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Comparison of the antiemetic effect of aprepitant/granisetron and palonosetron combined with dexamethasone in gynecological cancer patients treated with paclitaxel and carboplatin combination regimen

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A triple antiemetic therapy combining aprepitant (APR) with conventional double antiemetic therapy, including 5-hydroxytryptamine 3 receptor antagonist (5-HT_3-RA) and dexamethasone (DEX), is recommended for preventing chemotherapy-induced nausea and vomiting induced by a carboplatin (CBDCA) regimen. However, consensus on the additive effects of APR for gynecological patients on a combined regimen of paclitaxel and CBDCA (TC regimen) has yet to be reached. This retrospective study investigated the antiemetic effects of palonosetron and DEX (PD therapy) and granisetron and DEX with APR (GDA therapy) in patients with gynecologic cancer and who underwent their first TC regimen cycle between April 2017 and March 2020 at the Gunma University Hospital Outpatient Chemotherapy Center. The results showed that the complete response rate of the 92 patients who underwent PD therapy (PD group) and the 46 patients who underwent GDA therapy (GDA group) were both 80.4% (p = 1.000), and the complete control rates of the PD and GDA groups were 78.3% and 80.4%, respectively (p = 0.828), resulting in no significant difference. Furthermore, we observed no significant difference between the PD and GDA groups in the incidence of grade ≥2 nausea, vomiting, and anorexia (nausea: 7.6% vs. 0%, p = 0.095; vomiting: 4.3% vs. 0%, p = 0.301; and anorexia: 9.8% vs. 2.2%, p = 0.164). Concerning adverse events, compared to the PD group, the GDA group showed significantly higher incidence of grade ≥2 malaise (7.6% vs. 19.6%, p = 0.039). Given the lack of difference in the antiemetic effects of PD and GDA therapies, antiemetic therapy should be selected carefully for individual patients by accounting for the incidence of adverse reactions and interactions with APR.

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the worst adverse reactions that cancer patients experience from chemotherapy. A recent report demonstrated the clinical effectiveness of neurokinin 1 receptor antagonist (NK1-RA) aprepitant (APR) for CINV induced by regimens containing carboplatin (CBDCA), which is classified as a moderate emetic risk (Di Maio et al. 2018; Jordan et al. 2018). International guidelines on antiemetic therapy thus recommended NK1-RA, 5-hydroxytryptamine 3 receptor antagonist (5-HT_3-RA), and dexamethasone (DEX) triplet antiemetic therapy to prevent CINV induced by CBDCA regimens (Roila et al. 2016; Berger et al. 2017; Hesketh et al. 2017; Aogi et al. 2021). However, according to other reports, adding NK1-RA to 5-HT_3-RA and DEX double antiemetic therapy was not more effective at treating CINV induced by CBDCA regimens (Tanioka et al. 2013; Kusagaya et al. 2015; Yoshida et al. 2019; Watanabe et al. 2021). These conflicting outcomes might be linked to the differences between studies in 5-HT_3-RA types, DEX dosages, diseases, and patient characteristics, leaving room for further debate on the additive effects of APR to a CBDCA regimen.

Different types of 5-HT_3-RA are recommended for different types of antiemetic therapy. In double antiemetic therapy, palonosetron (PALO) is recommended for delayed nausea and vomiting, as evidence suggests that it is more effective than first-generation 5-HT_3-RA (Schwartzberg et al. 2014; Popovic et al. 2014; Kubota et al; 2016, Aogi et al. 2021), whereas first-generation 5-HT_3-RA is believed to be more cost effective for triplet antiemetic therapy (Shimizu et al. 2018). Therefore, first-generation 5-HT_3-RA triple antiemetic therapy is recommended for CBDCA and other agents with comparatively high emetic risk among those classified as moderate emetic risk by the guidelines (Aogi et al. 2021). In a study on gastrointestinal cancer patients who underwent cisplatin-, oxaliplatin-, or irinotecan-based regimens, triplet antiemetic therapy using first-generation 5-HT_3-RA granisetron (GRA), DEX, and APR (GDA therapy) showed better antiemetic effects than PALO and DEX doublet antiemetic therapy (PD therapy) (Ishido et al. 2016; Toda et al. 2017).

Sex is another known factor of individual variation related to CINV onset, where women are reportedly more affected by CINV in both frequency and severity (Sekine et al. 2013; Warr et al. 2014; Takemoto et al. 2017; Yokoi et al. 2018; Tsuji et al. 2019; Matsui et al. 2020). Another study reported that it is more difficult to achieve the effects of antiemetics for CBDCA-based regimens than for non-CBDCA regimens in women (Matsui et al. 2020). Therefore, it is important to distinguish between antiemetic therapies for CBDCA-based regimens for gynecologic cancers from those administered for other diseases.

Several studies analyzed and reported the effects of antiemetic therapies for patients on a combined regimen of paclitaxel (PTX)

and CBDCA (TC regimen), which is a regimen often used to study the effects of antiemetic therapies on CBDCA-based regimens for women with gynecological cancers. Several studies have compared doublet and triplet antiemetic therapy for patients who received a TC regimen for gynecologic cancer reported superior antiemetic effects of triplet antiemetic therapy; however, the majority of those studies used first-generation $5HT_3$-RA whether for doublet or triplet therapy (Maehara et al. 2015; Yahata et al. 2016; Ikeda et al. 2017; Koshiyama et al. 2017), and there is no consensus from studies comparing PD therapy to triplet antiemetic therapy using PALO (Sugimori et al. 2017; Watanabe et al. 2021). Furthermore, there are no studies comparing the guideline-recommended PD therapy with GDA therapy, and there are no established methods for selecting an antiemetic therapy for a TC regimen administered to patients with gynecologic cancer. Thus, this retrospective study compared the antiemetic effects of PD and GDA therapies for patients who underwent treatment with a TC regimen for gynecologic cancer.

2. Investigations and results

2.1. Patient characteristics

A total of 148 patients were enrolled in this study, of which 97 and 51 received PD therapy and GDA therapy, respectively. Five patients who underwent PD therapy and five who underwent GDA therapy and did not complete the first cycle of treatment due to allergies and other adverse reactions, as well as patients whose adverse reactions were not graded, were excluded, ultimately leaving 92 patients who underwent PD therapy (PD group) and 46 patients who underwent GDA therapy (GDA group) for analysis. The clinical characteristics of patients in the PD and GDA groups are presented in Table 1. Oral DEX was administered at doses of 4 mg to 8 mg daily at 2 to 6 day intervals depending on the patient. Metoclopramide was used as a rescue medication. There was no significant difference between the PD and GDA groups in the proportion of patients who used oral DEX or the rescue medication (oral DEX: 71.7% vs. 56.5%, p = 0.074; rescue medication: 14.1% vs. 15.2%, p = 0.864). Additionally, there were no significant differences between groups for any of the other reported factors that affect emesis, such as age.

Table 1: Clinical characteristics of patients treated with the TC regimen for gynecological cancer

	PD group (n = 92)	GDA group (n = 46)	p value
Age (y)	58.1 ± 9.9	58.5 ± 10.6	0.831 [c]
BMI (kg/m^2)	23.5 ± 5.1	23.2 ± 4.7	0.760 [c]
PTX dose (mg)	269.2 ± 26.0	263.0 ± 26.1	0.190 [c]
CBDCA dose (mg)	604.6 ± 123.3	590.9 ± 115.3	0.532 [c]
Primary diagnosis			
Ovarian cancer	45 (48.9)	16 (34.8)	0.385 [b]
Endometrial cancer	34 (37.0)	22 (47.8)	
Cervical cancer	10 (10.9)	5 (10.9)	
Others	3 (3.3)	3 (6.5)	
Cancer stages			
1	34 (37.0)	12 (26.1)	0.386 [d*]
2	11 (12.0)	5 (10.9)	
3	27 (29.3)	20 (43.5)	
4	10 (10.9)	9 (19.6)	
Unclear	10 (10.9)	0 (0)	
ECOG-PS			
0	77 (83.7)	36 (78.3)	0.153 [d*]
1	8 (8.7)	8 (17.4)	
2	0 (0.0)	1 (2.2)	
Unclear	7 (7.6)	1 (2.2)	
Use of oral DEX	66 (71.7)	26 (56.5)	0.074 [a]
Use of rescue medication	13 (14.1)	7 (15.2)	0.864 [a]
Use of opioids	2 (2.2)	1 (2.2)	1.000 [b]
Low alcohol tolerance	27 (29.3)	11 (23.9)	0.500 [a]
Previous chemotherapy	2 (2.2)	4 (8.7)	0.095 [c]

Values are presented as the mean ± SD or number (%).
[a] Chi-squared test; [b] Fisher's exact test; [c] Student's t test; [d] Mann–Whitney U test; [*] Excluded unclear patients.
TC, paclitaxel and CBDCA co-therapy; PD, palonosetron and dexamethasone; GDA, granisetron, dexamethasone, and aprepitant; BMI, body mass index; PTX, paclitaxel; CBDCA, carboplatin; ECOG-PS, Eastern Cooperative Oncology Group performance status; DEX, dexamethasone; SD, standard deviation.

2.2. Antiemetic efficacy

There were no significant differences between the two antiemetic therapies in the complete response (CR) rate (80.4%, PD and GDA groups; p = 1.000) and the complete control (CC) rate (78.3% and 80.4%, respectively; p = 0.828) (Fig. 1).
The incidence of nausea, vomiting, and anorexia is shown in Fig. 2. There was no significant difference between the PD and GDA groups in the incidence of grade ≥2 nausea, vomiting, and anorexia (nausea: 7.6% vs. 0%, p = 0.095; vomiting: 4.3% vs. 0%, p = 0.301; and anorexia: 9.8% vs. 2.2%, p = 0.164). We observed no grade ≥3 nausea, vomiting, and anorexia in any of the patients in either group.

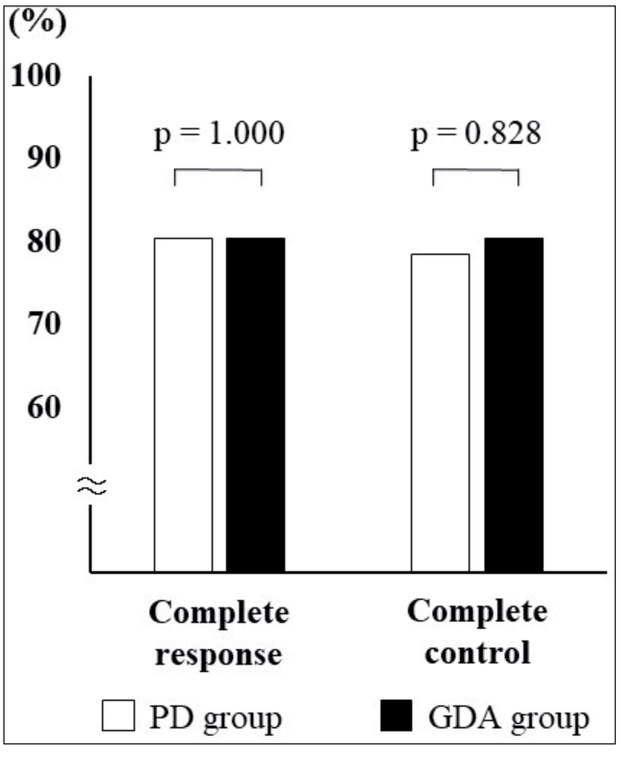

Fig. 1: Comparison of complete response and complete control rates between the PD and GDA groups. White bars represent the PD group (n = 92), which was treated with palonosetron and dexamethasone, and black bars represent the GDA group (n = 46), which was treated with granisetron, dexamethasone, and aprepitant.

2.3. Adverse events

The adverse events in the PD and GDA groups are compared in Table 2. Grade ≥2 malaise occurred significantly more frequently in the GDA group than the PD group (7.6% vs. 19.6%, p = 0.039), but there were no significant differences between the two groups in the incidence of grade ≥2 alopecia, constipation, dysgeusia, diarrhea, hand–foot syndrome, and fever. Additionally, no patients in either group experienced grade ≥2 stomatitis, nail changes, phlebitis, pigmentation, and stomach pain.

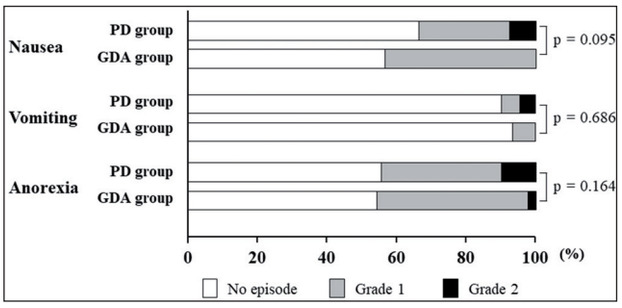

Fig. 2: Comparison of the incidences of nausea, vomiting, and anorexia between the PD and GDA groups. The cumulative proportion of each stacked column totals 100%, and columns represent the following: no episode (white), grade 1 (gray), and grade 2 (black). Nausea, vomiting, and anorexia were assessed using the CTCAE version 5.0. Regarding the antiemetic therapy used, the PD group (n = 92) was treated with palonosetron and dexamethasone, and the GDA group (n = 46) was treated with granisetron, dexamethasone, and aprepitant.

3. Discussion

This study compared the antiemetic effects of GDA therapy using first-generation $5HT_3$-RA, which is recommended as a cost-effective triplet antiemetic therapy, and PD therapy, the recommended doublet antiemetic therapy for gynecologic cancer patients treated with a TC regimen. The results revealed no significant difference between the two therapies in antiemetic effects or in the incidence of nausea, vomiting, and anorexia. These findings suggest that although triplet antiemetic therapy using first-generation $5HT_3$-RA is recommended for CBDCA regimens, doublet antiemetic therapy using PALO has equivalent efficacy in preventing CINV induced by a TC regimen for gynecologic cancer.

Table 2: Number of patients who experienced grade ≥2 side effects after the TC regimen

	PD group (*n* = 92)	GDA group (*n* = 46)	p value
Alopecia	40 (43.5)	23 (50.0)	0.468 [a]
Constipation	26 (28.3)	10 (21.7)	0.411 [a]
Malaise	7 (7.6)	9 (19.6)	0.039 [a]
Neuropathy	7 (7.6)	0 (0)	0.095 [b]
Diarrhea	2 (2.2)	0 (0)	0.552 [b]
Fever	2 (2.2)	0 (0)	0.552 [b]
Dysgeusia	1 (1.1)	0 (0)	1.000 [b]
Hand-foot syndrome	1 (1.1)	0 (0)	1.000 [b]

Values are presented as numbers (%).
[a] Chi-squared test; [b] Fisher's exact test.
TC, paclitaxel and carboplatin co-therapy; PD, palonosetron and dexamethasone; GDA, granisetron, dexamethasone, and aprepitant.

Compared with first-generation $5HT_3$-RA, PALO has higher affinity with the 5-HT_3 receptor and a longer half-life, as well as higher efficacy for delayed CINV (Tonini et al. 2005; De Leon 2006). Furthermore, NK1-RA shows high efficacy for delayed CINV by competitively inhibiting substance P from binding to NK1 receptors, which is believed to be the cause of delayed CINV (Saito et al. 2003; dos Santos et al. 2012). Ishido et al. (2016) and Toda et al. (2017), two studies on gastrointestinal cancer patients, reported better CR rates for GDA therapy than PD therapy at any period, which conflicts with the findings of the present study. This discrepancy is attributed to the fact that the Ishido and Toda studies were on male and female gastrointestinal cancer patients, whereas the patients in this study were all females. Since the improvement in the antiemetic efficacy of PALO compared with first-generation 5-HT_3-RA has been reported to be more notable in women (Kubota et al. 2016), no difference in the antiemetic effect between GDA and PD therapies was expected to be observed in this study. Another important factor is the DEX dose on day 1 of PD therapy. The DEX doses used for PD therapy in the reports by Ishido et al. (2016) and Toda et al. (2017) were 13.2 mg and between 3.3 mg and 6.6 mg, respectively, whereas the DEX dose in the present study was 16.5 mg. PTX requires high-dose DEX to prevent hypersensitivity, and it is believed that PD therapy demonstrated comparable antiemetic effects with GDA therapy, given that high-dose DEX on day 1 of PD therapy showed equivalent antiemetic effects with APR in GDA therapy. This speculation is similar to the findings of other previous studies on patients with gynecologic cancers. The DEX dose in PD therapy was 13.2 mg in the report by Sugimori et al. (2017) that compared the antiemetic effects of PD therapy and triplet antiemetic therapy of PALO, DEX, an APR (PDA therapy) for patients with gynecologic cancers treated using the TC regimen and reported the superiority of PDA therapy. By contrast, the DEX dose used in PD therapy was 16.5 mg (i.e., equal that used in the present study) in the study by Watanabe et al. (2021), which reported no difference between PD and PDA therapy. This point is important, and at least under conditions that use PALO as the 5-HT_3-RA, high-dose DEX produces antiemetic effects equivalent to APR, resulting in no apparent difference in the antiemetic effects of doublet and triplet therapy.

Although differences in the incidence of serious adverse events were not observed clinically between the two groups, the incidence of one adverse event (malaise) was significantly higher in GDA therapy. Previous studies comparing the adverse events of GRA and PALO also reported conflicting results on the incidence of malaise, with some reporting no difference between GRA and PALO (Uchida et al. 2017; Uchida et al. 2018a) and one study reporting a higher incidence of malaise with PALO (Uchida et al. 2018b). In this study, the rate of oral DEX use was higher in the PD group than in the GDA group, unlike past studies where the rate of steroids use was the same (Uchida et al. 2017, 2018a, b). The administration of steroids in patients with advanced cancer has been reported to significantly reduce cancer-related malaise (Yennurajalingam et al. 2013). In fact, the incidence rate of malaise was significantly lower in patients using oral DEX compared with those not using oral DEX in this study (6.5% vs. 21.7%, p = 0.008, Chi-squared test). Therefore, the onset of cancer-related malaise may have been strongly suppressed in the PD group where the rate of oral DEX use was high. Another factor is the possible influence of APR on the onset of general malaise. Although none of the three randomized controlled trials demonstrated an association between APR and the onset of malaise (Tanioka et al. 2013; Ito et al. 2014; Kusagaya et al. 2015), the meta-analysis by dos Santos et al. (2012) showed that the addition of APR significantly increases the incidence rate of general malaise. As mentioned above, the difference in the rate of oral DEX use and APR use/non-use is believed to have affected the difference in the rate of onset of general malaise between the PD and GDA groups in this study.

There are several limitations to this study. First, it is a retrospective cohort study; therefore, the data obtained is limited, and we could not account for other risk factors of vomiting, such as the amount of alcohol consumption and pregnancy-related factors, or obtain data on the accurate time of CINV onset. Second, this study did not investigate interactions between APR and PTX. APR is a mild-to-moderate inhibitor and inducer of CYP3A4 and inducer of CYP2C9; thus, it reportedly interacts with many other drugs (Patel et al. 2017). Although APR co-therapy reportedly does not affect the pharmacodynamics of several CYP-based anticancer agents (Nygren et al 2005; Loos et al. 2007; Bubalo et al. 2012; Sarantopoulos et al. 2014), to the best of our knowledge, there are no studies presenting evidence that APR does not affect the pharmacodynamics of PTX; therefore, this point should be investigated further in future studies. Thirdly, this study compared GDA therapy and PD therapy, but the oral DEX dose was not the same. Considering the possibility that the rate of use of oral DEX affects the onset of malaise, we believe it is necessary to evaluate side effects in more detail under the same DEX dose condition.

In conclusion, we found no difference in antiemetic effects between PD and GDA therapy for patients treated using a TC regimen for gynecologic cancer under the use of high-dose DEX in PD therapy. Therefore, given that the two therapies have equivalent antiemetic effects and economic benefits, it is important to carefully choose between them by weighing up the incidence of adverse reactions and interactions with APR.

4. Experimental

4.1. Subjects

The subjects were patients with gynecological cancer (ovarian, endometrial, and cervical cancers) who received a TC regimen (PTX 180 mg/m^2 + CBDCA; area under the curve: 6 mg/min/mL, on day 1) for the first time at Gunma University Hospital Outpatient Chemotherapy Center between April 2017 and March 2020. Between April 2017 and March 2019, the patients received antiemetic therapy comprising PD therapy. On day 1, the patients were intravenously administered PALO 0.75 mg and DEX 16.5 mg. From April 2019 onward, the antiemetic therapy comprised GDA therapy. On day 1, the patients were intravenously administered GRA 3 mg and DEX 8.25 mg and orally administered APR 125 mg. On days 2 and 3, they were orally administered APR 80 mg. Additionally, from day 2 onward, DEX and rescue medications were administered orally based on physician discretion. Subjects meeting any of the following criteria were excluded from this study: administration of drugs that could affect the study results (such as an antiemetic, steroid, and/or major or minor tranquilizers) before the start of chemotherapy; complications that induced nausea and/or emesis (e.g., symptomatic brain metastases, ulcerative diseases, and severe hepatic dysfunction); and/or a known allergy or severe reaction to any of the drugs investigated in the study.

4.2. Data collection and assessment

Electronic medical records from Gunma University Hospital were used to retrospectively survey patient background characteristics, details of antiemetic therapy, antiemetic effects, and adverse events. Specifically, the following were surveyed: age, height, body weight, type of cancer and stage, Eastern Cooperative Oncology Group performance status (ECOG-PS), alcohol tolerance, overall efficacy of the antiemetic therapy, incidence and grade of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, and the types dosages of antiemetics used for antiemetic therapy. Efficacy was assessed in terms of CR, CC, and the incidences of nausea, vomiting, and anorexia. CR rate was defined as the percentage of patients who did not experience vomiting and were not administered rescue medication, whereas the CC rate was defined as the percentage of patients who achieved CR and experienced grade 1 nausea or no nausea. To analyze adverse events, the incidence of the following conditions was assessed: alopecia, constipation, malaise, peripheral neuropathy, dysgeusia, diarrhea, hand–foot syndrome, fever, stomatitis, nail changes, phlebitis, pigmentation, and stomach pain. These adverse events were extracted from medical records that were based on interviews with nurses at the start of the second cycle of chemotherapy.

4.3. Statistical analysis

Pearson's chi-squared test or Fisher's exact test was used to compare rates between the two groups. Fisher's exact or the Mann–Whitney *U* test was used to compare three or more groups. For comparisons of means between the two groups, Student's *t* test was used. For all of these tests, a $p < 0.05$ was considered statistically significant. Nausea, vomiting, anorexia, and other adverse events were divided into two categories for analysis: grade ≥2 adverse events, which required treatment, and grade ≤1 adverse events, which did not require treatment. Statistical analysis was conducted using SPSS (v.25.0; IBM Corp.; Armonk, NY, USA).

4.4. Ethics statement

This study was approved by the ethics committee of Gunma University (approval number: HS2019-170) and Takasaki University of Health and Welfare (approval number: 1927). Consent was not obtained from the patients included, because the data were collected retrospectively from electronic medical records.

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Conflicts of interest: The authors declare that they have no conflicts of interest.

Authors' contributions: KO, AN, and SO contributed equally to the study design and drafting of the manuscript; HY and CU gathered patient data from the electronic medical records; HY, CU, ET, and YT made substantial contributions to the data analysis; and KO, AN, TA, and KY were involved in data interpretation and discussion. All authors have read and approved the final version of the manuscript.

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