after chemotherapy with HEC are shown in **Figure 2**. The highest severity level of nausea occurred at grade 2 (moderate) with 90 cycles (50.8%), followed by grade 1 (mild) with 72 cycles (40.7%) and grade 3 (severe) with 15 cycles (8.5%). Meanwhile, the highest severity level of vomiting occurred at grade 1 (mild) with 99 cycles (55.9%), followed by grade 2 (moderate) with 63 cycles (35.6%) and grade 3 (severe) with 15 cycles (8.5%). There were no CINV incidents at level 4 (life-threatening) and level 5 (death-related to AE).

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Table 1. Patient characteristics

Characteristics (n = 96)	Number of Patients (n = 96)	Percentage (%)
Age range (years)		
18–44	42	43.8
45–59	44	45.8
≥ 60	10	10.4
Gender		
Male	67	69.8
Female	29	30.2
Type of malignancy		
Malignant neoplasm of larynx	2	2.1
Malignant neoplasm of mandible	1	1.0
Malignant neoplasm of mouth	1	1.0
Malignant neoplasm of nasal cavity and middle ear	4	4.2
Malignant neoplasm of nasopharynx	83	86.5
Malignant neoplasm of oropharynx	1	1.0
Malignant neoplasm of tongue	2	2.1
Malignant neoplasm of other and unspecified parts of mouth	2	2.1
Chemotherapy regimen		
Cisplatin	16	16.7
Cisplatin-5FU	22	22.9
Cisplatin-Docetaxel	24	25.0
Cisplatin-Docetaxel-5FU	33	34.4
Cisplatin-Paclitaxel	1	1.0

Table 2. The antiemetic prophylaxis for head and neck cancer patients

CINV Prophylaxis	Number of cycles (n)	Percentage (%)
NK-1 RA (n = 3)		
Netupitant 300 mg PO	3	1.7
5-HT3 RA (n = 177)		
Palonosetron 0,5 mg PO followed by Ondansetron 3–4 x 8 mg IV/PO	3	1.7
Ondansetron 3-4 x 8 mg IV/PO	174	98.3
Corticosteroid (n = 177)		
Dexamethasone 8–16 mg IV	147	83.1
Methylprednisolone 10–20 mg IV	30	16.9
D-2 RA (n = 134)		
Domperidone 3–4 x 10 mg PO	75	42.4
Metoclopramide 3–4 x 10 mg IV/PO	59	33.3
PPI (n = 77)		
Esomeprazole 2 x 40 mg IV/PO	1	0.6
Lansoprazole 2 x 30 mg IV/PO	21	11.9
Omeprazole 2 x 40 mg IV/PO	55	31.1
H-2 Blocker (n = 94)		
Ranitidine 2 x 50 mg IV	94	53.1

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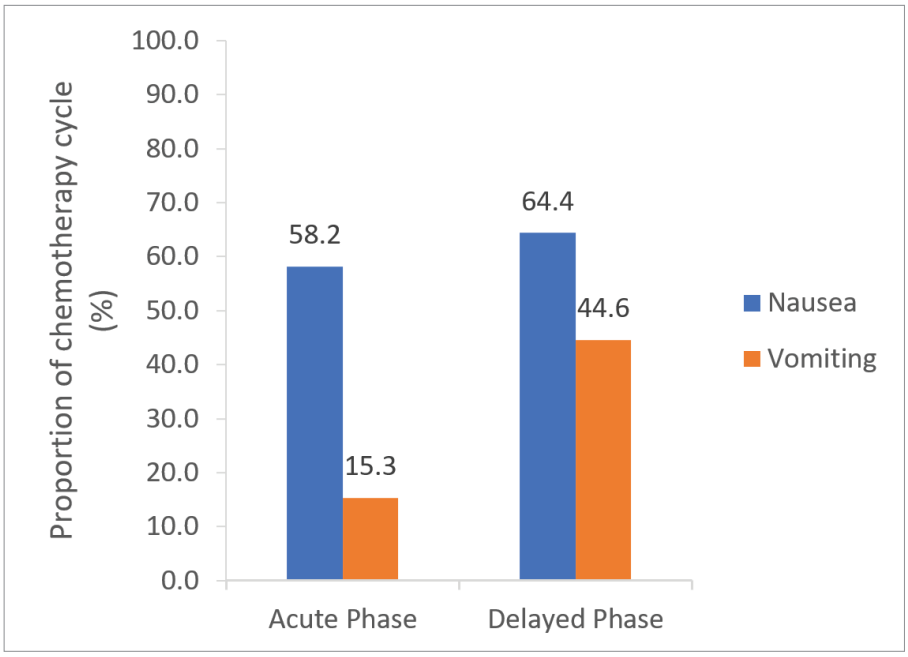

Figure 1. The occurrence of CINV in the acute and delayed phases.

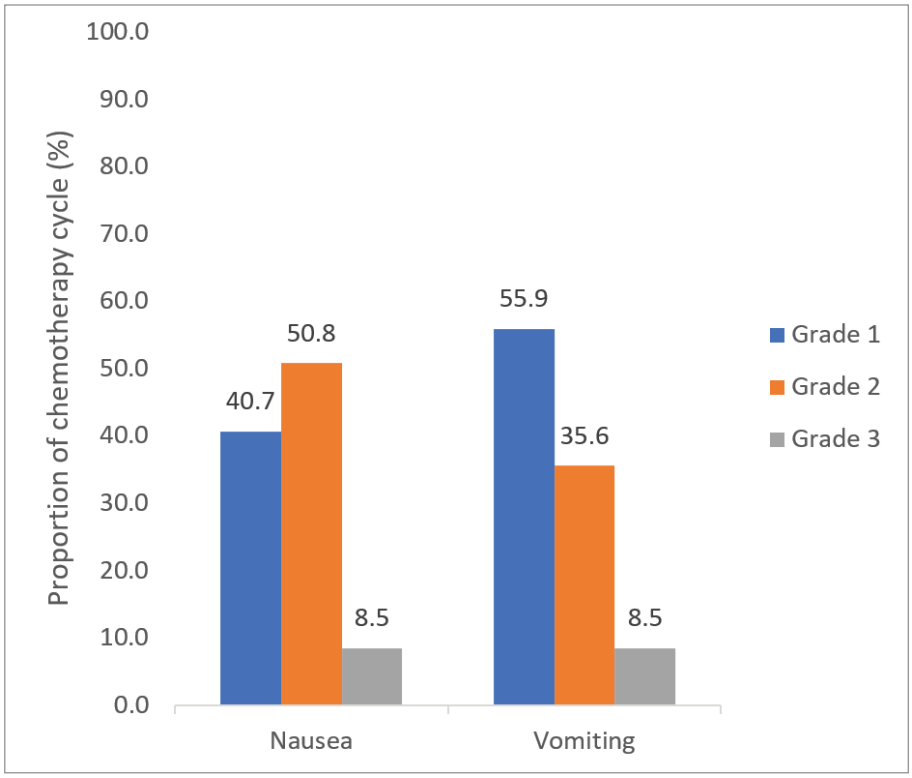

Figure 2. The severity level of CINV during HEC.

DISCUSSION

CINV is influenced by various factors, both from the patient and the chemotherapy drugs used. Regarding patient risk factors, gender and age can influence the occurrence of CINV. Meanwhile, regarding chemotherapy drug risk factors, the level of emetogenicity and combination therapy can increase the risk of CINV [2,6,20]. Several studies have shown that CINV often occurs in head and neck cancer patients, especially those undergoing chemotherapy with HEC, such as cisplatin [3,21,22].

According to guidelines from the American Society of Clinical Oncology (ASCO), the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO), and the National Comprehensive Cancer Network (NCCN), the use of antiemetic prophylaxis can reduce the risk of CINV. The guidelines recommended using NK-1 RA, 5-HT3 RA,

dexamethasone, and olanzapine on the first day of chemotherapy, followed by NK-1 RA, dexamethasone, and olanzapine from days 2 to 4 for the management of CINV caused by highly emetogenic chemotherapy [6–9].

The current study showed that the use of cisplatin, either alone or in combination with other chemotherapy agents, remains a therapeutic option for HNC. Most of the CINV prophylaxis used includes 5-HT3 RA (ondansetron; 100%) and dexamethasone (83.1%). The use of a combination of ondansetron and dexamethasone can enhance the effectiveness in preventing CINV, especially during the delayed phase of CINV, where ondansetron alone does not provide adequate control [23]. The use of another corticosteroid, methylprednisolone (16.9%), was observed in patients who did not receive dexamethasone as antiemetic prophylaxis. This is consistent with other research findings that show dexamethasone can be rotated with other corticosteroids, such as methylprednisolone [24,25]. The combination of NK-1 RA (netupitant) and 5-HT3 RA (palonosetron) remains limited (1.7%) and no use of olanzapine was found as recommended.

The use of olanzapine was not found in head and neck cancer patients, which could be due to the indication for olanzapine approved by the Indonesian Food and Drug Authority, BPOM, is as an antipsychotic, and there is no indication for its use as CINV prophylaxis. Concerns about increasing the risk of side effects such as metabolic syndrome, extrapyramidal syndrome, and sedation could also be considerations in the use of olanzapine [26–28].

The use of D-2 RAs (Domperidone, Metoclopramide), PPIs (Esomeprazole, Lansoprazole, Omeprazole), and H-2 blockers (Ranitidine) was also observed during chemotherapy. These medications were administered in both the acute and delayed phases. The administration of D-2 RAs indicates the occurrence of breakthrough CINV, which refers to nausea and vomiting that occur despite the administration of antiemetic prophylaxis. Breakthrough CINV is an event that is difficult to manage because it persists and is refractory. The management of breakthrough CINV generally involves adding therapy from a different class of drugs than the prophylactic antiemetic administered [8,29]. Several studies have shown that the administration of D-2 RA during chemotherapy can reduce the incidence of breakthrough CINV [30–32]. Patients often have difficulty distinguishing between dyspepsia and CINV. In this case, the use of antacids such as proton pump inhibitors and H-2 blockers may be considered [8].

The occurrence of CINV after chemotherapy administration was also observed in this study. Based on study by Putri et al. [3], it was shown that nausea was the most reported side effect at Dharmais Cancer Hospital. A similar finding was observed in this study, where nausea was the most frequently occurring event during chemotherapy. In the delayed phase, chemotherapy administration caused a higher incidence of nausea compared to the acute phase (64.4% vs. 58.2%). A similar pattern was observed with vomiting, where the incidence of vomiting in the delayed phase was higher than in the acute phase (44.6% vs. 15.3%) out of a total of 177 chemotherapy cycles included in this study. This result reinforces previous research indicating that CINV in patients receiving HEC often occurs more frequently in the delayed phase than in the acute phase [33,34].

The severity levels of nausea were observed at ≥ grade 2 (moderate), where nausea caused a decrease in oral intake without significant weight loss, dehydration, or malnutrition. Meanwhile, the severity level of vomiting was mostly found at grade 1 (mild), where patients did not require further medical intervention in the hospital. The use of antiemetic prophylaxis is one of the factors that can reduce the severity of CINV [30]. In this study, the administration of D-2 RAs (Domperidone, Metoclopramide), PPI dan H-2 Blocker in cases of persistent and refractory nausea and vomiting can help reduce the severity of CINV.

The results of this study indicate that the use of ondansetron and dexamethasone is not sufficient for the prophylaxis of CINV in patients undergoing chemotherapy with cisplatin. Most of these patients still experience CINV events in both the acute and delayed phases, so the addition of antiemetics from different therapeutic classes is needed. Therefore, the administration of prophylactic antiemetics according to guidelines and on a routine, around-the-clock basis is recommended to reduce the incidence of CINV caused by HEC [35,36].

The limitation of this study is that it is a retrospective observational study with a relatively small number of patients, and thus, it does not fully represent the use of antiemetics and the occurrence of CINV in the head and neck cancer population in Indonesia. Prospective and multicenter studies need to be conducted to obtain results that can represent the entire population. In addition, the chemotherapy regimens and CINV prophylaxis administered in this study varied, requiring further research to explain the factors that influence the effectiveness of antiemetic use.

CONCLUSIONS

The majority of head and neck cancer patients participating in this study were aged between 45 and 59 years and were male. Based on the type of malignancy, most subjects were patients with malignant neoplasms of the nasopharynx. In terms of chemotherapy, the majority of subjects underwent combination chemotherapy with cisplatin-docetaxel and 5-FU. The

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most commonly used antiemetic prophylaxis was the use of 5-HT3 RA and corticosteroids, with the addition of D-2 RA, PPI, or H-2 blockers. The occurrence of CINV was more frequent in the delayed phase. The highest severity of nausea was observed at grade 2, and vomiting at grade 1, leading to a decrease in food intake, but no extension of inpatient care was required.

DECLARATIONS

Competing interest

The authors declare no competing interests in this study.

Ethics approval and consent to participate

This study was conducted after receiving approval from the Research Ethics Committee of Dharmais National Cancer Hospital with reference number DP.04.03/11.5/175/2024, on August 6, 2024.

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