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Original Article

Antiemetic effect of palonosetron and first-generation serotonin inhibitors in combination with aprepitant and dexamethasone

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Abstract: Background/Aims: Palonosetron has shown to be more effective than serotonin inhibitors, like ondansetron and dolasetron, in preventing chemotherapy-induced nausea and vomiting (CINV) among patients undergoing moderately emetogenic chemotherapy (MEC), while being similarly effective as ondansetron among patients undergoing highly emetogenic chemotherapy (HEC). The present study aimed to examine the antiemetic effectiveness of palonosetron and other serotonin inhibitors in combination with aprepitant and dexamethasone for MEC or HEC. Methods: A retrospective analysis was performed with the data from patients who were treated with serotonin inhibitors, aprepitant, and dexamethasone for MEC or HEC between July 2009 and January 2011. Patients in Group A were treated with palonosetron, aprepitant, and dexamethasone. Patients in Group B were treated with first-generation serotonin inhibitors, aprepitant, and dexamethasone. Results: Final data for analysis included 370 patients (i.e., 223 and 117 patients respectively in Groups A and B). The numbers of patients who received MEC and HEC were respectively 110 and 260. No case of grade 3-4 nausea/vomiting was detected. There were no significant differences between the Groups A and B across the acute and delayed CINV phases. The proportions of emesis-free patients during the acute phase (0-24 h) in both groups were similar: 78% and 76% respectively in Groups A and B (P=0.57). The proportions of emesis-free patients during the delayed phase (24-120 h) in both groups were similiar: 67% and 71% respectively (P=0.48). Conclusions: When combined with aprepitant and dexamethasone, all serotonin inhibitors seem to be equally effective for MEC orr HEC.

Keywords: Chemotherapy-induced nausea and vomiting, serotonin antagonist, aprepitant, highly emetogenic chemotherapy, moderately emetogenic chemotherapy

Introduction

A common adverse effect of cancer treatment is chemotherapy-induced nausea and vomiting (CINV) [1, 2]. To address this, drugs with various antiemetic action mechanisms have been developed. Types of widely used antiemetic drugs include serotonin 5-HT_3 receptor antagonists (5-HT_3 RAs), dexamethasone, and neurokinin-1 receptor antagonists (NK1 RAs). Ondansetron was the first kind of 5-HT_3 RA used. Later, different 5-HT_3 RA drugs such as granisetron and dolasetron were also approved by the United States Food and Drug Administration (US FDA) [1]. These first generation 5-HT_3 RAs represent a significant advancement in antiemetic therapy. All of these agents have been shown to be effective in controlling acute CINV. In 2003, palonosetron (PAL) was approved as a medication to treat CINV. PAL is the second generation 5-HT_3 RA with an approximately 100-fold higher binding affinity for the serotonin receptor than the first generation 5-HT_3 RAs (i.e., ondansetron, granisetron, dolasetron). Aprepitant, a NK1 RA, was also approved as a medication to prevent CINV in 2003. Aprepitant works by selectively blocking the substance P from landing on the NK-1 receptor in the central nervous system. It has a unique mechanism of action that is complementary to the action mechanisms of other antiemetics. Aprepitant can augment antiemetic activities of 5-HT_3 RAs and dexamethasone, preventing both acute and delayed CINV [3-5].

Several large, multicenter, double-blind, and randomized phase III trials have demonstrated the superiority of PAL over other 5-HT_3 RAs in preventing emesis associated with both moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC) regimens, particularly for delayed emesis [6-9]. Therefore, PAL has been preferred over other 5-HT_3 RAs. That being said, these studies were carried out prior to the administration of aprepitant. After the administration of aprepitant, a three-drug combination (i.e., 5-HT_3 RA, dexamethasone, aprepitant) has been recommended to prevent CINV in MEC or HEC. However, it is still not clear which 5-HT_3 RA would be most effective as this three-drug combination regimen. The present study aimed to examine the effectiveness of PAL and other serotonin inhibitors in combination with aprepitant and dexamethasone for preventing emesis associated with MEC or HEC.

Methods

Study subjects

We conducted a retrospective analysis of the electronic medical records (EMR) data from cancer patients who were treated with 5-HT_3 RA, aprepitant, and dexamethasone for MEC or HEC at the Bucheon Soonchunhyang University Hospital from July 2009 to January 2011. The conditions of HECs included cisplatin ≥ 50 mg/m^2, carboplatin AUC ≥ 4, cyclophosphamide >1,500 mg/m^2, doxorubicin ≥ 60 mg/m^2, epirubicin >90 mg/m^2, ifosfamide ≥ 2 g/m^2 per dose, and anthracycline and cyclophosphamide (AC) combination. The conditions of MECs included oxaliplatin, irinotecan, cisplatin <50 mg/m^2, carboplatin AUC <4, cyclophosphamide ≤ 1,500 mg/m^2, doxorubicin <60 mg/m^2, epirubicin ≤ 90 mg/m^2, and methotrexate ≥ 250 mg/m^2. The 5-HT_3 RAs used in this study were ondansetron, granisetron, dolasetron, and PAL. Patients were excluded if they had met any of the following conditions: (1) they were <18 years of age; (2) they were with an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 3; (3) those who had any non-chemotheraphy factor affecting nausea and vomiting such as total parenteral nutrition, history of malignant bowel obstruction, and brain metastasis. EMR data included information on demographics, diagnosis, symptoms, physical examination, type and date of prescribed medications, and so on. All data were anonymized in order to maintain patient confidentiality and privacy.

Based on the types of the prescribed 5-HT_3 RAs, patients were classified in two groups: Group A, patients treated with PAL, aprepitant, and dexamethasone; and Group B, patients treated with the first generation 5-HT_3 RAs (ondansetron, granisetron, or dolasetron), aprepitant, and dexamethasone.

Assessment

We reviewed the records of the date and time of emetic events, severity of nausea, and use of rescue medication for the first 120 hours since the chemotherapy. Acute CINV was operationalized as nausea and vomiting that occurred within 24 hours after the chemotherapy infusion. Delayed CINV was operatinalized as nausea and vomiting that occured 24 hours after chemotherapy and thereafter, lasted up to 120 hours. Nausea refers to a queasy feeling or an inclination to vomit. Vomiting refers to the reflexive and forceful act of ejecting stomach contents through the mouth. Severity of CINV was evaluated in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Grade 1 was charaterized by loss of appetite without a change in eating habits. Grade 2 was charaterized by decreased oral intake without symptoms like significant loss of weight, dehydration, or malnutrition. Grade 3 was characterized by inadequate oral caloric/fluid intake, tube feedings, total parenteral nutrition (TPN), or hospitalization indicated. Complete response (CR) rate was operationalized as the absence of emesis without the need for rescue medication. Rescue medications were metoclopramide, haloperidol, lorazepam, and corticosteroids. The present study was conducted in full compliance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol of the present study was approved by the Institutional Review Board of the Soonchunhyang University Bucheon Hospital (Approval No. 2020-06-020).

Statistical analyses

Means ± standard deviations (SDs) were presented for continuous variables and numbers (frequencies) and percentages (%s) of subjects

Table 1. Patients characteristics

	Group A[a] (n=223)	Group B[b] (n=147)	*p*-value
Age (yr), mean ± SD	56±13	55±11	0.485
BSA[c], mean ± SD	1.60±0.17	1.58±0.17	0.239
Male, N (%)	99 (44)	67 (46)	0.823
ECOG performance status[d], N (%)			>.999
0-1	214 (97)	140 (97)	
Tumor type, N (%)			<.001
Breast cancer	34 (15)	39 (27)	
Gastric cancer	23 (10)	47 (32)	
Colorectal cancer	23 (10)	25 (17)	
Gynecologic cancer	32 (14)	8 (5)	
Hepatobiliary cancer	22 (10)	16 (11)	
Head and neck cancer	19 (9)	3 (2)	
Small cell lung cancer	12 (5)	3 (2)	
Nonsmall cell lung cancer	26 (12)	3 (2)	
Hematologic malignancy	11 (5)	1 (1)	
Others	21 (9)	2 (1)	
Previous chemotherapy, N (%)			0.014
Naïve	138 (62)	109 (74)	
Previous surgery, N (%)			<.001
Yes	112 (50)	108 (74)	
Previous radiotherapy, N (%)			0.355
Yes	16 (7)	7 (5)	
Emetic risk, N (%)			<.001
High	173 (78)	87 (60)	
Moderate	50 (22)	60 (40)	

Values are presented as number of patients (%) or mean ± SD unless otherwise indicated. *P*-values were obtained from Student's t-test, Pearson's Chi-squared test, or Fisher's exact test. [a]Palonosetron, aprepitant, and dexamethaxone. [b]First-generation serotonin inhibitors (ondansetron, granisetron, or dolasetron), aprepitant, and dexamethaxone. [c]Body Surface Area. [d]Eastern Cooperative Oncology Group.

were presented for categorical variables. Patient characteristics were compared between Groups A and B using Pearson's Chi-squared test or Fisher's exact test for categorical variables. Also, Student's t-test were used for normally distributed continuous variables. The proportions of complete responses (CRs) were compared between Groups A and B using Pearson's Chi-squared test. In multivariable logistic regression analysis, variables with *p*-values less than 0.1 in the comparisons of the baseline characteristics were selected as potential confounders and controlled for in the statsistical analysis. All statistical analyses were performed with SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was considered when a two-sided *p*-value was less than 0.05.

Results

Patient characteristics

Between July 2009 and January 2011, 410 cancer patients were treated for MEC or HEC at the study site. Among them, 40 patients were excluded for the data analysis due to incomplete information. Final data included 370 patients (i.e., 223 and 147 patients respectively in Groups A and B). Demographic and clinical characteristics at the baseline are summarized in **Table 1**. The majority (67%) of the study subjects were chemotherapy-naïve. There were no significant differences in age, body surface area, sex, Eastern Cooperative Oncology Group (ECOG) performance status, or previous radiotherapy between the two groups. Breast cancer, gastric cancer, and colorectal cancer were the most commonly reported primary cancers for the patients in both groups. The numbers of patients who received MEC and HEC were respectively 110 and 260. More patients in Group A than in Group B received HEC (i.e., 78% versus 60%; *P*<0.001). Among those who received HECs, cisplatin was the most commonly prescribed medication (70.3%), followed by AC regimens (25%). Among those who received MECs, cisplatin <50 mg/m^2 was the most commonly used medication (30.9%), followed by oxaliplatin (30%) and irinotecan (20.9%).

Efficacy

There were no significant differences in CR rates for CINV between the Groups A and B (**Table 2**). Overall CR rates in the Groups A and B were respectively 56% and 59%. CR rates for the acute CINV were similar in both groups: 78% (174 out of 223 patients) in the Group A versus 76% (111 out of 147 patients) in the Group B. CR rates for the delayed CINV were also similar in both groups: 67% (150 out of 223 patients) in the Group A versus 71% (104

Table 2. Results of crude analysis for complete response (CR)

	Group A[a] (n=223) N (%)	Group B[b] (n=147) N (%)	*p*-value[c]
Acute CINV (0-24 h)	174 (78)	111 (76)	0.573
Delayed CINV (24-120 h)	150 (67)	104 (71)	0.480
Overall CINV (0-120 h)	125 (56)	87 (59)	0.552
Highly emetogenic chemotherapy, N=260			
	Group A (n=173) N (%)	Group B (n=87) N (%)	*p*-value
Acute CINV (0-24 h)	133 (77)	68 (78)	0.816
Delayed CINV (24-120 h)	114 (66)	59 (68)	0.757
Overall CINV (0-120 h)	94 (54)	50 (57)	0.631
Moderately emetogenic chemotherapy, N=110			
	Group A (n=50) N (%)	Group B (n=60) N (%)	*p*-value
Acute CINV (0-24 h)	41 (82)	43 (72)	0.204
Delayed CINV (24-120 h)	36 (72)	45 (75)	0.722
Overall CINV (0-120 h)	31 (62)	37 (62)	0.971

[a]Palonosetron, aprepitant, and dexamethaxone. [b]First-generation serotonin inhibitors (ondansetron, granisetron, or dolasetron), aprepitant, and dexamethaxone. [c]*P*-values were obtained from Pearson's Chi-squared test.

Table 3. Results of multivariable-adjusted logistic regression analysis for complete response (CR) of CINV

	Acute CINV (0-24 h)		Delayed CINV (24-120 h)		Overall CINV (0-120 h)	
	OR	95% CI	OR	95% CI	OR	95% CI
Groups A vs. B	1.17	(0.66, 2.08)	0.75	(0.45, 1.26)	0.85	(0.52, 1.38)
Highly emetogenic chemotherapy, N=260						
Groups A vs. B	1.06	(0.51, 2.19)	0.68	(0.36, 1.30)	0.77	(0.42, 1.42)
Moderately emetogenic chemotherapy, N=110						
Groups A vs. B	1.55	(0.56, 4.33)	1.00	(0.37, 2.67)	1.04	(0.43, 2.50)

Adjusted for previous chemotherapy experience, previous surgery experience, emetic risk, and tumor type.

out of 147 patients) in the Group B. Subset analyses across the conditions by emetogenic risk (i.e., high vs. moderate) were also performed between the Groups A and B. For those who received HECs, CR rates in acute, delayed, and overall phases were not significantly different between Groups A and B (acute phase: 77% vs. 78%; delayed phase: 66% vs. 68%; and overall phage: 54% vs. 57%). For those who received MECs, CR rates in acute, delayed, and overall phases were not significantly different either between Groups A and B (acute phase: 82% vs. 72%; delayed phase: 72% vs. 75%; overall phase: 62% vs. 62%). There was a significant difference in the rescue medication use between Groups A and B in the high emetogenic risk condition, but not in the moderate emetogenic risk condition. Among those who received HECs, 18% (31 out of 173 patients) of Group A and 32% (28 out of 87 patients) of Group B (p=0.015) used the rescue medication. Among those who received MECs, however, 24% (12 out of 50 patients) of Group A and 32% (19 out of 60 patients) of Group B (p=0.498) used the rescue medication.

Adjusted risk analysis for complete response of CINV

In the multivariable logistic regression model, group membership, previous chemotherapy experience, previous surgery experience, and high emetic risk were not significantly associated with the odds of CR for CINV (i.e., acute, delayed, overall) (**Table 3**). When the analysis was conducted across the conditions by emeto-

genic risk, odds of CR in acute, delayed, and overall CINV for each of these subgroups (i.e., Groups A vs. B, presence vs. absence of previous chemotherapy and previous surgery) were not significantly different in HEC, MEC, or both.

Discussion

This is the first retrospective study examining the effectiveness of PAL and first generation 5-HT_3 RAs used in conjunction with aprepitant and dexamethasone as a three-drug combination in patients undergoing MEC and HEC. PAL was shown to have a higher binding affinity and a longer half-life than first generation 5-HT_3 RAs [10]. It has been suggested that PAL is associated with prolonged inhibition of the serotonin receptor and this mechanism of action is distinct from those of other 5-HT_3 RAs [11]. A study on patients undergoing MEC has shown that PAL (0.25 mg IV) is superior to dolasetron in prevention of delayed emesis (CR rate: 54% vs. 39%; P=0.004) [7]. In another study on patients undergoing MEC, PAL (0.25 mg IV) has been found to be more effective than ondansetron in prevention of both acute emesis (CR rate: 81% vs. 69%; P<0.01) and delayed emesis (CR rate: 74% vs. 55%; P<0.01) [8]. However, these studies did not use PAL in combination with dexamethasone. Whether PAL would still be more effective than other serotonin inhibitors when used in conjunction with dexamethasone remains unknown. In a phase III randomized trial which compared PAL with ondansetron in patients undergoing HEC, about 67% of the patients concomitantly received dexamethasone. Patients who were pre-treated with palonosetron in conjunction with dexamethasone had significantly higher CR rates than those who were treated wtih ondansetron plus dexamethasone when it comes to the prevention of emesis at the delayed CINV phase (CR rate: 42.0% vs. 28.6%; P=0.021) and overall phase (40.7% vs. 25.2%; P=0.005) [6]. Consequently, PAL has been recommended as a first-line treatment because of its better antiemetic effect than other first generation 5-HT_3 RAs. However, Popovic et al. [12] in 2014 analyzed 16 RCTs and found that the effectiveness of PAL and other 5-HT_3 RAs might differ depending on the conconmitant use of dexamethasone and endpoints. Due to the limited evidence supporting the superiority of PAL over its alternatives, current guidelines of Multinational Association of Supportive Care in Cancer (MASCC), American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) do not indicate a specific preference for 5-HT_3 RAs [13].

In 2003, aprepitant, the first kind of NK1 receptor antagonist, received marketing approval from the US FDA. Aprepitant is a novel class of medication that works by selectively blocking the substance P from landing on the NK1 receptor in the central nervous system. Aprepitant is effective in prevention of both acute and delayed CINV. The discovery of NK1 receptor antagonists was a turning point in the prevention of CINV. Currently, antiemetic guidelines recommend a combination of three drugs, namely NK1-RAs, 5-HT_3 RAs, and dexamethasone, for CINV prevention in HEC and MEC. When aprepitant is being used, we wondered which 5-HT_3 RAs might be most effective as a three-drug combination regimen. Most randomized phase III studies regarding aprepitant have compared the effects of first generation 5-HT_3 RAs such as ondansetron and granisetron [3-5, 14-16]. Meanwhile, the effect of PAL as a three-drug combination regimen has been demonstrated mainly through phase II clinical trials. A phase II study has found that combining PAL, aprepitant, and dexamethasone is effective for preventing both acute and delayed CINV (CR rate: 78%) [17]. Another phase II study on patients with breast cancer undergoing MEC has also found that the combination of PAL, aprepitant, and dexamethasone is effective: 76% and 66% of patients reported CR respectively for the acute and delayed phases [18]. However, there has been no controlled trials directly comparing the effectiveness of PAL and first generation 5-HT_3 RAs in patients receiving a three-drug combination regimen (PAL, aprepitant, and dexamethasone) who are undergoing HEC and MEC.

We retrospectively compared the effects of PAL and first generation 5-HT_3 RAs (ondansetron, granisetron, or dolasetron) as a three-drug combination in prevention of CINV. There were no significant differences in CR rates between the Groups A (treated with PAL, dexamethasone, aprepitan) and B (treated with first generation 5-HT_3 RAs, dexamethasone, aprepitan) across the acute or delayed CINV phases. At the acute CINV phase, CR rate was 78% for the

Group A and 76% for the Group B. At the delayed CINV phase, CR rate was 67% for the Group A and 71% for the Group B. There were no signficant differences in CR rates between the two groups in subgroup analysis across the conditions by emetogenic risk. In HECs, CR rate during the acute CINV phase was 77% for the Group A and 78% for the Group B. CR rate during the delayed CINV phase was 66% for the Group A and 68% for the Group B. In MECs, CR rate was 82% for the Group A and 72% for the Group B at the acute CINV phase and 72% for the Group A and 75% for the Group B at the delayed CINV phase. In MECs, the PAL condition tended to have a higher CR rate than other conditions at the acute CINV phase, although the difference was not statistically significant. Ironically, however, PAL was associated with the reduced rescue medication use in HECs. This suggests that more patients in the PAL group had mild emesis that did not require rescue medications. In fact, PAL has been shown to have 100-fold greater affinity than other 5-HT_3 RAs. In addition, it has an enduring half-life of 40 hours. Thus, PAL is the only 5-HT_3 RA approved for the delayed CINV [19]. However, several trials have examined the efficacy of a triple combination regimen with PAL, dexamethasone, and NK1 RA as prophylaxis in patients undergoing MEC and these studies failed to offer evidence that a single dose of PAL is more effective than a single dose of a first-generation 5-HT antagonist when used as a regimen for MEC that contains NK1 RA. The benefit of using PAL as a triple antiemetic prophylaxis was not shown in our study. It is thought that the efficacy of PAL might have been offset by the aprepitant and dexamethasone that were used in conjunction with PAL.

According to the baseline characteristics, PAL was used more frequently than other 5-HT_3 RAs during the same period (223 vs. 147). This shows that PAL is preferred over other 5-HT_3 RAs in the clinical practice. This might be due to the PAL's unique mechanism of action, allowing it to be administered only once per cycle. The National Comprehensive Cancer Network (NCCN) recommends the use of a single dose of PAL for a 3-day chemotherapy regimen than multiple daily doses of another oral or intravenous 5-HT_3 RA. Currently, the cost per dose is not considerably different across PAL and other 5-HT_3 RAs in South Korea. For example, 0.25 mg of PAL costs approximately 20 dollars, whereas 1 mg of granisetron costs approximately 9 dollars. Considering that granisetron needs to be administered more frequently than PAL, the two medications are similar in terms of the total cost. Because of the National Health Insurance system, cost-effectiveness of these medications are of less concern in South Korea, as long as their effects are similar. However, their costs can vary substantially by countries and an economic analysis is critical for the selection of the most reasonable option of 5-HT_3 RAs [20].

Our study has several limitations. First, it was based on a retrospective design with a relatively small number of patients and several viable risk factors were not analyzed. Second, our study focuses on CR as a main outcome. Therefore, it is necessary to validate the efficacy and safety of PAL by improving total control (i.e., CR plus no nausea) in consideration of safety profiles (i.e., cardiac events) and quality of life (QOL). Third, the dosage of chemotherapeutics was not evaluated. Reduced dosage of anticancer drugs is one of the risk factors that may affect the outcome. Therefore, large-scale randomized controlled trials are needed to replicate and confirm the antiemetic effect of PAL in combination with NK1 RA and dexamethasone among patients undergoing HEC and MEC.

In conclusion, we found that PAL could still be preferred over other serotonin inhibitors for moderate or high emetic risk chemotherapy as a three-drug combination regimen in conjunction with aprepitant and dexamethasone. In combination with aprepitant, all serotonin inhibitors seem to be equally effective for moderate or high emetic risk chemotherapy. However, PAL is a promising option due to its convenience of administration, especially for multi-day chemotherapy regimens.

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Disclosure of conflict of interest

None.

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