Original Article

Late Chemotherapy-Induced Nausea and Vomiting after Cisplatin Treatment for Patients with Esophageal or Gastric Cancer

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ABSTRACT

Background: Chemotherapy-induced nausea and vomiting (CINV) usually resolves within 5 days of chemotherapy initiation. However, some patients have CINV at 6 days or later after chemotherapy initiation (late CINV). We evaluated the incidence of late CINV and the effectiveness of aprepitant plus palonosetron in preventing late CINV.

Methods: We retrospectively reviewed the records of 102 patients with esophageal or gastric cancer to determine CINV incidence on days 1 through 21 after initiation of cisplatin treatment. Sixty-six patients received a first-generation 5-hydroxytryptamine (serotonin) type 3 receptor antagonist, and 36 received aprepitant plus palonosetron. In addition, we compared the effectiveness of antiemetic regimens before and after administering aprepitant and palonosetron. CINV was defined as presence of grade 1 or higher vomiting or grade 2 or higher nausea.

Results: In the aprepitant plus palonosetron group, the highest incidence of CINV (42%) was seen at 7 days after initiation of cisplatin treatment. CINV incidence started to gradually decrease at 8 days after cisplatin initiation. There was no significant intergroup difference in the incidence of late CINV.

Conclusions: Late CINV may develop in patients receiving cisplatin for treatment of esophageal or gastric cancer. Our findings suggest that the widely used prophylaxis for delayed CINV resulting from highly emetogenic chemotherapy is not satisfactorily effective against late CINV.

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KEYWORDS: chemotherapy-induced nausea and vomiting (CINV), antiemetics, aprepitant, palonosetron

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Chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing side effects for patients with cancer.[1, 2] Patients who develop CINV are occasionally forced to discontinue or postpone chemotherapy, which can worsen clinical outcomes.

According to the cisplatin treatment model, acute CINV is defined as emesis during the first 24 hours of treatment, and delayed CINV is defined as emesis after 24 hours of treatment. Cisplatin-containing chemotherapy is the most frequent treatment option for upper gastrointestinal cancer. The Japan Clinical Oncology Group (JCOG) 9907 study recommends preoperative chemotherapy (*i.e.*, cisplatin and 5-fluorouracil) followed by surgical resection as the standard of care for patients with esophageal carcinoma.[3] On the basis of the results of S-1 plus cisplatin versus S-1 alone for the first-line treatment of advanced gastric cancer trial (the SPIRITS trial), combination chemotherapy with cisplatin plus S-1 (a mixture of tegafur, gimeracil, and oteracil potassium) is considered the standard chemotherapy regimen for patients with advanced gastric cancer.[4] However, cisplatin is highly emetogenic, with a greater than 90% risk of CINV.[5] To prevent CINV in patients receiving highly emetogenic chemotherapy, the antiemetic guidelines[6, 7] suggest the use of 3 antiemetic drugs: a neurokinin-1 (NK1) receptor antagonist, a 5-hydroxytryptamine (serotonin) type 3 receptor antagonist (5-HT_3RA), and dexamethasone. In particular, the NK1 receptor antagonist aprepitant was found to significantly decrease the incidence of acute and delayed CINV.[8] Although first-generation 5-HT_3RAs such as granisetron, ramosetron, ondansetron, and azasetron have shown considerable efficacy in preventing acute CINV, palonosetron—a second-generation 5-HT_3RA—was more effective than first-generation 5-HT_3RAs in preventing acute and delayed emesis.[9–11]

Although CINV usually resolves within 5 days after chemotherapy initiation,[7] some patients have CINV at 6 days or later. In this study, we defined substantially delayed CINV as "late" CINV. Although several studies found that aprepitant and/or palonosetron were effective in treating CINV within 5 days after initiation of cisplatin treatment,[11–13] no study evaluated the effectiveness of these agents in preventing late CINV. Therefore, we evaluated the incidence of late CINV and the effectiveness of aprepitant plus palonosetron in preventing late CINV.

Methods

Patients and treatment

We retrospectively reviewed the records of patients treated at Toho University Omori Medical Center for esophageal or gastric cancer during the period from July 2010 through June 2012. The following inclusion criteria were applied: (1) age 20 years or older, (2) treatment with cisplatin (50 mg/m^2 or greater), (3) no prior chemotherapy, (4) no emesis within 24 hours before cisplatin administration, (5) absence of a brain metastasis, and (6) absence of gastrointestinal disturbances. Thirty-six consecutive patients treated with aprepitant, palonosetron, and dexamethasone were analyzed (aprepitant plus palonosetron group). Sixty-six consecutive patients treated with first-generation 5-HT_3RAs and dexamethasone from January 2009 through June 2010 were included as a historical control (first-generation 5-HT_3RA group).

All data on CINV episodes were extracted from patient medical records. This study was approved by the Ethical Review Board of Toho University Omori Medical Center (No. 23-2).

Chemotherapy

Patients with esophageal cancer were administered cisplatin 80 mg/m^2 via intravenous (IV) drip infusion for 2 hours on day 1 and 5-fluorouracil 800 mg/m^2 using continuous infusion on days 1 through 5. Patients with gastric cancer were administered oral S-1 twice daily for 3 weeks. S-1 doses were calculated according to the patient's body surface area, as follows: less than 1.25 m^2, 40 mg; 1.25 through 1.5 m^2, 50 mg; and greater than 1.5 m^2, 60 mg. Cisplatin 60 mg/m^2 was administered via IV drip infusion for 2 hours on day 8.

Antiemetic treatment

In the first-generation 5-HT_3RA group, first-generation 5-HT_3RA (granisetron, 3 mg; ramosetron, 0.3 mg; and azasetron, 10 mg) and dexamethasone infusion (IV 9.9 mg) were administered in a single IV infusion approximately 30 minutes before cisplatin administration. In the aprepitant plus palonosetron group, eligible patients were given oral aprepitant (125 mg), palonosetron infusion (IV 0.75 mg), and dexamethasone infusion (IV 9.9 mg) before the cisplatin infusion. Oral aprepitant (80 mg) was administered on 2 subsequent days and oral dexamethasone (8 mg) was given on 3 subsequent days. All patients were given a prescription for a rescue antiemetic if nausea or vomiting developed during the observation period.

Table 1 Patient characteristics

	Antiemetic therapy regimen		
	First-generation 5-HT$_3$RA	Aprepitant plus palonosetron	p value
Number of patients	66	36	
Duration of data collection (months)	18	24	
Age (years), median (range)	62 (31–84)	67 (46–77)	p = 0.06*
Sex (Male/Female)	58/8	29/7	p = 0.32†
Cisplatin dose (mg/m^2), median (range)	60 (56–80)	70 (60–80)	p = 0.01*
Primary cancer diagnosis			
Esophagus/Stomach	32/34	28/8	p < 0.01†

*Mann-Whitney *U* test, †Chi-square test
5-HT$_3$RA: serotonin type 3 receptor antagonist

Observation period and study outcome measures

The observation period after cisplatin infusion was divided into 3 phases: acute (0–24 hours), delayed (days 2–5), and late (days 6–21). The primary endpoint was CINV incidence during the late phase. CINV was defined as grade 1 or higher vomiting or grade 2 or higher nausea (according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4).

Statistical analysis

The chi-square test and Mann-Whitney *U* test were used to assess relationships among patient variables. In addition, either Fisher's exact probability test or the chi-square test was used to compare CINV incidence between the first-generation 5-HT$_3$RA group and aprepitant plus palonosetron group. A p value of less than 0.05 were considered to indicate statistical significance.

Results

Characteristics of patients and chemotherapy regimens

The characteristics of the patients are summarized in Table 1. The esophageal cancer/gastric cancer ratio was higher in the aprepitant plus palonosetron group than in the first-generation 5-HT$_3$RA group. In addition, cisplatin doses were significantly higher in the aprepitant plus palonosetron group than in the first-generation 5-HT$_3$RA group.

Incidence of CINV

Late CINV was observed in both groups (Fig. 1). At 6 through 10 days after cisplatin infusion, late CINV was observed in 25% to 42% patients in the aprepitant plus palonosetron group. In this group, the highest incidence of CINV (42%) was seen at 7 days after cisplatin treatment. Although CINV incidence gradually decreased after that, approximately 10% of patients had late CINV at 14 days after cisplatin treatment. In the first-generation 5-HT$_3$RA group, the highest CINV incidence (63%) was observed at 4 days after cisplatin treatment. Although CINV incidence gradually decreased after that, 39% patients had late CINV at 6 days after cisplatin treatment.

In the acute phase (day 1), there was no significant intergroup difference in CINV incidence. In the delayed phase (days 2 through 5), CINV incidence was significantly lower in the aprepitant plus palonosetron group than in the first-generation 5-HT$_3$RA group, except on day 5. In the late phase (days 6 through 21), there was no significant intergroup difference in CINV incidence.

Discussion

Our data show that some patients who received cisplatin treatment for esophageal or gastric cancer had late CINV. This suggests that the widely used prophylaxis for delayed CINV resulting from highly emetogenic chemotherapy is not sufficiently effective against late CINV.

Although cisplatin doses were higher in the aprepitant plus palonosetron group than in the first-generation 5-HT$_3$ RA group in the present study, aprepitant plus palonosetron therapy was effective in suppressing acute and delayed CINV. Nevertheless, the incidence of late CINV was similar in these groups. In fact, the incidence of late CINV was higher in the aprepitant plus palonosetron group than in the first-generation 5-HT$_3$RA group, although the difference was not significant. The fact that the aprepitant plus palonosetron therapy was so effective during the delayed phase might have made patients in that group more likely to report late CINV, as compared with patients in the first-generation 5-HT$_3$RA group. In 2003 Hesketh et al. reported that a 3-day aprepitant regimen protected patients against

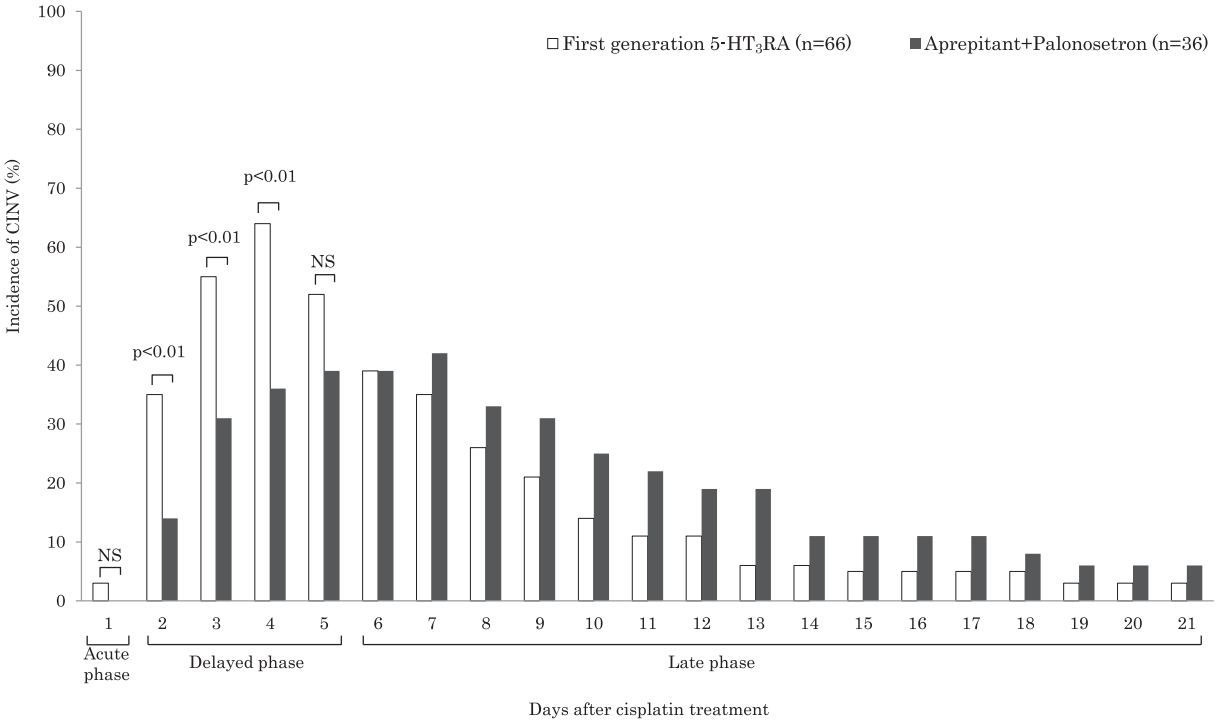

Fig. 1 CINV incidence. CINV was defined as grade 1 or higher vomiting or grade 2 or higher nausea. The first day after cisplatin infusion was set as day 1. Each patient was evaluated on day 1 (acute phase), days 2 through 5 (delayed phase), and days 6 through 21 (late phase). Group differences were analyzed using Fisher's exact probability test or the chi-square test.
CINV: chemotherapy-induced nausea and vomiting, 5-HT$_3$RA: serotonin type 3 receptor antagonist

CINV during a 5-day observation period.[12] Herrington et al. reported a trend toward better effectiveness in preventing nausea on days 4 and 5 after cisplatin treatment with 3-day versus 1-day aprepitant administration.[8] This observation suggests that a regimen of 4 or more days of aprepitant administration is better than a 3-day regimen in preventing late CINV in patients receiving cisplatin.

A recent study showed that prochlorperazine was as effective as aprepitant in preventing delayed CINV.[14] Another study reported that a combination of olanzapine, dexamethasone, and palonosetron was effective in controlling acute and delayed CINV in patients receiving highly emetogenic chemotherapy.[15] In addition, a recent phase III trial found that oral olanzapine was significantly better than oral metoclopramide in controlling breakthrough CINV.[16]

There are several limitations to our study. Retrospective studies are subject to two types of bias. First, physicians had different standards for CINV assessment. Second, the characteristics of the patients and chemotherapy regimens significantly differed between the two patient groups. For instance, because of the difference in esophageal cancer/gastric cancer ratio, cisplatin doses were significantly higher in the aprepitant plus palonosetron group than in the first-generation 5-HT$_3$RA group.

Conclusion

Although delayed CINV was significantly suppressed by aprepitant plus palonosetron therapy, 42% patients still experienced late CINV. Therefore, longer administration of antiemetic treatment, *e.g.*, aprepitant administration for 4 days or longer, may be needed to control late CINV. Prospective studies are required in order to evaluate the effectiveness of antiemetic treatments against late CINV.

Conflict of interest: The authors have no conflicts of interest to declare.

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食道癌または胃癌患者に対するシスプラチン投与後6日目以降まで残存する超遅発性嘔気・嘔吐に関する調査

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要約

背景と目的：抗がん剤により引き起こされる嘔気・嘔吐（chemotherapy-induced nausea and vomiting：CINV）は，投与後5日以内に消失すると考えられている．しかし，6日目以降も嘔気を訴える「超遅発性CINV」の患者も散見される．超遅発性CINVの発現頻度と，アプレピタント＋パロノセトロンの制吐効果を調査した．

対象および方法：食道癌または胃癌の患者102名を対象に，シスプラチン投与後21日間のCINV発現頻度を後ろ向きに調査した．アプレピタント＋パロノセトロンの採用前後での制吐療法の効果も比較した．

結果：アプレピタント＋パロノセトロン群では，シスプラチン投与後7日目にCINV発現頻度が最高値（42%）となった．超遅発性期では，2群間の制吐効果に有意差はなかった．

結論：シスプラチン投与を受ける食道癌または胃癌患者において，超遅発性CINVが存在することが示された．広く使われている制吐療法が，超遅発性CINVに対しては効果が十分ではないことが示唆された．

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