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ORIGINAL ARTICLE

Comparison of palonosetron and granisetron in triplet antiemetic therapy in nonmetastatic breast cancer patients receiving high emetogenic chemotherapy: a multicenter, prospective, and observational study

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Abstract

Purpose We aimed to investigate the efficacy of 0.25 mg dose of palonosetron and granisetron in triplet antiemetic prophylaxis in breast cancer patients receiving HEC.

Methods Patients with nonmetastatic breast cancer who received HEC [doxorubicin or epirubicin plus cyclophosphamide (AC/EC)] were enrolled in the study. The prophylactic triplet antiemetic regimens were used according to the doctor's preference during the first cycle of HEC as intravenous dexamethasone and palonosetron 0.25 mg or granisetron 3 mg on day 1 as well as oral aprepitant (125 mg on day 1 and 80 mg on days 2 and 3).The primary endpoint was complete response rate (CR) on acute and delayed chemotherapy-induced nausea and vomiting (CINV), separately.

Results A total of 118 female patients were included in the study. Patients received AC (83%), EC (3%), and dose-dense AC (14%) as adjuvant (88%) or neoadjuvant (12%). The majority of patients received palonosetron (59%) containing antiemetic treatment. The CR rate on acute and delayed vomiting was very high and not statistically different in both of the arms (acute 87% vs. 96%, $p=0.089$; delayed 90% vs. 92%, $p=0.489$), respectively. Nevertheless, the CR rate on either acute or delayed nausea was lower than vomiting (acute 51% vs. 51%; delayed 38% vs. 29%, $p=0.203$; respectively).

Conclusions This is the second study that compared a 0.25 mg dose of palonosetron with first-generation setron in triplet antiemetic prophylaxis in cancer patients receiving HEC. We could not find meaningful statistical differences between two arms, regarding CR rate on acute and delayed CINV.

Keywords Breast cancer · Granisetron · High emetogenic chemotherapy · Palonosetron · Triplet antiemetic

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) continue to be an essential adverse event which has a negative effect to the treatment adherence of patients and may result to discontinuation of therapy and can lead to a reduction in survival by treatment [1]. CINV control rates have been observed enhancing when starting to use first-generation 5-hydroxytryptamine three receptors (5HT3R) antagonists with dexamethasone in the years of the 1990s. In 2003, two new antiemetic drugs, second-generation 5HT3R antagonist palonosetron and first neurokinin-1 (NK-1) receptor antagonist aprepitant were approved by the Food and Drug Administration and thus, a substantial increase arriving at 80s% from 60s% on CINV control rate was provided especially when aprepitant used with 5HT3R antagonist and dexamethasone in triplet antiemetic prophylaxis [2].

CINV is classified into two major categories as acute and delayed phase, depending on when it starts after chemotherapy. Although the all first-generation 5HT3R antagonists have similar clinical efficacy on acute CINV when used in the recommended doses [3], it is accepted that they have no or little activity on delayed CINV [4]. Palonosetron differs from first-generation 5-HT3R antagonists with some characteristics; longer plasma elimination half-life, at least 30-fold higher receptor binding affinity to the 5HT3R, a different molecular interaction with 5-HT3 receptors, and inhibition of crosstalk between 5-HT3 and NK-1 receptor [5, 6]. Because of these properties, palonosetron is thought that it will be able to provide better antiemetic prophylaxis for both acute and delayed CINV, unlike the other 5-HT3 receptor antagonists. Studies which compared the second- and first-generation 5HT3R antagonists showed that palonosetron is noninferior in the acute phase and superior in the delayed and overall phase CINV as alone or in doublet regimen with dexamethasone [4]. Systematic metanalysis has demonstrated that when NK-1 receptor antagonist is added to 5HT3R antagonists plus dexamethasone, these triplet antiemetic regimens have provided statistically significantly better control in acute, delayed, and overall CINV compared with doublet regimens in patients receiving high emetogenic chemotherapy (HEC) and moderate emetogenic chemotherapy (MEC) [2, 7, 8]. However, in these trials, first- and second-generation 5-HT3R have not been compared head-to-head in triplet antiemetic prophylaxis.

To the best our knowledge, there are only three studies [9–11] which compare first-generation setrons with the palonosetron in the triplet antiemetic prophylaxis in the literature. In the first study [9], 0.25 mg dose of palonosetron has been compared with ondansetron, while in the other two phase III studies [10, 11] which had been performed with the Japanese patients, palonosetron 0.75 mg against different doses of granisetron. However, only 0.25 mg dose of palonosetron is approved in Turkey, the United States, and many European countries, while 0.75 mg is commonly used in the Far East countries. Therefore, we aimed to compare the efficacy of 0.25 mg palonosetron and granisetron on acute and delayed CINV in triplet antiemetic prophylaxis in Turkish patients with the diagnosis of nonmetastatic breast cancer receiving high emetogenic chemotherapy.

Materials and methods

This multicenter, nonrandomized, prospective, and observational study was carried out between April 2017 and December 2017 at four different cancer centers in Turkey. The study was approved by the local ethics committee at Afyon Kocatepe University Faculty of Medicine and each participating site and carried out following the Declaration of Helsinki principles and all relevant regulations.

Participants

Eligible patients were ≥ 18 years females with the diagnosis of nonmetastatic breast carcinoma who were chemo-naive and who will receive the first cycle of HEC [doxorubicin 60 mg/m^2 or epirubicin 100 mg/m^2 plus 600 mg/m^2 cyclophosphamide (AC/EC)] on day 1.

Exclusion criteria included: any previously diagnosed carcinoma and treated with chemotherapy; distant metastasis; opioid usage; using any antiemetic drugs for vomiting or nausea within 1 week before administration of chemotherapy. Also, patients with known hepatic and renal dysfunction were excluded. Eligible patients received palonosetron (0.25 mg) or granisetron (3 mg) and dexamethasone as intravenous with aprepitant 125 mg oral 30 min before chemotherapy on day 1. Additionally, aprepitant 80 mg was administered on days 2 and 3. The choice of palonosetron or granisetron and dose of dexamethasone were left to the doctor's preference.

Patients were called two times with phone by researchers after on the 24 h (acute phase) and 120 h (delayed phase) after finishing chemotherapy. Multinational Association of Supportive Care in Cancer (MASCC) antiemesis tool was used to evaluate acute and delayed CINV. All patients provided written informed consent before enrollment.

The study protocol

Endpoints

Primary endpoints in the trial were complete response rate on vomiting and nausea during the acute and delayed phase,

separately. CR was defined as no vomiting/no nausea and no rescue medication (Fig. 1).

Secondary endpoints were included; total control rate (TC was defined as no vomiting, no nausea, and no rescue medication) on CINV for the overall (0–120 h postchemotherapy) phases and differences in two arms regarding the frequency of treatment-related adverse events such as a headache, constipation, and hiccup.

Statistics

SPSS (Version 20) software was used for statistical analysis. Mean ± standard deviation, median, and percentage (%) values were found. A Chi-square test was used for comparing the categorical data. A *t*-test was used to assess the difference of mean for non-categorical data. Values of $P < 0.05$ were considered statistically significant.

Results

A total of 121 patients were enrolled in the trial. Three patients were excluded from the study because of a patient who has migraine disease history survived a migraine attack after chemotherapy, one of the patients did not answer the phone calls, and we detected multiple liver metastases on dynamic liver magnetic resonance imaging in the other patient. After the exclusion of 3 patients, the rest 118 female patients were analyzed in the study. The median age of the patients was 51 years (min–max: 28–78). The majority of patients had received palonosetron (59% versus 41%) containing triplet antiemetic treatment. The patients had received AC (83%), dose-dense AC (14%), and EC (3%) chemotherapy as adjuvant (88%) or neoadjuvant (12%). The dexamethasone dose had been preferred generally as 8 mg in the patients (%80). All patients had an ECOG performance status of 0 or 1. The majority of patients (64%) had no any comorbid disease. Patient's characteristics were similar in both groups. The descriptive statistics are summarized in Table 1.

The primary endpoint; The CR rates on vomiting in acute and delayed phases were also very high in the two arms. We achieved CR in the 60 patients (87%) of the palonosetron arm and 47 patients (96%) of the granisetron arm at

Table 1 Patients characteristics

	Palonosetron *n* (%)	Granisetron *n* (%)	*P*
Median age	52	51	
Triplet antiemetic group	69 (59)	49 (41)	0.39
Patient's age			
≤ 55	32 (46)	24 (49)	0.46
> 55	37 (54)	25 (51)	
Chemotherapy agents			
AC	56 (81)	42 (86)	0.64
EC	2 (3)	2 (4)	
Dose dense AC	11 (16)	5 (10)	
Treatment type			
Adjuvant	60 (87)	44 (90)	0.63
Neoadjuvant	9 (13)	5 (10)	
Dexamethasone dosage			
8 mg	58 (84)	37 (76)	0.18
> 8 mg	11 (16)	12 (24)	
Alcohol consumption history			
Yes	0 (0)	0 (0)	0.39
No	69 (100)	49 (100)	
ECOG			
ECOG 0	41 (59)	28 (57)	0.80
ECOG 1	28 (41)	21 (43)	
Comorbid diseases			
No	42 (61)	33 (67)	0.54
Diabetes	10 (14)	4 (8)	
Hypertension	12 (17)	10 (20)	
Others	8 (12)	4 (8)	

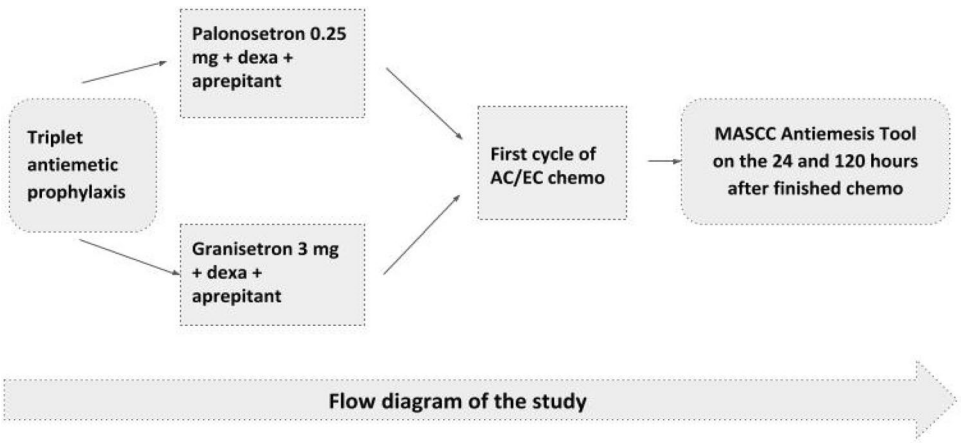

Fig. 1 Flow diagram of the study

the acute phase, whereas in the 62 patients (90%) of the palonosetron arm and 45 patients (92%) of the granisetron arm at the delayed phase. Although granisetron appears providing better control than palonosetron for acute vomiting, a statistical difference was not detected between the two arms ($p=0.089$). Nevertheless, the CR rates of either palonosetron or granisetron containing group on acute or delayed nausea were lower when compared with control rates of vomiting. In the acute phase, CR rates on nausea were the same in the two arms (51% vs. 51%, respectively). Even though there was numerical difference in favor of palonosetron in the delayed phase, a statistically significant difference could not be determined (38% vs. 29%, $p=0.203$; respectively). The results for primary endpoint are shown in Table 2.

The secondary endpoints; TC on both nausea and vomiting was achieved in 46 patients (67%) of the palonosetron group and 38 patients (77%) of the granisetron group. Nevertheless, the result was in favor of granisetron; this difference did not reach a statistical significance ($p=0.140$). Overall, 25 patients (36%) in the palonosetron and 18 patients (37%) in the granisetron group reported rescue antiemetic drugs usage during the study period. Rescue antiemetics usage was similar in the two arms ($p=0.536$). Constipation was reported in higher frequency in the palonosetron arm, but there was no statistically significant difference with the granisetron (49% vs. 39%, 0.173; respectively). The other treatment-related adverse events such as headache and hiccup were similar for two antiemetics. The results for the secondary endpoint are summarized in Tables 2 and 3.

Table 2 Complete response and total control rate of palonosetron vs granisetron on CINV

	Palonosetron no (%)	Granisetron no (%)	*P*
Vomiting			
Acute phase			
No	9 (13)	2 (4)	0.089
Yes	60 (87)	47 (96)	
Delayed phase			
No	7 (10)	4 (8)	0.489
Yes	62 (90)	45 (92)	
Nausea			
Acute phase			
No	34 (49)	24 (49)	1
Yes	35 (51)	25 (51)	
Delayed phase			
No	43 (62)	35 (71)	0.203
Yes	26 (38)	14 (29)	
Rescue antiemetics medication			
Yes	25 (36)	18 (37)	0.536
No	44 (64)	31 (63)	
Total control rate			
Yes	46 (67)	38 (77)	0.140
No	23 (33)	11 (23)	

Discussion

This study shows the efficacy of palonosetron in triplet antiemetic prophylaxis in cancer patients receiving HEC. We demonstrated that the efficacy of palonosetron 0.25 mg versus granisetron 3 mg did not have statistically significant difference on both acute and delayed CINV of HEC when combined with aprepitant and dexamethasone. The CR rates on vomiting in both acute and delayed phases reached 90s% also for two arms. In contrast to our study, CR rates in the delayed phase were lower than in acute phase in the previous three studies while only Suzuki et al. [11] had shown similar results in the acute phase (Table 4).

The first time, Wenzel et al. [9] compared the various generation 5HT3 antagonists in triplet antiemetic prophylaxis of HEC in a small, randomized, and prospective pilot study. The 39 patients of total 40 patients had received the first cycle of AC and one patient received AC plus bevacizumab chemotherapy for breast cancer, and the other patients had received ABVD chemo regimen for lymphoma. The primary endpoint was the overall CR rate. A statistically significant difference was not shown in the study while 0.25 mg palonosetron numerically higher rates of overall CR (65% versus 40%, respectively), acute CR (75% versus 55%, respectively), and delayed CR (65% versus 45%, respectively) than ondansetron group.

In the other two phase III and prospective trials, 0.75 mg dose of palonosetron had compared with granisetron on Japanese patients. The study of Tsuneizumi et al. [10] had been presented in MASCC/IS00 2016 Annual Meeting but, the full text has not been published yet. In this multicenter study, stage I–III, chemo-naive 486 women with breast cancer patients randomly assigned one-to-one palonosetron

Table 3 Adverse events

	Palonosetron no (%)	Granisetron no (%)	*P*
Constipation			
Yes	34 (49%)	19 (39%)	0.173
No	35 (51%)	30 (61%)	
Headache			
Yes	36 (52%)	26 (53%)	0.537
No	33 (48%)	23 (47%)	
Hiccup			
Yes	7 (10%)	6 (12%)	0.471
No	62 (90%)	43 (88%)	

Table 4 The results of the head-to-head trials comparing the palonosetron vs. granisetron in triplet antiemetic prophylaxis in patients receiving HEC

	Wenzel et al. [9]	Tsuneizumi et al. [10]	Suzuki et al. [11]
Patients no	40	491	842
Primary tumor site	Breast	Breast	Lung, esophageal and gastric, head and neck cancer, and others
HEC type	AC/EC	AC/EC	≥ 50 mg/m^2 cisplatin
Antiemetics	Palonosetron 0.25 vs ondansetron 24 mg	Palonosetron 0.75 vs granisetron 3 mg	Palonosetron 0.75 vs granisetron 1 mg
Acute CR	75% vs 55%	71.14% vs 72.65%	91.8% vs 91.8%
Delayed CR	65% vs 45%	58.13% vs 53.47%[a]	67.2% vs 59.1%, $p=0.0142$
Overall CR	65% vs 40%[a]	52.85% vs 46.94%	65.7% vs 59.1%[a], $p=0.0539$
Acute nause CR	60% vs 65%	ND	ND
Delayed nause CR	40% vs 45%	ND	ND
Overall TC	ND	ND	47.6% vs 40.7%, $p=0.0369$

TC total control, *ND* not defined

[a]Primary end point

0.75 mg and granisetron 40 mcg/kg arm before first cycle AC or EC chemotherapy. Majority of patients had received epirubicin containing chemo regimen than adriamycin, and each arm was similar concerning neoadjuvant and adjuvant treatment. In contrast to Wenzel et al. [9], dexamethasone had not been used on days 2–4, and the primary endpoint of the study was the CR rate of the delayed CINV. Palonosetron was numerically better than granisetron (58.5% versus 53.8%, respectively) regarding the primary endpoint, but the difference has failed to reach statistical significance. CR rate was similar in the two arms for acute phase (71.14% versus 72.65%, respectively). Overall CR rate was 52.85% versus 46.94, respectively.

The full text of the second phase III TRIPLE study which was performed by Suzuki et al. [11] was published in 2016 Annals of Oncology. Patients had different primary tumor sites (such as lung, head and neck, esophageal, gastric and the other cancers), all patients were not chemo-naive and had taken cisplatin (≥ 50 mg/m^2)-based chemo regimen, unlike the previous works. Also, the dose of granisetron had been chosen as 1 mg compared with palonosetron—0.75 mg. Totally 842 patients had been enrolled in the study. Both arms had received dexamethasone 12 mg on day 1, then 8 mg on days 2–4 as similarly with study of Wenzel et al. [9]. The primary endpoint was overall CR rate and secondary endpoints were CR rate in the acute and delayed phase, complete control (CC had been defined as no vomiting, no retching, no rescue medication, and no more than mild nausea) and total control (TC had been defined as no vomiting, no retching, no rescue medication, and no nausea). The study could not show the superiority of palonosetron when compared with granisetron regarding the primary endpoint overall CR (65.7% versus 59.1%, $P=0.0539$; respectively). However, CR rate was detected as the same in the acute phase (91.8% versus 91.8%) while CR rate was statistically significantly different in favor of palonosetron at the delayed phase (67.2% versus 59.1%, $p=0.0142$; respectively). Also, palonosetron achieved significantly higher CC and TC rates than granisetron only at the delayed phase.

Participants' characteristics of our study were similar to the trial of Tsuneizumi et al. [10] regarding the primary tumor site, disease stage, and HEC chemotherapy type. Although tumor metastasis sites and opioid usage can influence the CINV rate, we could not find any knowledge in the papers of Suzuki et al. [11] and Wenzel et al. [9].

Nausea has not been well controlled because the mechanism underlying is less well understood than vomiting and nausea has been used as a secondary endpoint in many studies [4, 5]. Saito et al. [12] and Kubota et al. [13] have shown that palonosetron plus dexamethasone was more effective than granisetron plus dexamethasone in the control of delayed nausea for HEC and this difference was statistically significant. A significant limitation of these studies was that the patients were not given an NK-1 receptor antagonist. In our study, nausea control rate was chosen as the primary endpoint in triplet antiemetic prophylaxis containing NK-1 receptor antagonist, but we did not find statistical differences in acute and delayed phases between palonosetron and granisetron arms. However, nausea CR rate was detected almost half lower than control of vomiting in our study. Only Wenzel et al. [9] had reported nausea control rates in the paper, and their results were better than ours (Table 4).

TC rate had been chosen as secondary endpoint only in the TRIPLE study [11] similarly with our study. They showed that palonosetron was statistically significantly better than granisetron arm regarding TC rate (47.6% vs. 40.7%, $p=0.0369$; respectively). However, we could not find statistical differences in the two arms in our study while TC rates were higher and this height was in favor of granisetron arm (67% vs. 77%, $p=0.14$) in contrast to TRIPLE study.

A metanalysis comparing the efficacy of different first-generation 5-HT3-receptor antagonists has shown that 24 mg dose of ondansetron had equivalent efficacy with 2 or 3 mg doses of granisetron and no significant differences in efficacy were seen between doses of granisetron 1 mg and granisetron 3 mg (or 40 mcg/kg) [3]. Also, phase 3 trials [12, 14, 15] and a meta-analysis [16] have demonstrated that 0.25 mg and 0.75 mg doses of palonosetron have nearly equal effectiveness.

The concomitant use of dexamethasone during cancer therapy in patients with cancer and diabetes may increase serum glucose levels. However, it is one of the main drugs for acute and delayed CINV prophylaxis. The guidelines do not make any additional recommendations except for careful use and, if clinically indicated, consider monitoring before and after treatment. However, this area still needs to be clearly explained.

Patient risk factors such as female sex, younger age, and non-habitual alcohol consumption have been identified as significantly related to both acute and delayed CINV [4]. Sekine et al. [17] had demonstrated that patients who had all three risk factors were statistically significantly related with treatment failure for prophylaxis of acute phase, while female sex was the only risk factor for CINV in the delayed phase. All our patients were female and had no alcohol consumption history, and there was no effect of age factor on the results in our study similarly with Tsuneizumi et al. [10].

In our study, there was no statistically significant difference in the two arms regarding common side effects of 5HT3 receptor antagonists such as a headache, constipation and the common side effects of aprepitant such as hiccup. However, side effects were seen more frequently than the previous studies. Almost half of the patients were compliant from constipation and headache in our study (Table 3).

Nonrandomizing design, low number of the participants, and lack of information about drug interactions particularly between the antiemetics and antidiabetic/antihypertensive drugs were limitations of our study. However, prospective observational design and homogeneity of our patient group regarding the sex, alcohol intake, primary tumor site, disease stage, and chemotherapy type were strengths of our work.

Rojas et al. [6] have shown that although the first-generation 5HT3R antagonists could not directly affect NK-1 receptors, palonosetron leads to crosstalk between 5HT3 and NK-1 receptors via an exact unknown mechanism and cause decrease of substance *P* level. NK-1 receptors by activating Substance *P* are admitted as the main responsible pathway for delayed CINV. Inhibition of this interaction suggests that palonosetron should be more effective, especially in delayed CINV. The clinical trials have shown that this suggestion is right when palonosetron is used alone or with dexamethasone [5, 18, 19]. However, the response to this question, will palonosetron be more effective than the first generation of CINV control when combined with an NK-1R antagonist in triplet antiemetic prophylaxis, is still unclear.

In conclusion, based on the three trials, only one study had shown that palonosetron was statistically meaningfully superior than the other first-generation 5-HT3R antagonists in triplet antiemetic prophylaxis of delayed CINV in patients receiving HEC, while their effectiveness was comparable in the acute phase. However, in our study, we could not demonstrate any differences in both acute and delayed phases of CINV similar to the other two studies. Because of an ever-increasing economic burden of drugs in all over the world, we suggest that cost-effectiveness should be considered if we choose any antiemetic drugs for prophylaxis of CINV.

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Compliance with ethical standards

Conflict of interest All of the authors declare that no any potential conflict of interest related to this manuscript. Any financial resource was not used for this work to be carried out.

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