International Journal of General Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Evaluation of Antiemetic Consistency in Chemotherapy-Induced Nausea and Vomiting Among NHL Patients in Sana'a, Yemen

Mohammed Mohammed Battah[1,2], Hadzliana Zainal[1], Doa'a Anwar Ibrahim[2], Nur Hafzan Binti Md Hanafiah[1], Syed Azhar Syed Sulaiman[1], Abdulsalam Halboup[1,2]

[1]Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia; [2]Department of Clinical Pharmacy and Pharmacy Practice, University of Science and Technology, Sana'a, Yemen

Correspondence: Mohammed Mohammed Battah, Departments of Clinical Pharmacy and Pharmacy Practice, University of Science and Technology, Sana'a, Yemen, Tel +967777404880, Email mmalbattah@gmail.com; Hadzliana Zainal, Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, 11800, Malaysia, Email hadz@usm.my

Background: Chemotherapy-induced nausea and vomiting (CINV) is a prevalent and distressing adverse effect that can negatively affect a patient's quality of life and treatment adherence.

Purpose: This study aimed to evaluate the consistency of antiemetic use with standard guidelines and to examine the factors influencing it.

Methods: This cross-sectional study was conducted at the National Oncology Center (NOC) of Al-Jomhouri Teaching Hospital, Sana'a, Yemen, from November 2022 to September 2023. Demographic data, chemotherapy and antiemetic regimens, dosages, and patient-related risk factors were collected via direct interviews, medical records, and treatment charts. This study evaluated the consistency of antiemetic practices among non-Hodgkin's Lymphoma (NHL) patients using the National Comprehensive Cancer Network (NCCN) guidelines. The chi-squared test and regression were used to determine the factors associated with guideline consistency.

Results: A total of 251 patients with NHL were recruited for the study; 57.4% were male and 60.6% were aged between 18–49. Most of the patients received moderately emetogenic chemotherapy (81.3%). The overall consistency with the NCCN guidelines was only 23.9%, with antiemetic drug selection and dosage reported inconsistently in 62.9% and 16.7% of patients, respectively. Furthermore, 62.5% of the patients received an under-prescribed antiemetic prophylactic regimen. Treatment duration, number of chemotherapy cycles, emetogenic risk potential, and overall patient risk, as well as age, sex, and marital status, were significantly associated with guideline inconsistency ($p < 0.05$).

Conclusion: This study revealed a notable gap in the consistency of antiemetic prescriptions among patients with NHL. Inappropriate drug selection, dosing, and under-prescription are common problems. Patient regimen risk factors significantly influenced the consistency of the National Comprehensive Cancer Network guidelines. Personalized approaches are essential to enhance adherence to guidelines and improve antiemetic strategies.

Keywords: non-Hodgkin's Lymphoma, chemotherapy, nausea, vomiting, antiemetics, Yemen

Introduction

Non-Hodgkin lymphoma (NHL) is a diffuse hematological malignancy that arises from immune cells in lymphoid tissue, with the diffuse large B-cell lymphoma (DLBCL) subtype being the most common.[1,2] Despite advances in antiemetic therapies, chemotherapy-induced nausea and vomiting (CINV) remains a troublesome issue affecting 70–80% of adult cancer patients undergoing chemotherapy.[3,4] These distressing complications not only cause physical discomfort, but also lead to various negative consequences, including metabolic dysfunction, nutritional depletion, appetite loss, potential

Received: 13 January 2024
Accepted: 7 May 2024
Published: 13 May 2024

esophageal damage, premature termination of treatment, deterioration of self-care and functional capacity,[5,6] and impact patients' quality of life and treatment adherence.[4,7]

Despite the guideline recommendations for antiemetic prophylaxis to improve CINV control, inconsistent adherence among healthcare providers has led to an increased incidence of CINV in cancer patients.[8] To address this issue, guidelines categorize anticancer drugs and regimens based on their emetogenic potential and classify chemotherapy protocols into highly emetogenic chemotherapy (HEC), moderately emetogenic chemotherapy (MEC), low emetogenic chemotherapy (LEC), and minimal emetogenic chemotherapy.[5,6] Although anthracycline- and cyclophosphamide-based regimens are known to induce CINV, the use of neurokinin-1 (NK1) receptor antagonists for CINV prophylaxis in aggressive NHL is uncertain, particularly in the context of the standard CHOP and rituximab combined CHOP (R-CHOP) regimens that are commonly used for both B-cell and T-cell NHL. This uncertainty arises from the inclusion of prednisone in these regimens as prednisone has been shown to lower the risk of CINV.[9,10] Therefore, NK1 receptor antagonists are often not routinely administered to patients receiving CHOP or R-CHOP therapy for CINV prophylaxis in clinical practice.

Prophylactic regimens of antiemetics are recommended based on the emetogenicity risk potential of the chemotherapy regimen, with triple antiemetic prophylaxis for highly emetogenic regimens being the standard.[11] The National Comprehensive Cancer Network (NCCN) guidelines recommend that antiemetic prophylactic regimens be selected based on the drug with the highest emetic risk as well as individual patient-specific risk factors, including younger age, female sex, high anxiety or pre-existing expectations of nausea and vomiting, history of CINV, motion and morning sickness, and minimal alcohol consumption.[12]

Although guidelines exist for CINV prevention, adherence is suboptimal, especially for patients undergoing highly emetogenic multi-day chemotherapy, as healthcare providers may lack awareness of the recent updates.[13] Additionally, clinical outcomes often fall short, and CINV remains a persistent complication in cancer treatment.[14] The implementation of evidence-based antiemetic regimens, as outlined by international and national guidelines, plays a crucial role in effectively managing CINV in cancer patients.[15] Adherence to these guidelines has been shown to prevent nausea and vomiting in the majority of cancer patients. On the other hand, deviation from these guidelines can lead to suboptimal CINV control, highlighting the importance of consistent adherence to established protocols.[15]

Research has mostly focused on the prevention of CINV in the context of solid tumors, often ignoring hematological malignancies and multi-day chemotherapy regimens. This knowledge gap calls for further studies to develop evidence-based approaches for preventing and managing CINV in specific settings.[13] The need for such research is particularly clear in Yemen, which has a high prevalence of NHL. NHL constitutes a significant portion of the prevalent cancer cases, with a 5-year prevalence of 1510 cases, accounting for 5.06% of all prevalent cancer cases.[16] NHL dominates among patients with lymphoma, accounting for 65% of all cases.[17] Despite this alarming prevalence, there is a notable lack of research focusing on CINV experiences of patients with Yemeni NHL. This study aimed to fill this research gap, evaluate the consistency of antiemetic medication practices with the NCCN guidelines, and explore the influencing factors among patients with NHL at the National Oncology Center (NOC), the largest oncology center in Yemen. To the best of our knowledge and based on existing literature, this is the first study in Yemen, providing valuable insights to improve CINV prophylaxis for NHL patients in this region.

Materials and Methods

Study Design and Setting

A cross-sectional study was carried out at the NOC, Al-Jomhouri Teaching Hospital in Sana'a, Yemen, from November 2022 to September 2023. This center was chosen based on several criteria: the first and largest oncology center in Yemen was established in February 2005 by the Ministry of Health under the supervision of the World Health Organization, which is the unique oncology center in Sana'a City. The majority of referrals to the NOC were from different governorates, including Sana'a, Amran, Al Mahwit, Hajah, Saada, Marib, Rima, Taiz, and Ibb. Moreover, the therapy costs in this center are largely funded by the government.

Study Population

This study was conducted on adult patients with NHL who attended the NOC during the study period. All admitted NHL patients were invited to participate, and those meeting the inclusion criteria were provided with a concise explanation of the study's objectives and were requested to sign an informed consent form before participating in this study. The study included all NHL patients who were 18 years or older, of any sex, who received chemotherapy as a part of treatment, and who had given their consent to participate. However, patients who experienced vomiting within 24 hours before the start of chemotherapy were excluded from the study.

Sample Size Calculation and Participants

Participants were recruited for this study using a population-based convenience sampling approach, adhering to the predetermined inclusion and exclusion criteria. According to the latest report from the World Health Organization (WHO), there are 862 NHL cases annually in both sexes and all ages.[16] However, 30% of these cases were excluded because they were under the age of 18 years based on data obtained from the statistics department of the NOC. Consequently, the total study population consisted of 604 patients with NHL, and the sample size was calculated using Yaman's formula accordingly:[18]

$$n = \frac{N}{1 + \mathrm{N}(\alpha\ 2)} = \left[604/1 + 604^{*}(0.05)^{2}\right]$$

Where n is the minimal sample size, N is the study population (total NHL patients), and α is the margin of error which was 0.05 at a significant level of 95%. So, the calculated sample size was 251 NHL patients.

Data Collection Procedure

A data collection form was developed with modifications based on previous literature[14,19] to collect the patient's demographic data, baseline clinical characteristics, and associated risk factors. The principal investigator collected the data on the first day of the treatment cycle. Details regarding specific chemotherapy regimens, antiemetic prescription regimens, dosage, cycles, and patient-related risk factors were collected from each patient through direct interviews, medical records, and treatment charts.

Guideline Design

The consistency of the antiemetic medication regimens and guidelines used in this study was extracted and defined according to the NCCN guidelines, Version 1, 2022 Antiemetic guidelines (Table 1), and the NCCN guidelines have produced consensus-based antiemetic guidelines with frequently updated supporting evidence.[5] Additionally, the NCCN guidelines serve as the primary reference for antiemetic practices for CINV in the NOC.

Table 1 CINV Prophylaxis Recommendations for IV Chemotherapy

EPC	Phase	NCCN
HEC	Acute phase	Option A (preferred): olanzapine + NK1-RA + 5-HT3-RA + dexamethasone Option B: olanzapine + palonosetron + dexamethasone Option C: NK1-RA + Any 5-HT3-RA + dexamethasone
MEC	Acute phase	Option D: 5-HT3-RA + dexamethasone Option E: Olanzapine + palonosetron + dexamethasone Option F: NK1-RA + 5-HT3-RA + dexamethasone
LEC	Acute phase	Dexamethasone or metoclopramide or prochlorperazine or 5-HT3-RA
Minimal	Acute phase	No routine prophylaxis

Abbreviations: EPC, emetogenic potential risk chemotherapy; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; LEC, low emetogenic chemotherapy; NK1: neurokinin1 receptor antagonists; 5HT3-RA, 5-hydroxytryptamine-3 receptor antagonist. NCCN (2022): National Comprehensive Cancer Network.

Study Variables

The study variables were classified into two groups: the guideline-consistent chemotherapy prophylaxis group (GCCP), in which patients received antiemetic prophylaxis medications proposed by the NCCN guidelines, and the guideline-inconsistent chemotherapy prophylaxis group (GICP), in which patients received antiemetic prophylaxis medications inconsistent with the NCCN guidelines.[14,19] Guideline consistency was calculated based on the number and type of chemotherapy treatments.[15] Inconsistencies were further evaluated in terms of underprescribing/overprescribing regimens and overdose/underdose of antiemetic medications.[20]

Chemotherapy regimens containing prednisolone or dexamethasone, even at a reduced 8mg dose, are considered consistent with the guidelines, as the NCCN guidelines stated that dexamethasone may be omitted or modified when the chemotherapy regimen already includes a corticosteroid.[12]

Chemotherapy regimens received by patients with NHL were classified based on potential emetogenic risk into HEC, MEC, LEC, and minimal categories.[21,22] Patients receiving chemotherapy regimens that are categorized as MEC risk with additional risk factors such as being female, under the age of 50, and having a previous history of CINV, or those at the higher end of the risk spectrum, such as cyclophosphamide, carboplatin, doxorubicin, ifosfamide, and irinotecan, are at greater risk of emesis and require three antiemetic prophylactic medications.[12] Furthermore, NHL chemotherapy regimens were categorized as antiemetic therapy based on the drugs with the highest emetogenic risk in accordance with the guidelines, and the pattern of prescribing antiemetic regimens was evaluated based on the number of antiemetic prescriptions.[20]

The factors associated with the consistency of the guidelines for patients with NHL undergoing chemotherapy were investigated. Additionally, the impact of patient-related risk factors, including age < 50, female sex, history of previous chemotherapy and radiotherapy, history of motion sickness or morning sickness, anxiety, and higher-end spectrum chemotherapy, on guideline consistency was considered.[12–14]

Ethical Approval

This study adheres to the principles outlined in the Declaration of Helsinki regarding ethical research involving human subjects. It was approved by the Ethical Committee of Medical Research at the University of Science and Technology in Sana'a, Yemen, as part of a broader project on (Medication Use Evaluation for Non-Hodgkin Lymphoma in Yemen, with a reference: EAC/UST201).

Statistical Analysis

The data obtained were analyzed using SPSS software (version 27.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to assess the demographic and clinical characteristics, including age, sex, cancer stage, and risk factors. Consistency with the NCCN guidelines was considered as the dependent variable. The association between guideline-consistent chemotherapy prophylaxis and other patient-related variables was analyzed using the chi-square test. Factors with a p-value of less than 0.25 in the chi-square test were included in multivariate binary logistic regression to identify independent predictors of antiemetic inconsistency to the NCCN guidelines.[23] Statistical significance was set at $P < 0.05$.

Results

Patients' Sociodemographic Data

Of the 251 patients, the majority (60.6%) were aged between 18 and 49 years, 23.1% were aged between 50 and 64 years, and 16.3% were 65 years or older. Participants were mostly male (57.4%), married (84.5%), unemployed (89.2%), and residing outside the Sana'a Governorate (77.3%). Less than half of the patients (45%) were illiterate (neither reading nor writing), had more than four children (41.4%), 19.1% had a family history, and the same proportion had a disease history. Furthermore, the most common social habits among the participants were khat chewing (63.3%), smoking (29.5%), and shamma (a form of smokeless tobacco) (14.7%). Table 2 summarizes the sociodemographic data of the participants.

Table 2 Socio-Demographic Data of Participants

Variable		Count (N=251)	(%)
Age (years)	18–49	152	60.6
	50–64	58	23.1
	≥ 65	41	16.3
Sex	Male	144	57.4
	Female	107	42.6
Marital status	Married	212	84.5
	Single	36	14.3
	Divorced	3	1.2
No. of children	No children	54	21.5
	One child	12	4.8
	Two to four children	81	32.3
	More than four	104	41.4
Occupation	Employed	27	10.8
	Unemployed	224	89.2
Residency	Sana'a governorate	57	22.7
	Other governorates	194	77.3
Education level	Neither read nor write	113	45.0
	Read and write	97	38.6
	Secondary school or above	41	16.3
Diseases history	Yes	48	19.1
	No	203	80.9
Family history	Yes	48	19.1
	No	203	80.9
Smoking	Yes	74	29.5
	No	177	70.5
Khat chewing	Yes	159	63.3
	No	92	36.7
Shamma	Yes	37	14.7
	No	214	85.3

Patients'-Related Clinical Data and Prescribing Pattern of Antiemetics for CINV

Table 3 provides insights into NHL treatment and patient response. Most patients received short-term treatment for 1 year or less (63.7%), had the non-DLBCL NHL subtype (55.0%), and were in advanced stages (77.3%). Rituximab-containing therapy was the most common treatment (61.4%), and most patients received four or more cycles (48.2%).

Table 3 Patients' Related Clinical Data and Prescribing Patterns of Antiemetics for CINV

Variable		**Count (N=251)**	**(%)**
Treatment duration	≤ 1 year	160	63.7
	2–5 years	72	28.7
	≥ 6 years	19	7.6
NHL subtype	DLBCL	113	45.0
	Non-DLBCL	138	55.0
Stage	Early stage	57	22.7
	Progress stage	194	77.3
Protocol type	Rituximab-containing therapy	154	61.4
	Non-Rituximab-containing therapy	97	38.6
Cycle number	1st cycle	57	22.7
	2nd /3rd cycle	74	29.1
	4th cycle or more	121	48.2
Treatment modality(es)	Chemotherapy	190	75.7
	Chemotherapy with surgery	37	14.7
	Chemotherapy with radiotherapy	19	7.6
	Chemotherapy with radio and surgery	5	2.0
Emetogenic potential risk	Minimal	21	8.4
	LEC	4	1.6
	MEC	204	81.3
	HEC	22	8.8
Overall consistency with guidelines	Consistent	60	23.9
	Inconsistent	191	76.1
Antiemetic drug selection	Consistent with NCCN guidelines	93	37.1
	Inconsistent with NCCN guidelines	158	62.9
Antiemetic dosage	Consistent with NCCN guidelines	209	83.3
	Inconsistent with NCCN guidelines	42	16.7
Dosage inconsistency sub-type:			
Overdose	No	248	98.8
	Yes	3	1.2
Underdose	No	212	84.5
	Yes	39	15.5

(*Continued*)

Table 3 (Continued).

Variable		Count (N=251)	(%)
Regimen inconsistency sub-type:			
Over-prescribing	No	227	90.4
	Yes	24	9.6
Under-prescribing	No	94	37.5
	Yes	157	62.5
Total number of prescribed antiemetic medication	1 medication	0	0
	2 medications	73	29.1
	3 medications	173	68.9
	4 medications	5	2.0

Abbreviations: CINV, chemotherapy-induced nausea and vomiting; NHL, Non-Hodgkin lymphoma; LEC, low emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; HEC, highly emetogenic chemotherapy; DLBCL, diffuse large B-cell Lymphoma; NCCN, National Comprehensive Cancer Network.

Chemotherapy was the main treatment modality (75.7%) and most patients received chemotherapy regimens with a moderate risk of emetogenicity (81.3%). Overall consistency with the National Comprehensive Cancer Network guidelines was low (23.9%). Among 76.1% of NHL patients in the GICP category, inconsistencies in antiemetic drug selection and dosage occurred in 62.9% and 16.7% of patients, respectively. Dosage inconsistency, including over- and under-dosing, was observed, with 15.5% of dexamethasone being prescribed as a low dose for moderate and high risks of emetogenicity. Underprescription was the most common subtype of regimen inconsistency (62.5%), while 9.6% were overprescriptions. Most patients with NHL patients received three antiemetic medications (68.9%) (Table 3).

Patients'-Related Risk Factors for CINV

Patients'-related risk factors may increase the likelihood of experiencing CINV. Most patients had a previous history of CINV (77.3%), most had not undergone radiotherapy (90.0%), and a small percentage reported motion sickness/ pregnancy morning sickness (4.8%). The age distribution was 61.0% in those under 50 years of age and 42.6% were females. The majority of patients experienced higher-end spectrum chemotherapy (81.3%) and 17.5% reported anxiety. The median overall risk score was 3, with an interquartile range of 2, indicating the risk scores among the study participants (Table 4).

Association Between Patients' Characteristics and Consistency of Antiemetic to the NCCN Guidelines

Table 5 summarizes the association between various patients' characteristics and the consistency of the NCCN guidelines for patients with NHL undergoing chemotherapy. Data were categorized as either consistent (GCCP) or inconsistent (GICP) according to the guidelines. The chi-square test was used to determine the significance of these associations. There were no statistically significant associations between the consistency of the NCCN guidelines and relevant factors, such as residency, education level, diseases and family history, common social habits, NHL subtype, disease stage, protocol type, and treatment modalities in NHL patients. Nevertheless, both age and sex groups showed highly significant association (<0.001), with patients in the age group 50–64 being significantly more likely to be consistent with guidelines (48.3%) compared to other age groups (9.2%) and (43.9%),-while male patients were more likely to be consistent with the guidelines (34.7%) compared to female patients (9.3%). The duration of treatment exhibited a significant association with consistency ($p < 0.001$), with patients undergoing ≤ 1 year of treatment showing higher consistency (31.9%) than

Table 4 Patients' Related Risk Factors for CINV

Risk factor		**Count (N=251)**	**(%)**
Previous history of CINV	No	57	22.7
	Yes	194	77.3
Previous history of receiving radiotherapy	No	226	90.0
	Yes	25	10.0
History of motion sickness/pregnancy morning sickness	No	13	5.2
	Yes	12	4.8
	No Record	226	90.0
Age of patients	≥ 50 years	98	39.0
	< 50 years	153	61.0
Gender of patients	Male	144	57.4
	Female	107	42.6
Higher-end spectrum chemotherapy	No	47	18.7
	Yes	204	81.3
Anxiety	No	207	82.5
	Yes	44	17.5
Overall risk score: Median (IQR)	**3 (2)**		

Abbreviations: IQR, interquartile range; CINV, chemotherapy-induced nausea and vomiting.

Table 5 Association Between Patients' Characteristics and Consistency of Antiemetic Guidelines

Variable		**Consistency with Guidelines**				**Chi-square**	**P value**
		Consistent (GCCP)		**Inconsistent (GICP)**			
		Count (N=251	**(%)**	**Count (N=251**	**(%)**		
Age (Years)	18–49	14	9.2	138	90.8	45.995	**<0.001***
	50–64	28	48.3	30	51.7		
	≥ 65	18	43.9	23	56.1		
Gender	Male	50	34.7	94	65.3	21.732	**<0.001***
	Female	10	9.3	97	90.7		
Marital status	Married	59	27.8	153	72.2	11.560	**0.001***
	Single/Divorced	1	2.8	38	97.4		
Occupation	Employed	7	25.9	20	74.1	0.068	0.794
	Unemployed	53	23.7	171	76.3		

(*Continued*)

Table 5 (Continued).

Variable		Consistency with Guidelines				Chi-square	P value
		Consistent (GCCP)		Inconsistent (GICP)			
		Count (N=251	(%)	Count (N=251	(%)		
Residency	Sana'a governorate	13	22.8	44	77.2	0.049	0.825
	Other governorates	47	24.2	147	75.8		
Education level	Neither read nor write	29	25.7	84	74.3	0.629	0.730
	Read and write	23	23.7	74	76.3		
	Secondary school or above	8	19.5	33	80.5		
Diseases history	Yes	15	31.3	33	68.8	1.761	0.185
	No	45	22.2	158	77.8		
Family History	Yes	13	27.1	35	72.9	0.330	0.566
	No	47	23.2	156	76.8		
Smoking (Social activities)	Yes	21	28.4	53	71.6	1.155	0.283
	No	39	22.0	138	78.0		
Khat chewing (Social activities)	Yes	41	25.8	118	74.2	0.844	0.358
	No	19	20.7	73	79.3		
Shamma use (Social activities)	Yes	9	24.3	28	75.7	0.004	0.948
	No	51	23.8	163	76.2		
Treatment duration	≤ 1 year	51	31.9	109	68.1	15.413	**<0.0001***
	> 1 year	9	9.9	82	90.1		
NHL Subtype	DLBCL	28	24.8	85	75.2	0.086	0.769
	Non-DLPCL	32	23.2	106	76.8		
Stage	Early stage	14	24.6	43	75.4	0.018	0.895
	Progress stage	46	23.7	148	76.3		
Protocol type	Rituximab-containing therapy	35	22.7	119	77.3	0.304	0.582
	Non-Rituximab-containing therapy	25	25.8	72	74.2		
Cycle number	1st cycle	28	50.9	27	49.1	28.603	**<0.001***
	2nd /3rd cycle	14	18.7	61	81.3		
	4th cycle or more	18	14.9	103	85.1		
Treatment modality(es)	Chemotherapy alone	50	26.3	140	73.7	2.499	0.114
	Chemotherapy with other interventions (radio and/or surgery)	10	16.4	51	83.6		

(*Continued*)

Table 5 (Continued).

Variable		Consistency with Guidelines				Chi-square	P value
		Consistent (GCCP)		Inconsistent (GICP)			
		Count (N=251	(%)	Count (N=251	(%)		
Emetogenic risk potential	Minimal/LEC	1	4.0	24	96.0	15.179	**0.001***
	MEC	59	28.9	145	71.1		
	HEC	0	0	22	100.0		
Overall patients' risk	1 to 2 risk factors	54	63.5	31	36.5	109.72	**<0.001***
	> 2 risk factors	6	3.7	158	96.3		

Note: *Chi-Square test; p-value in bold indicates a significant association.
Abbreviations: NCCN, National Comprehensive Cancer Network; GCCP, guideline-consistent chemotherapy prophylaxis; GICP, guideline-inconsistent chemotherapy prophylaxis group; LEC, low emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; HEC, highly emetogenic chemotherapy; DLBCL, diffuse large B-cell Lymphoma.

those undergoing > 1 year of treatment (9.9%). Moreover, consistency was significantly higher among patients in the first treatment cycle (50.9%) than in those in the second or third cycle (18.7%) and fourth cycle or more (14.9%). Additionally, a significant association was identified between consistency with guidelines and emetogenic risk potential as well as overall patient risk factors (p = 0.001). Specifically, patients with MEC risk or one or two risk factors were associated with higher GCCP (28.9% and 63.5%, respectively) than those with minimal/LEC risk (4.0%) or more than two risk factors (3.7%).

Factors Associated with Antiemetic Inconsistency to the NCCN Guidelines

Table 6 presents the results of a multivariate binary logistic regression analysis examining factors associated with inconsistency to the NCCN guidelines for antiemetic treatment among 251 patients with NHL undergoing chemotherapy.

Table 6 Factors Associated with Antiemetic Inconsistency to the NCCN Guidelines

Variable		Multivariate Binary Logistic Regression	
		AOR (95% C.I.)	P value
Age	18–49	Reference	
	50–64	0.119 (0.026, 0.545)	**0.006***
	≥ 65	0.224e (0.043, 1.160)	0.075
Sex	Male	Reference	
	Female	7.386 (1.467, 37.175)	**0.015***
Marital status	Married	Reference	
	Single/Divorced	28.854 (2.099, 396.716)	**0.012***
Diseases history	Yes	Reference	
	No	0.495 (0.140, 1.746)	0.274
Treatment duration	≤ 1 year	Reference	
	> 1 year	8.363 (2.422, 28.874)	**0.001***

(*Continued*)

Table 6 (Continued).

Variable		Multivariate Binary Logistic Regression	
		AOR (95% C.I.)	P value
Cycle number	1st cycle	Reference	**0.009***
	2nd /3rd cycle	6.777 (1.529, 30.043)	**0.012***
	4th cycle or more	9.609 (2.172, 42.502)	**0.003***
Treatment modality(es)	Chemotherapy alone	Reference	
	Chemotherapy with other interventions (radio and/surgery)	4.049 (1.105, 14.828)	**0.035***
Overall patients' risk	1 to 2 risk factors	Reference	
	> 2 risk factors	22.579 (5.864, 86.939)	**<0.001***

Note: Variables of <0.25 in the univariate analysis were included in the multivariable regression model; Method used for regression. *p-value in bold means it is significant.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

The results showed that various demographic and clinical factors are associated with inconsistency with antiemetic guidelines. Female gender, individuals who are unmarried or divorced, longer duration of treatment, undergoing more treatment cycles, receiving multiple types of treatment, and having multiple risk factors all significantly increased the likelihood of inconsistency. Specifically, female patients had substantially higher odds of being inconsistent with the guidelines compared to male patients (AOR: 7.386, CI: 1.467–37.175, p = 0.015) single or divorced patients had significantly higher odds of inconsistency compared to married patients (AOR: 28.854, CI: 2.099–396.716, p = 0.012), patients with treatment duration longer than 1 year had significantly higher odds of inconsistency compared to those with treatment duration of 1 year or less (AOR: 8.363, CI: 2.422–28.874, p = 0.001), patients undergoing their 2nd or 3rd cycle, as well as those undergoing their 4th cycle or more, had significantly higher odds of inconsistency compared to those in their 1st cycle (AOR: 6.777, CI: 1.529–30.043, p = 0.012) and (AOR: 9.609, CI: 2.172–42.502, p = 0.003) respectively. Patients receiving chemotherapy along with other interventions (such as radiotherapy or surgery) had significantly higher odds of inconsistency compared to those receiving chemotherapy alone (AOR: 4.049, CI: 1.105–14.828, p = 0.035), and patients with more than two risk factors had substantially higher odds of inconsistency compared to those with 1 to 2 risk factors (AOR: 22.579, CI: 5.864–86.939, p < 0.001). Conversely, being older (especially in the 50–64 age group) appears to be associated with lower odds of being inconsistent with the guidelines compared to those aged 18–49 (AOR: 0.119, CI: 0.026–0.545, p = 0.006).

Discussion

This study provides crucial insights into the clinical data of patients with NHL and factors affecting the consistency of the NCCN guidelines for CINV. This comprehensive analysis highlights various variables, emphasizing the need to address these variations for more standardized and effective care, ultimately enhancing antiemetic medication selection for patients with NHL.

The current study revealed a significant gap between the NCCN guidelines and the practical implementation of antiemetic prophylaxis in patients with NHL. Only 23.9% of patients received regimens consistent with these guidelines, indicating suboptimal consistency, likely due to physicians' lack of awareness and inadequate resources. These findings are consistent with those of previous studies that reported suboptimal adherence rates, ranging from 11% to 23%.[20,24,25] However, these findings contradict those of a study by Vazin and Eslami, who reported that the majority of patients (71.2%) received antiemetic regimens in accordance with guidelines.[14] These disparities can be attributed to various factors, including regional variations, patient demographics, prescriber characteristics, and evolving antiemetic therapies. Diverse study populations, methodologies, regional practices, and exact explanations of the guidelines may also have

contributed to the observed discrepancies. Additionally, the lack of standardized local guidelines for CINV management in Yemen exacerbates the issue. Recognizing these factors is vital for interpreting conflicting results and enhancing guideline implementation for the management of nausea and vomiting in patients with NHL.

The findings of the present study revealed that the majority of NHL patients received under-prescribed antiemetic medications. These findings are mainly attributed to the lack of chemotherapy classification based on emetogenic potential, as patients with risk of MEC or HEC received under-prescribed treatment, lacking aprepitant and olanzapine, while NCCN guidelines recommend a triple prophylactic antiemetic regimen for HEC, including olanzapine, NK1-RA, 5-HT3-RA, and dexamethasone. Furthermore, patients with additional risk factors, such as those receiving higher-end spectrum chemotherapy, should receive a triple prophylactic antiemetic regimen.[12] Similar issues have been observed in previous studies by Nikbakht et al, and Alamri et al[20,24] In contrast to the NCCN guidelines, which recommend a single-agent prophylaxis for LEC, such as dexamethasone, metoclopramide, prochlorperazine, or 5-HT3-RA, and no routine minimal-risk prophylaxis, the current findings revealed an over-prescribing regimen for patients with low and minimal emetogenic chemotherapy risk.[12] This issue aligns with the findings of Nikbakht et al, who observed a similar excessive use of antiemetic.[20] Consistent with previous studies,[14,24] our findings indicate the routine use of ondansetron and dexamethasone for acute emesis prophylaxis in all patients, regardless of their risk of emetogenicity. This practice mainly contributes to the observed overprescription, exposing patients to avoidable burdens, such as adverse effects, drug interactions, and unnecessary costs.

In terms of the number of antiemetics used in NHL patients, the current study found that most cases received three antiemetic medications. A previous study reported a common pattern for the four antiemetics.[20] Underdose inconsistency was observed in the current study mainly in patients receiving MEC/HEC, with 15.5% of dexamethasone administered at 8 mg for MEC/HEC risk, deviating from the recommended 12 mg IV/po per the NCCN guidelines.[12] These findings reflect the unwariness of the optimal dose of dexamethasone, as 8 mg can be prescribed for LEC, but a higher dose of dexamethasone (12 mg) is required for MEC and HEC. These inconsistencies, along with the reported inconsistency in antiemetic drug selection, highlight the significant variability and lack of standardization in prescribing practices, likely contributing to overall guideline inconsistency and suboptimal CINV prevention.

In terms of patient-related risk factors, the current study showed a significant proportion of patients received MEC agents at the higher end of the risk spectrum, emphasizing the necessity for a more intensive prophylactic antiemetic regimen, and highlighting the potential contribution of chemotherapy regimen intensity or type to CINV risk. Furthermore, the calculated overall risk score, with a consistent median of 3 (IQR 2), signifies that most patients in the study possessed multiple risk factors for CINV and underscored the necessity for personalized antiemetic approaches, particularly for those at the higher end of the risk spectrum. These findings are consistent with previous studies demonstrating the significant impact of patient-related risk factors on the incidence of CINV.[14,26,27]

Moreover, the study provides valuable insights into the factors associated with the consistency of antiemetic dispensing in accordance with the NCCN guidelines among patients with NHL undergoing chemotherapy. Several risk factors, including treatment duration, cycle number, emetogenic risk potential, treatment modalities, and overall patient risk, as well as age, sex, and marital status were significantly associated with guideline consistency for CINV prophylaxis ($p < 0.05$). Specifically, patients undergoing short-term treatment ($\leq$ 1 year) and earlier cycles (first cycle) were associated with higher guideline consistency. Moreover, patients with MEC risk potential or those with one or two risk factors were associated with higher GCCP than those with minimal/LEC risk or more than two risk factors. This is likely due to the increased risk of nausea and vomiting associated with MEC regimens and the moderate risk posed by fewer risk factors, leading to the need to prioritize stricter adherence to antiemetic protocols for these patients to ensure effective symptom management.

Conversely, the study findings derived from multivariate binary logistic regression analysis identified that patients who had longer treatment durations and underwent four cycles or more were associated with higher guideline inconsistency, likely due to factors like fatigue, toxicity, and changing patient needs. Patients with high emetogenic chemotherapy (HEC) risk potential, combined therapies (radiotherapy and surgery), and multiple risk factors were associated with increased deviation from standardized guidelines, possibly due to the complexity of controlling severe nausea and vomiting, which requires more intensive antiemetic regimens. Moreover, younger patients might receive more

standardized treatments and have fewer comorbidities, leading to being associated with higher guideline consistency. Consistent with these issues in the current study, previous studies have indicated an association between acute CINV and various risk factors, including a history of CINV, highly emetogenic chemotherapy, and pain/insomnia.[20,28] Furthermore, previous studies have stressed the benefits of guideline consistency for antiemetic prophylaxis in optimizing CINV management.[24,29]

Overall, the study revealed significant inconsistencies in antiemetic regimens for CINV among patients with NHL, highlighting the necessity of adhering to standard guidelines and considering patient demographics and treatment-related factors in the implementation of antiemetic guidelines to improve adherence and optimize patient outcomes in clinical practice.

Study Strengths and Limitations

This study has limitations, as it relied on data from a single center and was conducted using a convenience sampling approach, potentially limiting the generalizability of the findings. However, the study's strengths provide valuable insights into antiemetic prophylaxis for CINV in NHL patients in Yemen as the first study conducted addressing this important issue. Furthermore, its representative setting at the NOC, Al-Jomhouri Teaching Hospital, which is the largest oncology center in Yemen, enhances the ability of this study to reflect the broader population of patients in the country.

Recommendations

The study recommended a more comprehensive approach to address inconsistencies in adherence to antiemetic prescription guidelines for NHL patients undergoing chemotherapy in all regions of Yemen. Key recommendations include targeted interventions to enhance adherence to the NCCN, such as regular education for healthcare professionals on the latest guidelines and implementation of standardized protocols and decision support systems in healthcare facilities. Additionally, multicenter studies are recommended to evaluate antiemetic prescribing practices and medication efficacy in Yemeni patients with NHL.

Conclusion

This study identified significant inconsistency with NCCN antiemetic guidelines in the treatment of patients with NHL in Yemen. This inconsistency mainly includes inappropriate drug selection, dosing discrepancies, and underprescribed regimens. Patient demographics, treatment-related variables, and individual risk factors likely contribute to this observed inconsistency. Given the identified differences between the study population and the population upon which the guideline was developed, there is a necessity to evaluate and potentially adapt the existing guideline to better suit the local context.

Acknowledgments

We are grateful to all individuals who made valuable contributions to this study. We would also like to thank the National Oncology Center in Sana'a, Yemen, for providing access to data and facilities.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Cai P, Hao J, Wang D, Xu J. Comparative efficacy of different chemotherapies for non-Hodgkin lymphoma: a network-meta analysis. *Oncotarget*. 2017;8(53):91238. doi:10.18632/oncotarget.20437
2. Wen H, Lou X, Qu Z, et al. Pre-clinical efficacy of CD20-targeted chimeric antigen receptor T cells for non-Hodgkin's lymphoma. *Discov Oncol*. 2022;13(1):122. doi:10.1007/s12672-022-00588-w
3. Celio L. Emetogenicity of chemotherapy regimens and recommended prophylaxis: a review of MASCC/ESMO guidelines. *Emerg Med J*. 2022;7(2):60–67.
4. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO guideline update. *J Clin Oncol*. 2020;38(24):2782–2797. doi:10.1200/jco.20.01296
5. Clemmons A, Gandhi A, Clarke A, Jimenez S, Le T, Ajebo G. Premedications for cancer therapies: a primer for the hematology/oncology provider. *J Adv Pract Oncol*. 2021;12(8):810–832. doi:10.6004/jadpro.2021.12.8.4

6. Dipiro JT, Yee GC, Posey LM, Haines ST, Nolin TD, Ellingrod V. *Pharmacotherapy: A Pathophysiologic Approach, 11th Ed*. McGraw-Hill Education; 2020.
7. Piechotta V, Adams A, Haque M, et al. Antiemetics for adults for prevention of nausea and vomiting caused by moderately or highly emetogenic chemotherapy: a network meta-analysis. *Cochrane Database Syst Rev*. 2021;11(11):Cd012775. doi:10.1002/14651858.CD012775.pub2
8. Yokoe T, Hayashida T, Nagayama A, et al. Effectiveness of antiemetic regimens for highly emetogenic chemotherapy-induced nausea and vomiting: a systematic review and network meta-analysis. *Oncologist*. 2019;24(6):e347–e357. doi:10.1634/theoncologist.2018-0140
9. Tamura K, Aiba K, Saeki T, et al. Testing the effectiveness of antiemetic guidelines: results of a prospective registry by the CINV study group of Japan. *Int J Clin Oncol*. 2015;20(5):855–865. doi:10.1007/s10147-015-0786-7
10. Aogi K, Takeuchi H, Saeki T, et al. Optimizing antiemetic treatment for chemotherapy-induced nausea and vomiting in Japan: update summary of the 2015 Japan Society of Clinical Oncology clinical practice guidelines for antiemesis. *Int J Clin Oncol*. 2021;26(1):1–17. doi:10.1007/s10147-020-01818-3
11. Roila F, Warr D, Hesketh PJ, et al. 2016 updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following moderately emetogenic chemotherapy. *Support Care Cancer*. 2017;25(1):289–294. doi:10.1007/s00520-016-3365-1
12. NCCN. National Comprehensive Cancer Network. clinical practice guidelines in oncology: antiemesis. v. 1.2022; 2022.
13. 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):119–126. doi:10.1177/1078155220985919
14. Vazin A, Eslami D, Sahebi E. Evaluating the antiemetic administration consistency to prevent chemotherapy-induced nausea and vomiting with the standard guidelines: a prospective observational study. *Ther Clin Risk Manag*. 2017;13:1151–1157. doi:10.2147/tcrm.S133820
15. Aapro M, Scotte F, Escobar Y, et al. Practice patterns for prevention of chemotherapy-induced nausea and vomiting and antiemetic guideline adherence based on real-world prescribing data. *Oncologist*. 2021;26(6):e1073–e1082. doi:10.1002/onco.13716
16. Globocan. Cancer in Yemen. The Global Cancer Observatory; 2020. Available from: https://gco.iarc.fr/today/data/factsheets/populations/887-yemen-fact-sheets.pdf. Accessed May 7, 2024.
17. Aldaeri M, Hamid GA, Al Amad M, Ghaleb Y Response to rituximab in non-Hodgkin lymphoma patients at national oncology center, Aden, Yemen, 2017–2020: retrospective cohort study; 2022.
18. Yamane T. *Research Methodology/Sample Size*. Florida: University of Florida; 1973.
19. Kandasamy G, Sivanandy P, Khobrani M, et al. Effectiveness of antiemetics in the management of chemotherapy-induced nausea and vomiting in cancer patients following chemotherapy guidelines. *Indian J Pharm Sci*. 2019;81(4):757–765. doi:10.36468/pharmaceutical-sciences.567
20. Nikbakht Z, Rajabi M, Shahrasbi A, Roohi E, Hashemian F. Evaluation of adherence to antiemetic treatment guidelines in patients with chemotherapy-induced nausea and vomiting in teaching hospitals in Tehran. *J Cancer Educ*. 2021;36(5):1022–1029. doi:10.1007/s13187-020-01689-2
21. Wakasugi Y, Noda S, Ikuno Y, et al. Granisetron plus aprepitant versus granisetron in preventing nausea and vomiting during CHOP or R-CHOP regimen in malignant lymphoma: a retrospective study. *J Pharm Health Care Sci*. 2019;5(1):1–5. doi:10.1186/s40780-019-0153-3
22. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35(28):3240–3261. doi:10.1200/JCO.2017.74.4789
23. Kirkwood BR, Sterne JA. *Essential Medical Statistics*. John wiley & sons; 2010.
24. Alamri A, Alawlah YA, Qiao Y, Wang J. A retrospective review of treatment patterns of antiemetic agents for chemotherapy-induced nausea and vomiting. *SAGE Open Med*. 2018;6:2050312118767234. doi:10.1177/2050312118767234
25. Aapro M, Caprariu Z, Chilingirov P, et al. Assessing the impact of antiemetic guideline compliance on prevention of chemotherapy-induced nausea and vomiting: results of the nausea/emesis registry in oncology (NERO). *Eur J Cancer*. 2022;166:126–133. doi:10.1016/j.ejca.2022.01.028
26. Jordan K, Sippel C, Schmoll H-J. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. *Oncologist*. 2007;12(9):1143–1150. doi:10.1634/theoncologist.12-9-1143
27. Molassiotis A, Aapro M, Herrstedt J, Gralla R, Roila F. MASCC/ESMO antiemetic guidelines: introduction to the 2016 guideline update. *Support Care Cancer*. 2017;25(1):267–269. doi:10.1007/s00520-016-3324-x
28. Huang X, Li X, Li J, et al. Chemotherapy-induced nausea and vomiting in breast cancer patients: a multicenter prospective observational study. *Asia Pac J Oncol Nurs*. 2021;8(4):433–437. doi:10.4103/apjon.apjon-2120
29. Molassiotis A, Aapro M, Dicato M, et al. Evaluation of risk factors predicting chemotherapy-related nausea and vomiting: results from a European prospective observational study. *J Pain Symptom Manage*. 2014;47(5):839–848. e4. doi:10.1016/j.jpainsymman.2013.06.012