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Efficacy and Safety of Aprepitant in Combination with Dexamethasone, Granisetron and Metoclopramide as a Prophylaxis of Chemotherapy-Induced Nausea and Vomiting in a Cute and Delayed Emesis in Arab Cancer Patient

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Abstract

Background: Chemotherapy Induced Nausea and Vomiting (CINV) is one of the greatest sources of distress for patients. Severe CINV may force interruption of chemotherapy, it is important to control CINV to achieve successful chemotherapy.

Objective: This study to evaluate the efficacy and safety of aprepitant in a regimen containing aprepitant in combination with dexamethasone, granisetron and metoclopramide (APRDGM) versus a regimen dexamethasone, granisetron and metoclopramide (DGM) only, as a prophylaxis in (CINV) in highly emetogenic chemotherapy(HEC) in Arabic cancer patients.

Setting: This study was conducted at King Abdul-Aziz Medical city (Eastern Region, AlHasa, Saudi Arabia).

Methods: 309 patients all Arab population, treated with HEC, were enrolled in a retrospective, cohort study to investigate the efficacy and safety of (APR-DGM) compared to (DGM) regimen.

Main outcome measure: The primary efficacy endpoint was the complete response (CR) for acute emesis and determines the adverse drug events. Secondary endpoint was the CR for delayed emesis.

Results: The APR-DGM regimen showed a significantly improved control in the management of CINV in patients treated with HEC in acute emesis compared to the DGM regimen (P=0.0021). No significant difference was observed between the two regimens regards to delayed emesis (P=0.145). Both regimens were well tolerated, and the rates of adverse events were not significantly different between the regimens.

Conclusion: The addition of aprepitant to the standard regimen of dexamethasone, granisetron and metoclopramide was found to be significantly better than dexamethasone, granisetron and metoclopramide alone, but only in the control of acute emesis, with no significant change in delayed emesis in Arab population.

Keywords: Aprepitant; CINV; Nausea; Vomiting; Safety; Efficacy

Introduction

According to the world statistics, 14.1 million adults in the world were diagnosed with cancer in 2012. There were 8.2 million deaths from cancer in the world in 2012 [1]. Therefore a lot of research is directed towards the treatment of cancer and the management of related side effects of chemotherapy. There are many side effects associated with chemotherapy but chemotherapy-induced nausea and vomiting (CINV) is considered an extreme side effect that affects the quality of life of the patient. CINV is a common adverse event in cancer therapy. Because CINV has a strong negative influence on patient quality of life (QOL), CINV management is highly important. The most problematic effects caused by CINV are dehydration, malnutrition, metabolic imbalances, and potential withdrawal from future cycles of chemotherapy.

The incidence of acute and delayed nausea and vomiting (N&V) was investigated in highly and moderately emetogenic chemotherapy treatment regimens. Patients were recruited from 14 oncology practices in six countries. More than 35% of patients experienced acute nausea and 13% experienced acute emesis. In patients treated with highly emetogenic chemotherapy, 60% experienced delayed nausea, and 50% experienced delayed emesis. In patients treated with moderately emetogenic chemotherapy, 52% experienced delayed nausea, and 28% experienced delayed emesis [2].

At the 2009 MASCC/ESMO Consensus Conference, an expert panel used data to establish rankings of emetogenicity for chemotherapy agents [3,4]. Oral chemotherapy agents are now ranked separately from IV agents as there are intrinsic differences in emetogenicity as well as different schedules of administration [4,5].

Emesis is classified according to the two following major types:

Acute emesis is vomiting that occurs during the first 18-24 hours after chemotherapy administration with peak occurring at 4-6 hours depending on the agent given.

Delayed emesis with vomiting occurring >18-24 hours after chemotherapy administration, but may occur up to 5 days after chemotherapy with the peak in 2 to 3 days [6]. CINV can range from mild, to moderate and severe [7].

Chemotherapeutic agents are generally classified by their emetogenic effects, namely, "highly emetogenic chemotherapy" (HEC), "moderately emetogenic chemotherapy" (MEC), and "lower-minimal emetogenic chemotherapy", according to the frequency and strength of vomit-inducing effects [8,9].

The triple antiemetic therapy, using a 5-HT3 receptor antagonist, dexamethasone, and a neurokinin-1 (NK1) receptor antagonist, is the established and recommended treatment for HEC regimens. This triple antiemetic therapy prevents vomiting, and, to a lesser extent, nausea in the majority of patients [6,10,11].

While the majority of trials in literature have studied triple medication including dexamethasone, granisetron and aprepitant for prophylaxis of CINV, the aim of this study was to compare aprepitant in combination with DGM as a prophylaxis of CINV to the DGM regimen (without aprepitant) as prophylaxis of CINV in highly emetogenic chemotherapy.

Aim and Objectives

The aim of this study is to determine if aprepitant is safe and effective by comparing aprepitant in combination with DGM as a prophylaxis of CINV to the DGM regimen (without aprepitant) as prophylaxis of CINV in highly emetogenic chemotherapy in Arabic cancer patient.

Objectives of the Study

Primary objectives

Efficacy of aprepitant: The primary end point is to evaluate the acute emesis within 24 hours after administration of chemotherapy (0-24 hours) by using complete response (CR): no emesis, no admission because of emesis and no rescue therapy needed.

Efficacy of aprepitant will be determined by comparing the incidence of acute emesis (0-24 hours) in regimen 1 (DGM) vs. regimen 2 (APR-DGM) via the following:

a) Cases with emesis.

b) Administration of antiemetic rescue medication including metoclopramide, lorazepam, granisetron or dexamethasone.

c) Hospital admissions due to CINV.

Safety of the aprepitant

Determine the observed adverse drug events in the regimen 1 (DGM) compared to regimen 2 (APR-DGM).

The secondary objective

The secondary end point is the proportion of Arabic patients with a complete response (CR), no emesis or use of rescue therapy, after the administration of chemotherapy in delayed (24-20 hours) phase of emesis.

Evaluate the incidence of delayed emesis (25-120 hours) in regimen 1 (DGM) 25-120 hours after administration of chemotherapy compared to regimen 2 (APR-DGM) 25-120 hours after administration of chemotherapy.

Ethics Approval

This study received approval from the Investigational Review Board KAIMRC Research Office - King Abdullah International Medical Research Center under Subject RA15/002/A-"Efficacy and safety of Aprepitant as a prophylaxis of CINV in highly emetogenic level of chemotherapy in combination with Dexamethasone, Granisetron and Metoclopramide (DGM)". Full ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE050/1).

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with International Conference on Harmonization, Good Clinical Practices, and all applicable regulatory guidelines.

Methods

Study design

This study was designed as a retrospective medical chart review, single-center study, conducted at the National Guard Hospital in King Abdul-Aziz Medical city (Eastern Region, Saudi Arabia). This study is a cross sectional study for the period 2010-2014. The study population consisted of cancer patients treated with a highly emetogenic regimen as treatment for either breast cancer, lymphoma NHL (Non Hodgkin Lymphoma) or HL (Hodgkin Lymphoma), in the period from April 2010 till the end of 2014.

The HEC protocols included:

- **Breast cancer protocols**

AC: Intravenous doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2,

CAF: Intravenous doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2, and fluorouracil 500 mg/m^2,

CEF: Intravenous epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2, and fluorouracil 500 mg/m^2 [12].

- **Lymphomas protocols**

RCHOP (rituximab 375 mg/m^2 doxorubicin 50 mg/m^2 cyclophosphamide 750 mg/m^2 vincristine 1.4 mg/m^2, prednisone 45 mg/m^2 PO or methylprednisolone 125 mg IV) [13],

ABVD (doxorubicin 25 mg/m^2 vinblastine 6 mg/m^2 bleomycin 10 mg/m^2 dacarbazine 375 mg/m^2) [14].

Participants

309 Subjects were selected for inclusion in the study; this included 156 in group DGM and 153 in group APR-DGM.

Inclusion criteria

- Arabic patients aged between 18 to 75 years;
- Chemotherapy naïve patients (have not received chemotherapy before);
- Patients diagnosed with breast cancer stage II, III, IV or lymphoma stage II, III, and IV;
- Patients who failed on standard antiemetic therapy with a 5HT3 antagonist plus dexamethasone for moderately emetogenic regimens;
- Patients with performance statues Eastern Cooperative Oncology Group (ECOG SCORE) less than 5.

Exclusion criteria

- Hypersensitivity to aprepitant/fosaprepitant, polysorbate 80 or any ingredients in the formulation
- Patients on concurrent pimozide or cisapride (aprepitant is a weak to moderate dose-dependent inhibitor of CYP3A4 and therefore contraindicated for use with terfenadine, astemizole cisapride, or pimozide (concurrent use may result in life threatening reactions)
- Chemotherapy regimens with minimal, low, or moderate potential for incidence of emetogenicity
- Pregnant and lactating woman
- Patients with any psychological problems
- Patients with a history of depression

Interventions

DGM treatment group: 156 patient charts for the period April 2010 to April 2012 were selected. The DGM regimen was administered according to Table 1.

Acute emesis	Delay emesis			
Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Dexamethasone 16 mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 min infused over 30 min	Dexamethasone 8 mg PO twice daily	Dexamethasone daily 8 mg twice	Dexamethasone daily 8 mg twice	Dexamethasone daily 8 mg twice
Dexamethasone 4 mg PO evening of chemotherapy	-	-	-	-
Granisetron 1 mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 min infused over 5 min	Granisetron 2 mg PO twice daily	Granisetron 2 mg PO twice daily	Granisetron 2 mg PO twice daily	Granisetron 2 mg PO twice daily
Metoclopramide 10 mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 min infused over 30 min and every 6 hours	Metoclopramide 10 mg every 6 hours and PRN	Metoclopramide 10 mg every 6 hours and PRN	Metoclopramide 10 mg every 6 hours and PRN	Metoclopramide 10 mg every 6 hours and PRN

Table 1: Schedule of doses in DGM regimen.

DGM-APR treatment group: 153 patient charts for the period May 2012 till the end of year 2014 were selected. The DGM-APR regimen was administered according to Table 2.

Acute emesis	Delay emesis		
Day 1	**Day 2**	**Day 3**	**Day 4**
Aprepitant 125 mg before chemotherapy 45-60 min	Aprepitant 80 mg	Aprepitant 80 mg	-
Dexamethasone 12 mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 min infused over 30 min	Dexamethasone 8 mg oral once daily	Dexamethasone 8 mg oral once daily	Dexamethasone 8 mg oral once daily
Granisetron 1 mg IV mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 min infused over 5 min	-	-	-
Metoclopramide 10 mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 min infused over 30 min	Metoclopramide 10 mg every 6 hours and PRN	Metoclopramide 10 mg every 6 hours and PRN	Metoclopramide 10 mg every 6 hours and PRN

Table 2: Schedule of doses in APR-DGM regimen.

It is important to note that dexamethasone should not be added to a chemotherapeutic regimen that already contains corticosteroids; therefore, in the RCHOP protocol used for treatment of Non Hodgkin Lymphoma, dexamethasone was omitted. Methyl prednisolone 125 mg, as part of RCHOP protocol, can cover acute and delayed emesis.

Results

Outcomes and statistical analysis

The test statistic used was the two-sided Z test with continuity correction and unpooled variance. The significance level of the test was

targeted at 0.05. Baseline patient demographics and clinical characteristics as well as safety data were summarized using descriptive statistics. Descriptive summary statistics are presented for each of the efficacy parameters. Chi square tests of independence were performed on nominal variables and used to determine the CR. All statistical tests were two-sided, and p <0.05 was considered significant. All statistical analyses were performed using IBM SPSS software VERSION 20.

Sociodemographic characteristics

A total of 309 patient files were analysed, 156 receiving regimen DGM (50.49%) and 153 receiving regimen APR-DGM (49%).

205 from the 309 cases were female (66.34%); 60% female patients (94/156) were on the DGM regimen, and 71% (111/153) on the APR-DGM regimen. 33.66% male patients (62/156) were on the DGM regimen and 42/153 (27%) on the APR-DGM regimen (Table 3).

Characteristics	Early emesis	No early emesis	Chi-square
Group	25 (75.76)	-	9.4395
DGM	8 (24.24)	131 (47.46)	-
APR-DGM	-	145 (52.54)	-
Characteristics	**Late emesis**	**No late emesis**	
Group	35 (22.43%)	121 (77.56%)	1.44
DGM	26 (16.99%)	127 (83.01%)	-
APR-DGM	-	-	-
Characteristics	**Rescue medication (acute phase)**	**No rescue medication**	

Table 3: Univar ate analysis for early and late emesis per each group (N=309).

Patients with surface area equal to 2 were 263 (85.11%) and patient with surface area equal to 1 was 46 (14.89%). Performance statues of the patient according to ECOG score was 267 with 0 score (86.41%), 32 (10.36%) with score 1 and 10 (3.24%) with score 2. The mean age of the population was 47.3 ± 4.7.

Efficacy

The results show a statistically significant difference in complete response (no emesis, no admission and no use of rescue therapy) in acute emesis when comparing the two treatment regimens (p-value 0.002). The number of emesis in acute phase was statistically significantly lower in the APR-DGM group compared to the DGM group (p-value 0.0021).

The need for rescue medication was also statistically significantly in acute phase (p-value 0.001) for APR-DGM regimen compared to the DGM regimen.

No statistical significant differences between the two regimens were observed in the management of delayed emesis (p-value 0.145). The need for rescue medication when receiving treatment with the two different regimens also showed no statistically significance in the delayed phase (p-value 0.075). The numbers of hospital admission between two groups have been decreased (p-value 0.013) (Table 3).

Characteristics	N (%)	DGM Group (n=156)	APR-DGM Group (n=153)	P-value
Abdominal pain				
Yes	41 (13.27)	20 (12.28)	8 (5.23)	0.02
No	268 (86.73)	136 (78.18)	145 (94.77)	
Agitation				
Yes	23 (7.44)	9 (5.77)	14 (9.15)	0.258
No	286 (92.56)	147 (94.23)	139 (90.85)	
Anal burning				
Yes	14 (4.53)	7 (4.49)	7 (4.58)	0.971
No	295 (95.47)	149 (95.51)	146 (95.42)	
Anorexia				
Yes	44 (14.24)	20 (12.82)	24 (15.69)	0.471
No	265 (85.76)	136 (87.18)	129 (84.31)	
Allergic reaction				
Yes	9 (2.91)	4 (2.56)	5 (3.27)	0.713
No	300 (97.09)	152 (97.44)	148 (96.73)	
Yes	29 (9.39)	13 (8.3)	22 (14.38)	0.537
No	280 (90.61)	143 (91.67)	131 (85.62)	
Constipation				
Yes	33 (10.86)	15 (9.62)	2 (1.31)	0.541
No	276 (89.32)	141 (90.38)	151(98.69)	
Convulsion				
Yes	16 (5.18)	12 (7.69)	4 (2.61)	0.044
No	293 (94.82)	144 (92.31)	149 (97.39)	
Diarrhea				
Yes	29 (9.39)	13 (8.3)	16 (10.46)	0.522
No	280 (90.61)	143 (91.67)	137 (89.54)	
Dysuria				
Yes	4 (1.29)	2 (1.28)	2 (1.31)	0.984
No	305 (98.71)	154 (98.72)	151 (98.69)	
Fatigue				
Yes	37 (11.97)	17 (10.90)	20 (13.07)	0.556
No	272 (88.03)	139 (89.1)	133 (86.93)	
Face flushing				
Yes	16 (5.18)	10 (6.41)	6 (3.92)	0.324
No	293 (94.82)	146(93.59)	147(96.08)	
Headache				

Yes	23 (7.44)	10 (6.4)	13 (8.5)	0.485
No	286 (92.56)	146 (93.59)	140 (91.5)	
Hiccup				
Yes	43 (13.92)	20 (12.8)	23 (15)	0.574
No	266 (86.08)	136 (87.18)	130 (84.76)	
Insomnia				
Yes	23 (7.44)	12 (7.69)	11 (7.19)	0.866
No	286 (92.56)	144 (92.31)	142 (92.81)	
Tremor				
Yes	13 (4.21)	5 (3.21)	8 (5.23)	0.367
No	296 (95.79)	151 (69.79)	145 (94.77)	
Muscle pain				
Yes	22 (7.12)	12 (7.69)	10 (6.54)	0.693
No	287 (92.88)	144 (92.31)	143 (93.46)	
Sweating				
Yes	15 (4.85)	9 (5.77)	6 (3.85)	0.45
No	294 (95.15)	147 (49.23)	147 (96.08)	
Vaginal candida				
Yes	18 (5.83)	13 (8.31)	5 (3.27)	0.057
No	299 (96.76)	143 (91.78)	148 (96.73)	
Lacrimal duct obstruction and tearing				
Yes	25 (8.09)	15 (9.62)	10 (6.54)	0.975
No	284 (91.91)	141 (90.38)	143 (93.46)	

Table 4: Adverse events (N=309).

Safety

Safety and tolerability of the two treatment regimens were assessed and compared through clinical review of safety parameters using Chi-Square. Treatment comparisons were made with respect to the P- value and the proportion of patients who reported one or more adverse event(s), drug-related adverse event(s), or serious adverse event(s).

All side effects observed in both regimens were tolerable and manageable. The rates for frequently observed ADEs were not significantly different between the two regimens. None of the patients experienced severe toxicities (Table 4).

Conclusion

This study found that the APR-DGM regimen protected approximately 95% of patients from acute emesis after receiving highly emetogenic chemotherapy and enabled them to avoid the use of rescue therapy. This regimen also decreased the number of hospital admission due to CINV in the acute phase.

The addition of aprepitant to a standard therapy regimen consisting of a granisetron plus dexamethasone and metoclopramide improved the control of CINV associated with highly emetogenic chemotherapy in the acute phase. The aprepitant regimen was generally well tolerated, with adverse events similar to those associated with DGM regimen.

The time course and magnitude of improved control of emesis achieved with aprepitant support the hypothesis that superior control of CINV involves the blockade of substance P-mediated nausea and vomiting. The vomiting center in the medulla called the area postrema contains high concentrations of substance P and its receptor, in addition to other neurotransmitters such as choline, histamine, dopamine, serotonin, and opioids. Their activation stimulates the vomiting reflex. Different emetic pathways exist, and substance P/NK1R appears to be within the final common pathway to regulate vomiting [15]. Substance P is a member of a group of peptides known as tachykinins; these tachykinins bind to neurokinin-1, 2, and 3 receptors. NK1 receptors are found throughout the central nervous system, including the area postrema and nucleus tractus solitarius and NK1 receptors are also found in the GI tract. Aprepitant mediates the effect of substance P by blocking the neurokinin 1 (NK1) receptor [7,16,17].

In this study, it showed there was no significant difference in the response of DGM versus APR-GM in delayed phase emesis. Delayed vomiting occurs after treatment with many anticancer drugs, but has been most often studied following cisplatin or combinations of cyclophosphamide and anthracyclines. The mechanism of this phenomenon is unknown [18].

In the treatment of delayed emesis in non-cisplatin chemotherapy, corticosteroids and 5-HT3 receptor antagonists are considered the most useful agents [19,20].

Dexamethasone has consistently shown its antiemetic efficacy for delayed emesis induced by cisplatin and non-cisplatin agents, whereas the role of 5-HT3 antagonists alone remains controversial. Metoclopramide, the dopamine receptor antagonist, has been shown to be as efficacious as 5-HT3 antagonists when combined with dexamethasone for the prevention of delayed emesis [14]. Corticosteroids have synergistic effect with both serotonin antagonists and metoclopramide [21].

In conclusion, aprepitant represents an important medical advance that can substantially enhance the supportive care of Arabic patients with cancer who receive highly emetogenic chemotherapy in acute phase but little support in delayed phase. The aprepitant regimen was generally well tolerated. Either DGM or APR-DGM can be recommended in delayed phase of emesis, but because of the lower cost of DGM should be chosen as prophylaxis for delayed emesis. This study therefore supports the change of regimen in the management of acute with HEC to include aprepitant.

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