Effects of Palonosetron on Nausea and Vomiting Induced by Multiple-Day Chemotherapy: A Retrospective Study

Hirofumi Hamano, a,b Chisato Mitsuhashi, b Yoshiko Suzuki, c Yoshito Zamami,* a,b Kaito Tsujinaka, a Naoto Okada, b Takahiro Niimura, a Tatsuya Hayama, d Toru Imai, d Shunsuke Ishida, b Kumiko Sakamoto, b Mitsuhiro Goda, b Kenshi Takechi, e Kenta Yagi, f Masayuki Chuma, f Yuya Horinouchi, g Kazuuki Shinomiya, g Yasumasa Ikeda, h Yasushi Kirino, b Toshimi Nakamura, b Hiroaki Yanagawa, f Yasuhiro Hamada, c and Keisuke Ishizawa a,b

a Department of Clinical Pharmacology and Therapeutics, Institute of Biomedical Sciences, Tokushima University Graduate School; 3–18–15 Kuramoto-cho, Tokushima 770–8503, Japan; b Department of Pharmacy, Tokushima University Hospital; 2–50–1 Kuramoto, Tokushima 770–8503, Japan; c Department of Therapeutic Nutrition, Tokushima University Graduate School; 3–18–15 Kuramoto-cho, Tokushima 770–8503, Japan; d Department of Pharmacy, Nihon University Itabashi Hospital; 7–7–1 Narashinodai, Funabashi, Chiba 274–8555, Japan; e Department of Drug Information Analysis, College of Pharmaceutical Sciences, Matsuyama University; 4–2 Bunkyo-cho, Matsuyama, Ehime 790–8578, Japan; f Clinical Trial Center for Developmental Therapeutics, Tokushima University Hospital; 2–50–1 Kuramoto, Tokushima 770–8503, Japan; g Department of Clinical Care and Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Tokushima Bunri University; 180 Yamashiro-cho, Tokushima 770–8514, Japan; and h Department of Pharmacology, Institute of Biomedical Sciences, Tokushima University Graduate School; 3–18–15 Kuramoto-cho, Tokushima 770–8503, Japan.

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Patients who undergo multiple-day chemotherapy sessions experience hard-to-treat nausea and vomiting. Currently, there is no effective standard treatment for this condition. This study compared the preventive effect of first-generation 5-hydroxytryptamine 3 receptor antagonists (5-HT3 RAs) and second-generation 5-HT3 RA palonosetron in multiple-day chemotherapy-induced nausea and vomiting. The design of this study was a retrospective case-control study of patients who received a five-day cisplatin-based chemotherapy and were treated with aprepitant, dexamethasone, granisetron, and ramosetron or palonosetron. The patients were divided into two groups: patients given granisetron and ramosetron (the first-generation group), and those given palonosetron (palonosetron group). The percentage of patients with a complete response or total control was assessed. They were divided into three phases: 0–216 h (overall phase), 0–120 h (remedial phase), and 120–216 h (after phase). The remedial phase was further divided into 0–24 h (early phase) and 24–120 h (later phase). Moreover, the nutritional status of each patient was assessed by noting the patients’ total calorie-intake per day and total parenteral nutrition. First-generation 5-HT3 RAs and palonosetron were used for treatment in 18 and 28 patients, respectively. The complete response rate and caloric oral intake of the later phase were higher in the palonosetron group than in the first-generation group. We conclude that palonosetron treatment was more effective than first-generation 5-HT3 RAs in controlling multiple-day chemotherapy-induced nausea and vomiting.

Key words palonosetron; chemotherapy-induced nausea and vomiting; supportive care; 5-hydroxytryptamine 3 antagonist; multiple-day chemotherapy

INTRODUCTION

Nausea and vomiting are characteristic side effects of chemotherapy that may result in treatment discontinuation and a lower QOL.1) Chemotherapy-induced nausea and vomiting (CINV) may be caused by the stimulation of 5-hydroxytryptamine 3 (5-HT3) receptors on the vagal afferent nerves by serotonin released by the enterochromaffin cells in the stomach and large intestine.2) To prevent acute CINV, patients on chemotherapy are commonly administered 5-HT3-receptor antagonists (5-HT3 RAs), such as granisetron, ondansetron, and ramosetron in combination with steroids.3,4) However, 5-HT3 RAs cannot completely prevent CINV, and strategies for the prevention of CINV still need improvement.

The second-generation 5-HT3 RA palonosetron has more preventive effects than other 5-HT3 RAs because it is a highly selective receptor antagonist with a long serum half-life.5,6) In particular, a dose of 0.25 mg or more of palonosetron suggested an inhibitory effect on delayed CINV, and a dose of 0.75 mg of palonosetron showed the maximum effect in the delayed period.7,8) It is reportedly beneficial in the prevention of acute and delayed CINV after administration of antitumor drugs, such as cisplatin (CDDP), which is a highly emetogenic chemotherapeutic agent for germ cell tumors (GCTs). GCTs patients are generally treated with a 5-d CDDP-based chemotherapy regimen, which usually results in severe CINV.9–12)

Multiple-day chemotherapy treatment often causes acute- and delayed-phase CINV, with worsening symptoms in advanced emetogenic chemotherapy. CINVs induced by multiple-day chemotherapy are also treated with 5-HT3 RAs.13–15) In particular, palonosetron is effective for delayed vomiting.

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from CINV, and may be more effective than first-generation 5-HT₃ RAs by administering three divided doses in one chemotherapy cycle. However, palonosetron clinical trials for patients receiving multiple-day chemotherapy are limited and randomized studies on the direct comparison of palonosetron and first-generation 5-HT₃ RAs are lacking. This study aimed to establish the efficacy of palonosetron against CINV induced by multiple-day emetogenic chemotherapy, and compare it with that of first-generation 5-HT₃ RAs. In particular, we investigated the therapeutic effect of a single dose of palonosetron, which has not been adequately described in previous studies.

MATERIALS AND METHODS

Ethics Approval This study was approved by the Ethics Committee of Tokushima University Hospital (Approval No. 3128) and was conducted according to the principles of the Declaration of Helsinki.

Study Population Medical charts of 72 patients who received 5 d of CDDP-based bleomycin, etoposide, and platinum (BEP) (etoposide 100 mg/m² and CDDP 20 mg/m², both on days 1–5 plus bleomycin 30U weekly; every 21 d) or etoposide and platinum (EP) (etoposide 100 mg/m² and CDDP 20 mg/m², both on days 1–5; every 21 d) chemotherapy for primary GCTs (e.g., testicular GCTs, ovarian GCTs, and mediastinal tumor) as initial treatment from January 2010 to March 2020 at Tokushima University Hospital were retrospectively analyzed. All patients completed the first course of chemotherapy. Patients who had an Eastern Cooperative Oncology Group performance status of ≥3 (n = 1), neutropenia (neutrophil count below 1500 cells/µL) (n = 2), high blood creatinine levels (serum creatinine >1.5 times the upper limit of normal) (n = 1), received drugs with possible effects on the metabolism of the study drugs within 1 week before chemotherapy (n = 2), were under improper use of antiemetic drugs (n = 17), or were given a reduction of CDDP on the first course (n = 3), were excluded (Fig. 1). The patients were divided into two groups. The first-generation group consisted of patients administered granisetron 3 mg or ramosetron 0.3 mg intravenously daily before chemotherapy initiation on days 1–5, whereas the palonosetron group consisted of patients administered 0.75 mg of palonosetron once before chemotherapy initiation. All patients received dexamethasone at either 9.9 mg on d 1 and 6.6 mg on days 2–5, or 6.6 mg on days 1–5. The average dosage of dexamethasone was as follows: 6.86 ± 0.33 mg/d in the first-generation group and 7.24 ± 0.12 mg/d in the palonosetron group. All patients were also administered aprepitant on days 1–5 or fosaprepitant on day 1.

Data Collection We collected the patients’ sex, age, and laboratory data from electronic medical records. We then assessed treatment-related adverse events and analyzed the proportion of patients with complete response (defined as no vomiting and no rescue medication use throughout the treatment period) and total control (defined as no vomiting, no rescue medication use, and no nausea throughout the treatment period) as well as the time to treatment failure (TTF) (i.e., time to first vomit or time to administration of rescue therapy, whichever occurred first). The analysis period was up to 216 h after the start of treatment. Additionally, the overall analysis period (0–216 h) was divided during treatment days (0–120 h: remedial phase) and after treatment days (120–216 h: after phase). The remedial phase was further subdivided into the first CDDP administration period (0–24 h: early phase) and the remaining period (24–120 h: later phase). The severity of the adverse events was defined using the Common Terminology Criteria for Adverse Events v4.0.

A certified nutritionist assessed the medical records to identify patients with compromised nutritional status, such as anorexia. Nutritional status was evaluated according to the period of decreased oral intake and total parenteral nutrition. Decreased oral intake was defined as the intake of less than 50% of the amount taken before the administration of chemotherapy. A certified nutritionist assessed the medical records to identify patients with compromised nutritional status, such as anorexia. Nutritional status was evaluated according to the period of decreased oral intake and total parenteral nutrition. Decreased oral intake was defined as the intake of less than 50% of the amount taken before the administration of chemotherapy. A certified nutritionist assessed the medical records to identify patients with compromised nutritional status, such as anorexia. Nutritional status was evaluated according to the period of decreased oral intake and total parenteral nutrition. Decreased oral intake was defined as the intake of less than 50% of the amount taken before the administration of chemotherapy.

Statistical Analysis Data in the medical records were presented as mean ± standard deviation (S.D.). To assess differences in patient characteristics between the two groups, Fisher’s exact probability test, Pearson’s χ² test, Mann–Whitney U test, and Student’s t-test were used. Nutrition parameters (intake or total parenteral nutrition energy and protein) were compared using Student’s t-test. Complete response, total control, and adverse events were assessed via Fisher’s exact
probability test or Pearson’s \( \chi^2 \) test. The TTF and first onset of vomiting or nausea were analyzed using the Kaplan–Meier method, which compared the two groups using the log-rank test. All recorded \( p \)-values were two-sided, with \( p < 0.05 \) considered statistically significant. Data for statistical analyses were recorded using the R statistical software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) for tumor type analysis and the JMP statistical software from SAS (JMP® 14 (SAS Institute Inc., NC, U.S.A.)) for others.

RESULTS

Patient Characteristics  A total of 46 patients who had GCTs and were treated with BEP or EP were enrolled in this study. The characteristics of the patients in the first-generation group \( (n = 18) \) and the palonosetron group \( (n = 28) \) are summarized in Table 1, and the median patient age was 36 years (interquartile range (IQR): 27–60) and 36 (IQR: 31–47) years, respectively. There were no significant differences in sex, general state, type of chemotherapy, surgical history, alcohol consumption, cigarette use, hepatic function, and renal function between the two groups.

Palonosetron Alleviates CINV after Chemotherapy  The population of patients with a complete response is shown in Table 2. The difference in the early phase of complete response between the palonosetron and the first-generation groups was not statistically significant \( (25/28 [89.3\%] \text{ vs. } 15/18 [83.3\%]; \ p = 0.67) \). On the other hand, complete response in the later phase of CDDP treatment \( (days 2–5) \) was significantly higher in the palonosetron group than in the first-generation group \( (22/28 [78.6\%] \text{ vs. } 9/18 [50.0\%]; \ p = 0.04) \). The remedial phase \( (days 1–5) \) and after phase \( (days 6–9) \) of CDDP administration in the two groups were not significantly different.

Next, no significant difference between the two groups was

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### Table 1. Patient Characteristics

|                         | First-generation \( (n = 18) \) | Palonosetron \( (n = 28) \) | \( p \)-Value |
|-------------------------|---------------------------------|----------------------------|--------------|
| Sex, No. (%)            |                                 |                            |              |
| Male                    | 9 (50.0)                        | 17 (60.7)                  | 0.47\( ^a \) |
| Female                  | 9 (50.0)                        | 11 (39.3)                  |              |
| Age, years (median, IQR)| 36 (27–60)                      | 36 (31–47)                 | 0.96\( ^b \) |
| ECOG performance status, No. (%) |                    |                            |              |
| 0/1                     | 16 (88.9)                       | 27 (96.4)                  | 0.55\( ^c \) |
| 2                       | 2 (11.1)                        | 1 (3.6)                    |              |
| Tumor type, n (%)       |                                 |                            |              |
| Testicular germ cell tumor | 8 (44.4)                      | 16 (57.1)                  | 0.53\( ^c \) |
| Ovarian germ cell tumor | 9 (50.0)                        | 9 (32.1)                   |              |
| Mediastinal tumor       | 1 (5.6)                         | 3 (10.7)                   |              |
| Type of chemotherapy, No. (%) |                           |                            |              |
| BEP                     | 14 (77.8)                       | 27 (96.4)                  | 0.07\( ^d \) |
| EP                      | 4 (22.2)                        | 1 (3.6)                    |              |
| Previous surgery, No. (%) | 7 (38.9)                        | 18 (64.3)                  | 0.09\( ^e \) |
| Alcohol consumption, No. (%) |                           |                            |              |
| No/Rarely               | 13 (72.2)                       | 23 (82.1)                  | 0.43\( ^f \) |
| Sometimes/Everyday      | 5 (27.8)                        | 5 (17.9)                   |              |
| Cigarette use, No. (%)  | 5 (27.8)                        | 9 (32.1)                   | 0.75\( ^f \) |
| AST (IU/L), mean ± S.D. | 27.6 ± 15.7                     | 26.4 ± 12.4                | 0.79\( ^f \) |
| ALT (IU/L), mean ± S.D. | 30.4 ± 29.9                     | 34.5 ± 32.6                | 0.67\( ^f \) |
| Total bilirubin (mg/dL), mean ± S.D. |               | 0.5 ± 0.2                  | 0.85\( ^f \) |
| Serum creatinine (mg/dL), mean ± S.D. |                | 0.74 ± 0.26                | 0.85\( ^f \) |

\(<p> a) \chi^2 \text{ test, } b) \text{ Mann-Whitney } U \text{ test, } c) \text{ Fisher’s exact test, } d) \text{ Student’s } t \text{-test. Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BEP = bleomycin, etoposide, and platinum; ECOG = Eastern Cooperative Oncology Group; EP = etoposide and platinum; IQR = interquartile range; S.D. = standard deviation; } \gamma \text{-GTP = gamma-glutamyltransferase.}</p>
The mean time to treatment failure (time to first vomit or time to administration of rescue therapy, whichever occurred first) in patients receiving BEP or EP treatment with first-generation (n = 18) or palonosetron (n = 28) were 112.0 h and 166.3 h, respectively (p = 0.21 by log rank test). Values are expressed as percentages.

**DISCUSSION**

Multiple-day chemotherapies, particularly those that include highly emetogenic chemotherapeutic agents, induce complicated acute and delayed CINV that are difficult to control. Our findings from multiple-day chemotherapies showed that palonosetron treated CINV more efficiently than first-generation 5-HT3 RAs and, more importantly, that a single dose of palo-

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**Table 4. Comparison of Nutrition Parameters between the Two Groups of Hydroxytryptamine 3 Receptor Antagonists in BEP or EP Treated Patients**

| Parameter          | First-generation (No.) | Palonosetron (No.) | p-Value |
|--------------------|------------------------|--------------------|---------|
| Intake energy, kcal/d, mean ± S.D. |                        |                    |         |
| Before treat (~72-0h) | 1472.2 ± 671.1 (18)     | 1638.5 ± 382.2 (28) | 0.33    |
| Early phase (0-24h)  | 1499.7 ± 637.8 (18)     | 1620.2 ± 467.2 (28) | 0.51    |
| Later phase (24-120h) | 940.4 ± 672.8 (17)      | 1373.4 ± 594.7 (27) | 0.05    |
| Remedial phase (0-120h) | 1033.7 ± 631.7 (17)     | 1422.8 ± 530.2 (27) | 0.06    |
| After phase (120-216h) | 926.7 ± 747.2 (16)      | 1321.4 ± 544.1 (26) | 0.10    |
| Overall (0-216h)    | 1014.2 ± 693.2 (16)     | 1397.8 ± 505.1 (26) | 0.08    |
| TPN energy, kcal/d, mean ± S.D. |                        |                    |         |
| Before treat (~72-0h) | 11.5 ± 40.4 (18)        | 42.8 ± 117.1 (28)  | 0.20    |
| Early phase (0-24h)  | 341.2 ± 162.2 (18)      | 339.0 ± 203.1 (28) | 0.97    |
| Later phase (24-120h) | 345.6 ± 155.2 (18)      | 315.6 ± 210.5 (28) | 0.59    |
| Remedial phase (0-120h) | 344.7 ± 154.5 (18)      | 320.3 ± 208.4 (28) | 0.66    |
| After phase (120-216b) | 80.0 ± 92.1 (18)        | 54.0 ± 116.8 (28)  | 0.41    |
| Overall (0-216b)    | 228.1 ± 113.7 (18)      | 199.7 ± 134.9 (28) | 0.45    |

Table 5. Comparison of the Adverse Effects between the Two Groups of Hydroxytryptamine 3 Receptor Antagonists in BEP or EP Treated Patients

| Grade 2b, No. (%) | First-generation | Palonosetron | p-Value |
|-------------------|------------------|--------------|---------|
| Headache          | 1 (5.6)          | 1 (3.6)      | 1.000   |
| Constipation      | 4 (22.2)         | 8 (28.6)     | 0.740   |
| Angiopathy        | 2 (11.1)         | 1 (3.6)      | 0.550   |
| Increased AST concentrations | 1 (5.6) | 0 (0.0) | — |
| Increased ALT concentration | 2 (11.1) | 3 (10.7) | 1.000 |
| Increased blood bilirubin concentration | 0 (0.0) | 1 (3.6) | — |
| Increased creatinine | 1 (5.6) | 2 (7.1) | 1.000 |

* a) Unpaired t test. Abbreviations: BEP = bleomycin, etoposide, and platinum; EP = etoposide and platinum; S.D. = standard deviation; TPN = total parenteral nutrition.

**Fig. 2. Time to Treatment Failure in Patients Treated with First-Generation 5-HT3 RAs or Palonosetron**

The nutritional status of both groups was assessed in terms of calories per day of oral intake and total parenteral nutrition. Initially, the dietary calorie intake in both groups was lower during the treatment period than before chemotherapy. Furthermore, the decreased calorie intake persisted during the post-treatment period. However, during the treatment period, the decrease in calorie intake was lower in the palonosetron group than in the first-generation group. In the later phase, the caloric intake was significantly higher in the palonosetron group than in the first-generation group (1373.4 ± 594.7 kcal/d vs. 940.4 ± 672.8 kcal/d, p = 0.05; Table 4). The period of decreased oral intake was longer in the palonosetron group than in the first-generation group (Fig. 3).

**Adverse Events** Adverse events, such as headache, constipation, angiopathy, and decreased hepatic or renal function, showed no significant differences between the two groups (Table 5).

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**Fig. 3. Period of Reduced Oral Intake in the First-Generation Group or Palonosetron Group**

The mean period of reduced oral intake (defined as oral intake less than 50% of that before the administration of BEP or EP therapy) in patients treated with first-generation (n = 18) or palonosetron (n = 28) were 100.0h and 147.4h, respectively (p = 0.13 by log rank test). Values are expressed as percentages.
nosetron was effective in the treatment of CINV. However, comparing the two groups, total control was not suppressed, which suggested that palonosetron was significantly effective for vomiting, but not for nausea.

Our study directly compared the later phase complete response of the palonosetron group to that of the first-generation group. The efficacy of the former was superior to that of the latter. Our findings on the efficacy of palonosetron for CINV were consistent with those of previous clinical studies. A 2007 study of patients receiving 5-d CDDP-based chemotherapy for GCTs suggested that palonosetron (0.25 mg on days 1, 3, and 5) plus dexamethasone was well tolerated and effectively controlled both nausea and vomiting. Another study conducted in 2009 reported encouraging results from palonosetron (0.25 mg on days 1 and 4) plus dexamethasone as prophylaxis for CINV in patients receiving multiple-day chemotherapy for hematologic malignancy. A recent study in 2017 reported that palonosetron (0.75 mg on day 1) plus dexamethasone (days 1–7) and aprepitant (days 1–7) were effective for patients with testicular GCTs receiving 5-d CDDP-based chemotherapy. The remedial phase complete response observed in our study was 71.4%, whereas the values ranged from 34.1% to 70.8% in previous studies. The absence of neurokinin1 (NK1) antagonist treatment and the divided dosage of palonosetron may have caused the low remedial phase complete response in the 2007 study. A similar study by Feinberg et al. found that administration of palonosetron only (i.e., patients receiving palonosetron every other day) suppressed nausea and vomiting within 7 d significantly better than co-administration with ondansetron (i.e., patients receiving ondansetron every day with administration of palonosetron on the last day).

5-HT3 RAs are highly effective for acute vomiting. Palonosetron has also been reported to be effective for delayed vomiting. This may be due to its plasma half-life exceeding 40 h, which is 3 to 6 times longer than the half-life of first-generation 5-HT3 RAs. This may also be due to their different affinity for binding with 5-HT3 receptors. However, other mechanisms should be sought to better understand the efficacy of palonosetron. Multiple-day chemotherapy is administered beyond the plasma half-life of palonosetron. Theoretically, daily administration of the first-generation 5-HT3 RAs should lead to a better immediate preventive effect than the administration of palonosetron. However, even when ondansetron is administered more than 24 h after chemotherapy, ondansetron still does not possess the protective effect of palonosetron against delayed vomiting. Our data suggested that palonosetron had more preventive effects against CINV than daily administration of first-generation 5-HT3 RAs, other than ondansetron. It was presumed that the mechanism of action of palonosetron in delaying CINV was different from that of first-generation 5-HT3 RAs.

The exact mechanism of the efficacy of 5-HT3 RAs, particularly palonosetron, is not yet completely understood. However, there are three possible mechanisms specific to palonosetron. First, palonosetron infiltrates the central nervous system. A recent in vivo study reported that palonosetron levels were high in the dorsal vagal complex, which is responsible for the vomiting reflex. However, there have been reports. The second mechanism is that palonosetron suppresses the action of 5-HT3 receptors and reduces binding to cell surface 5-HT3 receptors. Its other proposed mechanisms include univalled allostERIC effects, delayed ligand dissociation, and receptor internalization, but the reasons for these properties are not fully understood. The third mechanism is that palonosetron limits the influence of the NK1 receptor. Palonosetron uniquely inhibits the cross-talk between the 5-HT3 and NK-1 receptors pathways in a dose- and time-dependent manner. Previous studies suggested that the pharmacokinetics of palonosetron is different from that of the first-generation 5-HT3 RAs, leading to its effectiveness in delayed CINV.

The dose of palonosetron for the prevention of CINV in multiple-day chemotherapy is an issue of debate. The single-day chemotherapy clinical trial used palonosetron 0.75 mg on the first day because palonosetron 0.75 mg showed the greatest effect on delayed CINV. However, there are few studies using palonosetron 0.75 mg on the first day in multiple-day chemotherapy, and the Multinational Association for Supportive Care in Cancer recommendation is based on the fact that palonosetron was divided into three in one chemotherapy cycle. In this article, we proposed the therapeutic effect of a single dose of palonosetron for multiple-day chemotherapy because there are good reasons to assume that a single dose of palonosetron may be more effective than existing treatment with first-generation 5-HT3 RAs.

CINV causes malnutrition due to reduced food intake. The serotonergic system plays an important role in controlling food intake. Activation of 5-HT3 receptors leads to reduced food intake, which is managed via the administration of 5-HT3 RAs. 5-HT3 RAs inhibit the effects of hormones, such as cholecystokinin-1 and reducing post-prandial motility. Furthermore, gastrointestinal discomfort may be improved by blocking 5-HT3 receptors. The exact effect of palonosetron on the nutritional status during chemotherapy is unknown. In this study, caloric intake during chemotherapy was significantly higher in the palonosetron group than in the first-generation group. Moreover, the period of decreased oral intake overlapped with the onset of nausea and vomiting. These findings suggest that palonosetron improves anorexia during chemotherapy by suppressing nausea and vomiting.

The major limitation of this study was that it was impossible to obtain information on motion sickness. Drinking history, smoking history, and motion sickness influence the development of nausea and vomiting. Additionally, this study was limited by the small number of included patients due to the rarity of GCTs. Other limitations include those intrinsic to a single-center retrospective study.

In conclusion, the efficacy of palonosetron was superior to that of first-generation 5-HT3 RAs for managing CINV. Palonosetron significantly reduced vomiting and maintained dietary intake without major side effects during chemotherapy. However, the optimal 5-HT3 RA dosage for CINV still needs to be determined.

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