



RESEARCH ARTICLE

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The efficacy of single-dose palonosetron in highly emetogenic chemotherapy protocols compared to oral aprepitant and ondansetron

Yaala Saady Raof Al-Bairmany^{a, *}, Noor Kasib Hadi^b, Abdul Karim Nazar^c

^a Head of the Medical Oncology department, Al-Andalus Private Hospital for Cancer Patients, Baghdad, Iraq

^b Medical oncology resident, Al Yarmook Teaching Hospital, Baghdad, Iraq

^c Clinical Pharmacist, University of Baghdad, Baghdad, Iraq

ARTICLE INFO ABSTRACT



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Background: Chemotherapy-induced nausea and vomiting (CINV) is a common problem during cancer treatment and its proper management is essential. The primary objective of this study was to compare the efficacy of a single dose palonosetron in the control of chemotherapy-induced nausea and vomiting (CINV) to that of oral aprepitant and ondansetron. The secondary objective is to determine age, gender, morning sickness, motion sickness, as well as chemotherapy protocols as risk factors in increasing chemotherapy-induced nausea and vomiting (CINV).

Methods: This is a prospective cohort study carried out at Al-Andalus Private Hospital for Cancer Patients in Baghdad, Iraq. The study included 296 patients, diagnosed with cancer, and receiving high emetogenic chemotherapy protocol. Patients were divided into 3 arms according to the antiemetic received. Arm 1 received aprepitant and ondansetron, arm 2 received ondansetron, and arm 3 received palonosetron. The primary endpoint was the response rate defined as the percentage of patients without nausea or vomiting episodes during the chemotherapy treatment cycles. Other secondary endpoints such as age, gender, morning sickness, motion sickness, as well as chemotherapy protocols, were measured as risk factors in increasing chemotherapy-induced nausea and vomiting (CINV).

Results: A total of 296 patients, diagnosed with cancer, and receiving high emetogenic chemotherapy protocol were evaluated. There was no significant association between age or gender and CINV. The incidence of nausea and vomiting with ondansetron was more than the incidence of nausea and vomiting with aprepitant, and the incidence of nausea and vomiting with palonosetron was less than the incidence of nausea and vomiting with aprepitant. There was no significant association between morning sickness and nausea or vomiting. On the other hand, there was a significant association between motion sickness and nausea or vomiting. The most common cycle reported in nausea and vomiting was cycle 3. Regarding suffering from nausea and vomiting with some chemotherapy drugs, the most common drugs were adriamycin cyclophosphamide (AC) and carboplatin.

Conclusion: The results of the present study confirm the previous reports on the superiority of palonosetron over ondansetron and its aprepitant in reducing the incidence of CINV. Regarding risk factors, motion sickness, chemotherapy cycle 3, as well as adriamycin cyclophosphamide (AC) and carboplatin were risk factors inducing CINV in high emetogenic chemotherapy protocols.

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* Corresponding Author

Yaala Saady Raof Al-Bairmany
E-mail: dryaala@yahoo.com
Contact: +9647801687813

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common problem during cancer treatment and its proper management is essential. CINV is mediated by an interaction of neurotransmitter pathways, including serotonin and substance P pathways, serotonin acting on the 5HT₃ receptor, and the substance P targeting the NK1 receptor (Adel, 2017; Lorusso, Russo, Giotta, & Codega, 2020). The incidence and severity of CINV depend mainly on the anticancer agents' emetogenicity, which is divided into high, moderate, low, and mild emetogenic chemotherapy, according to the incidence of emesis in the absence of antiemetic prophylaxis (Piechotta *et al.*, 2021).

Guidelines for the prevention of CINV recommend that patients scheduled to receive highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) should be given combination prophylaxis with drugs targeting different pathways (Herrstedt *et al.*, 2017; Hesketh *et al.*, 2020; Hesketh *et al.*, 2017). Different options for use in CINV prophylaxis include the dopamine and serotonin 2 (5-HT₂) receptor antagonist olanzapine, neurokinin 1 (NK1) receptor antagonists [e.g. (fos) aprepitant, (fos) netupitant, rolapitant], serotonin 3 (5-HT₃) receptor antagonists (e.g. dolasetron, granisetron, ondansetron, palonosetron) and corticosteroids (typically dexamethasone) (Herrstedt *et al.*, 2017; National Comprehensive Cancer Network, 2021).

Several drugs are currently available for prophylaxis and the control of nausea and vomiting associated with chemotherapy but the most effective belong to the class of the 5HT₃ receptor antagonists (5HT₃-RAs) or the NK1 receptor antagonists (NK1-RAs) (Berger *et al.*, 2017; Lorusso *et al.*, 2020; Roila *et al.*, 2016). These drugs are also available in different formulations (oral, intravenous, or transdermal patch). A combination of a 5HT₃-RA and an NK1-RA together with dexamethasone is the most recommended for CINV prophylaxis, in particular for highly emetogenic treatments (Hesketh *et al.*, 2017).

Palonosetron is a pharmacologically and clinically distinct new-generation 5-HT₃ receptor antagonist (Yang & Zhang, 2020) that various meta-analyses have shown to be more effective than older 5-HT₃ RAs (Chow *et al.*, 2018; Hsu, Chen, Tam, & Hsu, 2021). It exhibits a higher binding affinity for 5-HT₃ receptors and synergistically interacts with the neurokinin 1 (NK1) receptor signaling pathway (Hamano *et al.*, 2021; Shirley, 2021) which may partially account for palonosetron's effectiveness in the delayed phase. Palonosetron comes in two formulations, oral (0.50 mg) and intravenous (IV; 0.25 mg) (Cui *et al.*, 2020).

Aprepitant is the first commercially available drug from a new class of agents, the neurokinin NK1 receptor antagonists. Oral aprepitant, in combination with other agents, is indicated for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV)

associated with highly emetogenic chemotherapy in adults (Wang *et al.*, 2021). When added to standard therapy (a serotonin 5-HT₃ receptor antagonist and a corticosteroid), aprepitant is effective and generally well tolerated in the prevention of CINV associated with highly emetogenic chemotherapy in adults (Gilmore, D'Amato, Griffith, & Schwartzberg, 2018).

Ondansetron is one of the medications most commonly used for empiric treatment of nausea and vomiting. It is a serotonin 5-HT₃ receptor antagonist, and does not have any effect on dopamine receptors or muscarinic receptors. Ondansetron has extreme utility as an antiemetic drug, and it is effective against nausea and vomiting of various etiologies (Kamiya *et al.*, 2021). Common uses of ondansetron include the prevention of CINV, radiation-induced nausea and vomiting, the prevention of postoperative nausea and vomiting, and off-label use for the prevention of nausea and vomiting associated with pregnancy. However, it is not effective for motion sickness-induced nausea (Ruktrirong *et al.*, 2021).

Several risk factors are associated with the development of CINV and can be categorized into two main groups: chemotherapy-related and patient-related risk factors (D'Souza *et al.*, 2020). The proper assessment of the emetogenic potential of the drugs combined with the individual risk factors is essential to evaluate an appropriate CINV prophylaxis (Dranitsaris *et al.*, 2016). The type of antineoplastic drugs, administered in the chemotherapy regimen, is the first risk factor that has to be evaluated. Regimens that include highly emetogenic drugs are at higher risk of inducing CINV compared to regimens containing less emetogenic compounds (Clark-Snow, Affronti, & Rittenberg, 2018). Moreover, several clinical studies have established that the development of CINV is highly correlated with patient features and histories, such as age, gender, alcohol intake, limited sleep, number of previous chemotherapy cycles, nausea during pregnancy (morning sickness), and motion sickness (Dranitsaris *et al.*, 2017; Scotte, 2017).

The primary objective of this study was to compare the efficacy of a single dose palonosetron in the control of CINV to that of oral aprepitant and ondansetron. The secondary objective was to determine chemotherapy protocols, morning sickness, motion sickness, as well as age, and gender as risk factors in increasing CINV.

Method and Materials

Study design and participants

This is a prospective cohort study carried out at Al-Andalus Private Hospital for Cancer Patients in Baghdad, Iraq from October 2020 to July 2021. The study included 296 patients, diagnosed with cancer, and receiving high emetogenic chemotherapy protocol. Patients were divided into 3 arms according to the antiemetic received.

Study Treatment

The following treatment protocols were administered to the three study arms:

First arm: In the first arm, 123 patients received oral aprepitant 125 mg on day 1, 80 mg on day 2 + 3 in combination with ondansetron 8mg iv on day 1 followed by oral ondansetron for day 2-4 in combination with dexamethasone 16 mg daily.

Second arm: In the second arm, 107 patients received ondansetron 8 mg i.v. on day 1 followed by oral ondansetron for days 2-4 in combination with dexamethasone 16 mg daily.

Third arm: In the third arm, 66 patients received palonosetron 0.25 mg i.v. over 5 minutes on day 1 only in combination with dexamethasone 16 mg (for day 1-4 for dexamethasone)

Data Collected

Before data collection, oral consent was taken from patients. Clinical data were collected by a questionnaire and it included the following variables: Demographic information (age, gender) clinical characteristics (morning sickness, motion sickness, nausea, vomiting, cycle number, chemotherapy, antiemetic). The primary endpoint of the study was the prevention of emesis episodes and no use of rescue medication during the administration of chemotherapy (assessed as a complete response). The secondary endpoints as risk factors were age, gender, morning sickness, motion sickness, as well as chemotherapy protocols.

Inclusion / Exclusion criteria

Included in the study were:

- patients above 18 years
- any Cancer patients on chemotherapy
- patients receiving high emetogenic protocol
- patients from 2nd cycle of chemotherapy

Excluded from the study were:

- patients below 18 years
- patients with Brain Metastases
- patients with mechanical obstruction
- patients on moderate and low emetogenic chemotherapy protocols
- patients on concurrent chemo-radiotherapy to upper GI malignancy

Ethical considerations

Ethical approval was obtained from the Ethics Committee of Al-Andalus Private Hospital for Cancer Patients, Baghdad, Iraq. Moreover, the confidentiality of all information collected in this study was guaranteed, as well as all data were protected through appropriate measures.

Statistical analysis

Data were collected, coded, revised, and entered into the Statistical Package for Social Science (R studio) version 2.3.2. The data were presented as numbers and percentages for the qualitative data, mean, standard deviations, and ranges for the quantitative data with parametric distribution, and median with interquartile range (IQR) for the quantitative data with the non-parametric distribution. *Shapiro test* was used to verify the normality of distribution. *The Chi-square test* was used in the comparison between two groups with qualitative data and *Fisher exact test* was used instead of the Chi-square test when the expected count in any cell was found less than 5. The comparison between more than two groups with quantitative data and parametric distribution was done by using *the One Way Analysis of Variance (ANOVA) test* and *Kruskal–Wallis test* was used in the comparison between more than two groups with quantitative data and non-parametric distribution. *Logistic regression* was used to calculate OR (Odd ratio) to compare two groups with qualitative data as a dependent variable and one or more than one independent variable by estimating probabilities. The confidence interval was set to 95 % and the margin of error accepted was set to 5 %. So, the p-value was considered significant as the following: $P > 0.05$: Non-significant (NS), $P < 0.05$: Significant (S), $P < 0.01$: Highly significant (HS)

Results

Demographic data and baseline clinical characteristics

Demographic data and baseline clinical characteristics are presented in Table 1. A total of 296 Patients were recruited, where 224 patients (75.7 %) were females and 72 patients (24.3 %) were males. According to the age range, 64 patients (21.6 %) were less than 40 years, 147 patients (49.7 %) were between (40-60) years and 85 patients (28.7 %) were more than 60 years. Moreover, nausea was reported in 218 patients (73.6 %), vomiting was reported in 142 patients (48 %), morning sickness was reported in 71 patients (24.0 %), and motion sickness was reported in 67 patients (22.6 %),

Table 1: Demographic data and baseline clinical characteristics

		n (%)
Age: (n=296)	40-60	147 (49.7%)
	more than 60	85 (28.7%)
	less than 40	64 (21.6%)
Gender: (n=296)	Female	224 (75.7%)
	Male	72 (24.3%)
Nausea	No	78 (26.4%)
	Yes	218 (73.6%)
Vomiting	No	154 (52.0%)
	Yes	142 (48.0%)
Morning sickness	No	225 (76.0%)
	Yes	71 (24.0%)
Motion sickness	No	229 (77.4%)
	Yes	67 (22.6%)

Logistic regression of chemotherapy-induced nausea and vomiting and demographic characteristics

Logistic regression of chemotherapy-induced nausea and vomiting and demographic characteristics as risk factors is

presented in Table 2. There was no statistically significant difference in univariate and multivariate analysis between age or gender, and between chemotherapy-induced nausea and vomiting.

Table 2: Logistic regression of chemotherapy-induced nausea and vomiting and demographic characteristics

Nausea:					
		No	Yes	OR (univariable)	OR (multivariable)
Age	40-60	35 (23.8%)	112 (76.2%)	-	-
	Less than 40	21 (32.8%)	43 (67.2%)	0.64 (0.34-1.23, p=0.175)	0.59 (0.30-1.17, p=0.129)
	More than 60	22 (25.9%)	63 (74.1%)	0.89 (0.49-1.67, p=0.724)	0.90 (0.48-1.71, p=0.747)
Gender	Female	59 (26.3%)	165 (73.7%)	-	-
	Male	19 (26.4%)	53 (73.6%)	1.00 (0.55-1.85, p=0.993)	1.04 (0.54-2.05, p=0.901)
Vomiting					
Age	40-60	76 (51.7%)	71 (48.3%)	-	-
	Less than 40	36 (56.2%)	28 (43.8%)	0.83 (0.46-1.50, p=0.543)	0.75 (0.40-1.37, p=0.351)
	More than 60	42 (49.4%)	43 (50.6%)	1.10 (0.64-1.87, p=0.737)	1.08 (0.62-1.88, p=0.773)
Gender	Female	120 (53.6%)	104 (46.4%)	-	-
	Male	34 (47.2%)	38 (52.8%)	1.29 (0.76-2.20, p=0.349)	1.32 (0.74-2.36, p=0.342)

Logistic regression of chemotherapy-induced nausea and vomiting and antiemetic drugs

Logistic regression of chemotherapy-induced nausea and vomiting and antiemetic drugs is presented in Table 3. Regarding nausea, 98 patients (91.6 %) were suffering from nausea in the ondansetron group with a statistically significant association (OR=4.16, CI (1.96-9.67), p<0.001), 31 patients (47 %) were suffering from nausea in

palonosetron group with statistically significant association (OR= 0.34, CI (0.18-0.63), p=0.001), while 89 patients (72.4 %) were suffering from nausea in aprepitant group. Regarding vomiting, 88 patients (82.2 %) were suffering from vomiting in the ondansetron group with a statistically significant association at (OR= 7.75, CI (4.26 – 14.66), p<0.001) and 8 patients (12.1 %) were suffering from vomiting in palonosetron group with statistically significant

association (OR= 0.23, CI (0.09-0.50), $p<0.001$), while 46 patients (37.4%) were suffering from vomiting in aprepitant group.

Table 3: Logistic regression of chemotherapy-induced nausea and vomiting and antiemetic drugs

Nausea		No	Yes	OR (univariable)
Antiemetic	aprepitant	34 (27.6%)	89 (72.4%)	-
	ondansetron	9 (8.4%)	98 (91.6%)	4.16 (1.96-9.67, $p<0.001$)
	palonosetron	35 (53.0%)	31 (47.0%)	0.34 (0.18-0.63, $p=0.001$)
Vomiting		No	Yes	OR (univariable)
Antiemetic	aprepitant	77 (62.6%)	46 (37.4%)	-
	ondansetron	19 (17.8%)	88 (82.2%)	7.75 (4.26-14.66, $p<0.001$)
	palonosetron	58 (87.9%)	8 (12.1%)	0.23 (0.09-0.50, $p<0.001$)

Logistic regression of chemotherapy-induced nausea and vomiting and morning sickness & motion sickness

Logistic regression of chemotherapy-induced nausea and vomiting and morning sickness & motion sickness is presented in Table 4. There was a statistically significant association between motion sickness and incidence of

nausea in univariate analysis (OR= 2.11, $p=0.039$) and multivariate analysis (while controlling for morning sickness) (OR= 2.48, $p=0.017$), and there was a statistically significant association between motion sickness and the incidence of vomiting as multivariate analysis (while controlling for morning sickness) (OR= 1.84, $p=0.04$).

Table 4: Logistic regression of chemotherapy-induced nausea and vomiting and morning sickness & motion sickness

Nausea:		No	Yes	OR (univariable)	OR (multivariable)
Morning sickness	No	57 (25.3%)	168 (74.7%)	-	-
	Yes	21 (29.6%)	50 (70.4%)	0.81 (0.45-1.48, $p=0.480$)	0.62 (0.32-1.22, $p=0.165$)
Motion sickness	No	67 (29.3%)	162 (70.7%)	-	-
	Yes	11 (16.4%)	56 (83.6%)	2.11 (1.07-4.46, $p=0.039$)	2.48 (1.22-5.46, $p=0.017$)
Vomiting:		No	Yes	OR (univariable)	OR (multivariable)
Morning sickness	No	114 (50.7%)	111 (49.3%)	-	-
	Yes	40 (56.3%)	31 (43.7%)	0.80 (0.46-1.36, $p=0.405$)	0.73 (0.40-1.33, $p=0.307$)
Motion sickness	No	125 (54.6%)	104 (45.4%)	-	-
	Yes	29 (43.3%)	38 (56.7%)	1.57 (0.91-2.74, $p=0.105$)	1.84 (1.03-3.34, $p=0.040$)

Association between chemotherapy-induced nausea and vomiting and cycle number

Association between chemotherapy-induced nausea and vomiting and cycle number is presented in Table 5. The

most common cycle reported in nausea was cycle 3 in 73 patients (33.5%) with a highly significant association ($p<0.001$), and the most common cycle number reported in vomiting was also cycle 3 in 46 patients (32.4%) with highly significant association ($p<0.001$).

Table 5: Association between chemotherapy-induced nausea and vomiting and cycle number

Cycle No.	Nausea:			Vomiting:		
	No	Yes	p-value	No	Yes	p-value
2	46 (59.0%)	55 (25.2%)	<0.001	70 (45.5%)	31 (21.8%)	<0.001
3	23 (29.5%)	73 (33.5%)		50 (32.5%)	46 (32.4%)	
4	6 (7.7%)	60 (27.5%)		26 (16.9%)	40 (28.2%)	
5	1 (1.3%)	15 (6.9%)		3 (1.9%)	13 (9.2%)	
More than 6	1 (1.3%)	12 (5.5%)		3 (1.9%)	10 (7.0%)	

Logistic regression of chemotherapy-induced nausea and vomiting and cycle number

Logistic regression of chemotherapy-induced nausea and vomiting and cycle number as a risk factor is presented in Table 6. There was a statistically significant difference between cycles 3, 4, 5 and 6 and nausea (OR= 2.65,

p=0.002), (OR= 8.36, p<0.001), (OR= 12.55, p=0.016), (OR=10.04, p=0.030) respectively. Regarding vomiting, there was a statistically significant difference between cycles 3, 4, 5 and 6 and vomiting (OR=2.08, p=0.014), (OR= 3.47, p<0.001), (OR=9.78, p=0.001), (OR= 7.53, p=0.004) respectively.

Table 6: Logistic regression of chemotherapy-induced nausea and vomiting and cycle number

Nausea:				
Cycle No.		No	Yes	OR (univariable)
2		46 (45.5%)	55 (54.5%)	-
3		23 (24.0%)	73 (76.0%)	2.65 (1.45-4.95, p=0.002)
4		6 (9.1%)	60 (90.9%)	8.36 (3.54-23.22, p<0.001)
5		1 (6.2%)	15 (93.8%)	12.55 (2.40-231.13, p=0.016)
More than 6		1 (7.7%)	12 (92.3%)	10.04 (1.87-186.27, p=0.030)
Vomiting:				
Cycle No.		No	Yes	OR (univariable)
2		70 (69.3%)	31 (30.7%)	-
3		50 (52.1%)	46 (47.9%)	2.08 (1.17-3.74, p=0.014)
4		26 (39.4%)	40 (60.6%)	3.47 (1.83-6.73, p<0.001)
5		3 (18.8%)	13 (81.2%)	9.78 (2.91-44.92, p=0.001)
More than 6		3 (23.1%)	10 (76.9%)	7.53 (2.13-35.33, p=0.004)

Association between chemotherapy-induced nausea and vomiting and chemotherapy drugs

Association between chemotherapy-induced nausea and vomiting and chemotherapy drugs is presented in Table 7. Regarding suffering from nausea with some chemotherapy drugs, it was found that the most common drugs were adriamycin cyclophosphamide (AC) in 87 patients (39.9%) and Carboplatin in 67 patients (30.7%) with a statistically significant difference at (p=0.004). While regarding the suffering from vomiting with some chemotherapy drugs, it was found that the most common drugs were Carboplatin

in 51 patients (35.9%) and adriamycin cyclophosphamide (AC) in 43 patients (30.3%) with a highly statistically significant difference at p (p<0.001).

Logistic regression of chemotherapy-induced nausea and vomiting and chemotherapy drugs

Logistic regression of chemotherapy-induced nausea and vomiting and chemotherapy drugs is presented in Table 8. There was a statistically significant difference in Cisplatin and Cyclophosphamide inducing nausea (OR=0.10, p=0.032), (OR= 0.06, p=0.022) respectively.

Table 7: Association between chemotherapy-induced nausea and vomiting and chemotherapy drugs

Chemotherapy	Nausea:		P-value	Vomiting:		P-value
	No	Yes		No	Yes	
Adriamycin	39 (50.0%)	87 (39.9%)	0.004	83 (53.9%)	43 (30.3%)	<0.001
Cyclophosphamide (AC)						
Carboplatin	11 (14.1%)	67 (30.7%)		27 (17.5%)	51 (35.9%)	
Cisplatin	16 (20.5%)	20 (9.2%)		21 (13.6%)	15 (10.6%)	
Cyclophosphamide	6 (7.7%)	5 (2.3%)		8 (5.2%)	3 (2.1%)	
Cytarabine	1 (1.3%)	4 (1.8%)		2 (1.3%)	3 (2.1%)	
Ifosfamide	1 (1.3%)	7 (3.2%)		2 (1.3%)	6 (4.2%)	
Dacarbazine	3 (3.8%)	14 (6.4%)		4 (2.6%)	13 (9.2%)	
Doxorubicin	0 (0.0%)	1 (0.5%)		1 (0.6%)	0 (0.0%)	
Epirubicin	1 (1.3%)	13 (6.0%)		6 (3.9%)	8 (5.6%)	
Cyclophosphamide (EC)						

Table 8: Logistic regression of chemotherapy-induced nausea and vomiting and chemotherapy drugs

Nausea:		No	Yes	OR (univariable)
Chemotherapy	Epirubicin	1 (7.1%)	13 (92.9%)	-
	Cyclophosphamide (EC)			
	Doxorubicin	0 (0.0)	1 (100.0%)	162936.92 (0.00-NA, p=0.989) *
	Adriamycin	39 (31.0%)	87 (69.0%)	0.17 (0.01-0.91, p=0.095)
	Cyclophosphamide (AC)			
	Carboplatin	11 (14.1%)	67 (85.9%)	0.47 (0.02-2.74, p=0.486)
	Cisplatin	16 (44.4%)	20 (55.6%)	0.10 (0.01-0.56, p=0.032)
	Cyclophosphamide	6 (54.5%)	5 (45.5%)	0.06 (0.00-0.50, p=0.022)
	Cytarabine	1 (20.0%)	4 (80.0%)	0.31 (0.01-8.97, p=0.440)
	Ifosfamide	1 (12.5%)	7 (87.5%)	0.54 (0.02-15.03, p=0.678)
	Dacarbazine	3 (17.6%)	14 (82.4%)	0.36 (0.02-3.21, p=0.400)
Vomiting:		No	Yes	OR (univariable)
Chemotherapy	Epirubicin	6 (42.9%)	8 (57.1%)	-
	Cyclophosphamide (EC)			
	Doxorubicin	1 (100.0%)	0 (0.0)	0.00 (NA-Inf., p=0.987)*
	Adriamycin			
	Cyclophosphamide (AC)	83 (65.9%)	43 (34.1%)	0.39 (0.12-1.19, p=0.098)
	Carboplatin	27 (34.6%)	51 (65.4%)	1.42 (0.43-4.50, p=0.555)
	Cisplatin	21 (58.3%)	15 (41.7%)	0.54 (0.15-1.85, p=0.327)
	Cyclophosphamide	8 (72.7%)	3 (27.3%)	0.28 (0.05-1.44, p=0.143)
	Cytarabine	2 (40.0%)	3 (60.0%)	1.13 (0.14-10.69, p=0.912)
	Ifosfamide	2 (25.0%)	6 (75.0%)	2.25 (0.36-19.29, p=0.407)
	Dacarbazine	4 (23.5%)	13 (76.5%)	2.44 (0.53-12.27, p=0.257)

*An inflated confidence interval as one patient is taking Doxorubicin

Discussion

Several antiemetics are currently available for prophylaxis and the control of chemotherapy-induced nausea and vomiting. These drugs are also available in different formulations and used in different combinations. We carried out this prospective cohort study at Al-Andalus Private Hospital for Cancer Patients in Baghdad, Iraq to compare the efficacy of a single dose palonosetron in the control of CINV to that of oral aprepitant and ondansetron. We also explored chemotherapy protocols, morning sickness, motion sickness, as well as age, and gender as risk factors in increasing CINV.

Several patient-related factors like age and gender affect the risk of CINV. In our study, there is no significant association between age or gender and CINV. Regarding the age variable, it was analyzed in many studies where they confirmed that it is a risk factor for CINV (Di Mattei *et al.*, 2016; Dranitsaris *et al.*, 2017; Iihara *et al.*, 2016; Kawazoe *et al.*, 2018; Mizuno *et al.*, 2016; Molassiotis *et al.*, 2016; Nawa-Nishigaki *et al.*, 2018; Rha, Park, Song, Lee, & Lee, 2016; Shimokawa *et al.*, 2019; Tamura *et al.*, 2015; Tsuji *et al.*, 2017; Uchida *et al.*, 2017). Other studies confirmed that younger patients are at higher risk of CINV than older patients (Dranitsaris *et al.*, 2016; Iihara *et al.*, 2016; Jordan *et al.*, 2017; Kawazoe *et al.*, 2018; Murakami *et al.*, 2014; Nawa-Nishigaki *et al.*, 2018; Rha *et al.*, 2016; Sekine, Segawa, Kubota, & Saeki, 2013; Tsuji *et al.*, 2017; Uchida *et al.*, 2017). Furthermore, In a systematic review carried out by Mosa *et al.*, it was reported that the risk of CINV is reduced by 4% with the increase of age by 1 year (Mosa, Hossain, Lavoie, & Yoo, 2020). Regarding gender, in many studies, women persistently had a higher risk of CINV than men (Fujii *et al.*, 2017; Mosa *et al.*, 2020; Sekine *et al.*, 2013; Takemoto *et al.*, 2017; Tamura *et al.*, 2015; Tsuji *et al.*, 2017; Uchida *et al.*, 2017).

Regarding the antiemetic drugs and CINV, in our study, the incidence of nausea and vomiting with ondansetron is more than the incidence of nausea and vomiting with aprepitant, and the incidence of nausea and vomiting with palonosetron is less than the incidence of nausea and vomiting with aprepitant. This shows the superiority of palonosetron over aprepitant and ondansetron as an antiemetic agent. Similarly, in a study carried out by Parathoduvil *et al.*, which compared the effectiveness and safety of palonosetron versus ondansetron as an antiemetic agent in patients receiving cancer chemotherapy, they reported that Palonosetron was significantly more efficacious than ondansetron in controlling CINV, especially in delayed phase and overall period of emesis (Parathoduvil, Sisupalan, & Rema, 2017). In another study carried out by Kovacs *et al.*, it was reported that high-dose palonosetron was efficacious for the prevention of CINV in pediatric patients receiving high emetogenic chemotherapy and non-inferior to ondansetron (Kovacs *et al.*, 2014). Furthermore, similar studies on comparison of the effectiveness of

palonosetron versus ondansetron were also done by Wenzell CM *et al.*, Kovacs G *et al.*, Mattiuzzi GN *et al.*, and the results go hand in hand with our present study (Kovacs *et al.*, 2016; Mattiuzzi *et al.*, 2010; Wenzell *et al.*, 2013). On the other hand, in a study carried out by Warr *et al.*, where aprepitant was evaluated for the prevention of CINV, they reported that the aprepitant regimen (aprepitant and ondansetron) was more effective than the control regimen (ondansetron alone) for prevention of CINV in patients receiving both an adriamycin and cyclophosphamide (Warr *et al.*, 2005). Finally, in a study carried out by Zelek *et al.*, it was reported that a single dose of oral NEPA (netupitant, and palonosetron) was at least as effective as a 3-day aprepitant regimen, with the indication of a potential efficacy benefit for NEPA (Zelek *et al.*, 2021).

In our study, there is no significant association between morning sickness and nausea or vomiting. On the other hand, there is a significant association between motion sickness and nausea or vomiting. In a study carried out by Dranitsaris *et al.*, they reported that a history of morning sickness was significantly associated with CINV (Dranitsaris *et al.*, 2017). In another study carried out by Mosa *et al.*, they also reported that patients who experienced morning sickness were at higher risk of CINV (Mosa *et al.*, 2020). Regarding motion sickness, Tsuji *et al.* reported that a history of motion sickness was a risk factor for CINV (Tsuji *et al.*, 2017). Furthermore, Tamura *et al.*, reported that a history of both motion and morning sickness was significantly associated with CINV (Tamura *et al.*, 2015).

Regarding the chemotherapy cycle number, in our study, the most common cycle reported in nausea and vomiting is cycle 3. This variable was analyzed in seven studies, of which, two studies demonstrated that patients in earlier cycles (cycle no. < 3) were at higher risk of CINV (Dranitsaris *et al.*, 2017; Petrella T., 2009). Similar studies carried out by Molassiotis *et al.* and Dranitsaris *et al.* reported that patients in the first cycle of chemotherapy were at higher risk of CINV (Dranitsaris *et al.*, 2017; Molassiotis, Stamataki, & Kontopantelis, 2013). However, Shih *et al.*, Hayashi *et al.*, and Di Mattei *et al.* found no relationship between chemotherapy cycle numbers and the risk of CINV (Di Mattei *et al.*, 2016; T. Hayashi *et al.*, 2017; Shih, Wan, & Chan, 2009).

The type of antineoplastic drugs, administered in the chemotherapy regimen, is a very important risk factor that has to be evaluated. Regarding suffering from nausea and vomiting with some chemotherapy drugs, in our study, the most common drugs are adriamycin cyclophosphamide (AC) and carboplatin. Compared to each other, nausea in the cisplatin group and the cyclophosphamide group are less than nausea in the Epirubicin Cyclophosphamide

(EC) group. In a study carried out by Hayashi *et al.*, it was reported that the CBDCA + PEM (carboplatin plus

pemetrexed) regimen had a higher risk of causing delayed nausea than the CBDCA + PTX (carboplatin plus paclitaxel) regimen (Toshinobu Hayashi *et al.*, 2021). Again, in the study carried out by Dranitsaris *et al.*, it was reported that mostly the use of platinum or anthracycline-based regimens was significantly associated with CINV (Dranitsaris *et al.*, 2017).

Strengths and limitations

This study is evaluated in light of its strengths and limitations. There are some limitations to this study. The biggest limitation is the use of patient-reported diaries regarding nausea and vomiting. Another limitation is that data regarding the use of rescue antiemetics, scheduled antiemetics, retching, complete response, and partial response, and grades for emesis (Grade 1, Grade 2) were not differentiated and reported. Moreover, this is a single institution-based study. Results of the study need to be confirmed by further studies with larger sample sizes as multicenter trials.

Conclusion

In conclusion, this study shows that the newer 5-HT₃ RA, palonosetron, is an effective first-line agent in preventing CINV in patients receiving high emetogenic chemotherapy. The levels of emetic control observed along with its safety profile suggest that palonosetron is a very feasible prophylactic agent with a potentially improved therapeutic profile compared with ondansetron and aprepitant for controlling CINV. Moreover, we did not find any significant association between age or gender and CINV. On the other hand, motion sickness was a risk factor for CINV, the most common cycle reported in nausea and vomiting is cycle 3, and the most common chemotherapeutic drugs inducing nausea and vomiting are adriamycin cyclophosphamide (AC) and carboplatin. Oncologists can use these factors before the initiation of a chemotherapy regimen to identify patients at risk for CINV, and to focus on more comprehensive antiemetic treatment options for those high-risk patients. This may enable better outcomes and avoid complications.

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