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Original Article

Addition of aprepitant prevents chemotherapy-induced vomiting and nausea moderately when 5-Hydroxytryptamine-3 receptor antagonists and dexamethasone failed

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Abstract: Aprepitant is one of the effective antiemetic drugs that usually used for prevention of Capecitabine and oxaliplatin (XELOX) chemotherapy-induced nausea and vomiting (CINV). We aimed to evaluate the effect of aprepitant on the control of CINV when conventional antiemetics failed. Patients with gastric and colon cancer scheduled to receive XELOX regimens were enrolled in this study, initially receiving 5-Hydroxytryptamine-3 (5-HT3) receptor antagonists and dexamethasone as anti-emetics. After patients experienced vomiting of grade ≥2 and required rescue anti-emetic drugs in the first cycle, oral aprepitant was added in second cycle. Acute (day 1) and delayed (days 2-5) CINV and occurrence of adverse reactions were investigated after the start of chemotherapy. Thirty patients (19.7%) were administered aprepitant for rescue project against CINV during the second cycle of chemotherapy. Delayed CINV were 100% during the first cycle but became lower in the second cycle, which revealed significant effectiveness of the addition of aprepitant on the control of delayed CINV when 5-HT3 receptor antagonists and dexamethasone failed. The incidences of acute and delayed nausea and vomiting in the first cycle of chemotherapy were significantly higher than the second cycle added aprepitant as rescue antiemetic ($P<0.05$). The incidences of nausea and vomiting were significantly lower after taken the rescue medication aprepitant. Addition of aprepitant to 5-HT3 antagonists and dexamethasone resulted in significantly better prevention of nausea and vomiting than the first cycle for gastric and colon cancer patients receiving XELOX chemotherapy.

Keywords: Aprepitant, capecitabine and oxaliplatin chemotherapy, 5-Hydroxytryptamine-3 receptor antagonists, dexamethasone, nausea, vomiting

Introduction

Digestive cancers, a constellation of tumors originated from gastric, liver, pancreatic and colon, pose a heavy burden on the healthcare system. Among them, gastric cancer and colon cancer are collectively a major cause of malignancy incidence and mortality in the world [1, 2]. Although advances in diagnostic and therapeutic technologies have led to outstanding expectations, the outlook for patients with advanced gastrointestinal cancers is still disappointing [3].

Currently the application of therapy approach chemotherapy has made considerable progress [4]. Capecitabine and oxaliplatin (XELOX) chemotherapy is regarded as the gold standard for anticancer therapies of digestive cancers patients. Unfortunately, a lot of patients have been affected by chemotherapy-induced nausea and vomiting (CINV), which is becoming a major determinant of patients' life quality [5]. CINV is reported to clinically lead to severe complications such as weakness, weight loss, dehydration, and anorexia [6, 7].

The effectiveness of antemetics in the prophylaxis and control of CINV has been well established along with the rapid popularity of XELOX chemotherapy. Zhou et al. introduced 5-HT3 receptor antagonists in clinical applications, which leaded to a noteworthy improvement in the prevention of CINV occurring in the first 24

h post the start of chemotherapy [8]. The addition of dexamethasone to a 5-HT3 receptor antagonist has further improved the prevention of CINV [9]. However, this antiemetic combination appears to be noneffective against delayed nausea and vomiting after 24 h post chemotherapy [10, 11].

Furthermore, it has been reported that the application of aprepitant, the first agent available in the drug class of neurokinin-1 (NK-1) receptor antagonists, was effective on the control of delayed CINV [7, 12]. In clinical trials, addition of aprepitant to 5-HT3 and corticosteroids enhanced the prevention of CINV by 20% [13].

The combination proportion of antemetics and dose fractionation are main factors influencing the intensity of the emetogenic stimuli in chemotherapy. Therefore, different combinations of antiemetics play a critical role on the control of CINV, which appear to be hotspot in recent years.

In the current study, we introduced a two-cycle, prospective, cohort trial of patients with gastric and colon cancer. The aim of this study was to evaluate the effect of aprepitant on the prevention of CINV in patients receiving XELOX chemotherapy when 5-Hydroxytryptamine-3 receptor antagonists and dexamethasone failed.

Material and methods

Patient selection

The observational study was carried out from May 2013 to August 2014 at the Peoples Liberation Army General Hospital. Ethics Committee of the hospital approved the research and written informed consent was given by all participants prior to study entry. All patients were hospitalized during two cycles of chemotherapy with gastric cancer or colon cancer. The eligibility criteria on the basis of assessment, which included: age ≥18 years old; no prior experience of XELOX-containing chemotherapy. Patients excluded from participation were as following: nausea or vomiting preceding the chemotherapy; had an allergy to the study medications or were lactose intolerant; an Eastern Cooperative Oncology Group (ECOG) performance status ≥3.

Study design and setting

Two sequential trials with an appropriate study design were conducted to fully evaluate the effect of aprepitant on the rescue of nausea and vomiting in patients receiving XELOX chemotherapy.

Patients with gastric or colon cancer received XELOX-based chemotherapy, at a dose of capecitabine (Days 1-14) and oxaliplatin (Day 1) every 21 days.

In the first cycle, all cancer patients were treated with conventional antiemetic regimen 5-HT3 receptor antagonists and dexamethasone. Based on the clinical status, patients who underwent nausea and emesis were permitted to take rescue therapy in subsequent cycle. With assessment of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.0) system, patients who experienced vomiting of grade ≥2 received rescue antiemetic aprepitant. Exclusion criteria in the second stage included the following: dose adjustments due to intestinal obstructions; received concurrent radiotherapy; treatment interruption. Then in the second cycle of chemotherapy, oral aprepitant was added (Day 1: 125 mg; Days 2-3: 80 mg once daily).

Appraisement of responses

Clinicopathological characteristics of cancer patients received rescue therapy were recorded, including receipt of informed consent, procurement of a complete medical history, assessment of demographic data and general physical examination. The occurrence of adverse reactions were investigated during the administration of chemotherapy.

CINV was evaluated during the two sequential cycles when the chemotherapy began. The clinical symptoms nausea and vomiting appearing in a patient are classified into two phases ‘acute’ (occurring in 0-24 h post the start of chemotherapy) and ‘delayed’ (occurring 25-120 h post the start of chemotherapy) [14]. The severity of adverse events was graded on the basis of NCI-CTCAE v4.0. Complete response referred to no vomiting and no rescue antiemetics. Complete control represented an absence of nausea, emetic episodes, and rescue anti-

Table 1. Clinicopathological characteristics of gastric and colon cancer patients

Characteristic		Number of patients	
		Gastric cancer N (%)	Colon cancer N (%)
Patients enrolled		14 (46.7)	16 (53.3)
Gender	Male	8 (26.7)	11 (36.7)
	Female	6 (20.0)	5 (16.6)
Mean age (years)	≤60	9 (30.0)	7 (23.3)
	>60	5 (16.7)	9 (30.0)
Tumor size (cm) (mean ± SD)		4.8±1.9	5.2±2.6
TNM stage			
	I-II	8 (26.7)	3 (10.0)
	III-IV	6 (20.0)	13 (43.3)

Table 2. Symptoms and responses in cancer patients receiving aprepitant as rescue therapy

Responses	First cycle N (%)	Second cycle N (%)	*P* value
Acute nausea	17 (56.7)	4 (13.3)	5.689E-05
Acute vomiting	6 (20.0)	0 (0.0)	0.012
Delayed nausea	30 (100.0)	21 (70.0)	0.001
Delayed vomiting	30 (100.0)	15 (50.0)	8.699E-06
Intravenous rehydration	16 (53.3)	1 (3.3)	8.699E-06
Rescue therapy	30 (100.0)	5 (16.7)	1.138E-10
Complete response	0 (0.0)	20 (66.7)	2.138E-08
Complete control	0 (0.0)	12 (40.0)	1.349E-04

emetics. The main difference between the two endpoints was the degree of nausea severity: compared with Complete response, Complete control accounted for no appearance of nausea. Primary efficacy and point of the protocol was the rate of Complete response, and the secondary point was the rate of Complete control.

Statistical considerations

Clinicopathological characteristics of cancer patients were shown with percent of categorical variables, and continuous variables were shown as mean and standard deviation (SD). Comparisons between groups were performed using the chi-square test and a *P*-value <0.05 was considered statistically significant. The software SPSS (version 22.0) was applied for all analyses.

Results

A total of 152 patients with gastric and colon cancer scheduled to receive XELOX regimens were eligible in this study, initially receiving 5-Hydroxytryptamine (5-HT3) receptor antagonists and dexamethasone as anti-emetics in the first cycle. Thirty patients (19.7%) were administered aprepitant for rescue project against CINV during the second cycle of chemotherapy. The clinicopathological characteristics of these cancer patients were listed in **Table 1**. Approximately twenty percent of patients completed the planned two sequential trials, who experienced vomiting of grade ≥2 and received rescue antiemetic aprepitant. There were 14 gastric cancer patients and 16 colon cancer ones. They were well balanced for these characteristics.

The major responses of thirty patients evaluated in the first and second cycles of chemotherapy were shown in **Table 2**. Delayed CINV were 100% during the first cycle but became lower in the second cycle, which revealed significant effectiveness of the addition of aprepitant on the control of delayed CINV when 5-HT3 receptor antagonists and dexamethasone failed. The percent of acute and delayed nausea were 56.7 and 100% in the first cycle, but 13.3 and 70% in the second cycle (P<0.01). Similarly, the incidences of acute and delayed vomiting in the first cycle of chemotherapy were significantly higher than the second cycle added aprepitant as rescue antiemetic (P<0.05). **Figure 1** showed the severity of CINV assessed by NCI-CTCAE v4.0 during the first and second trials. It suggested that the incidences of nausea and vomiting were significantly lower after taken the rescue medication aprepitant.

In addition, for the thirty cancer patients, 16 patients (53.3%) required intravenous rehydration in the first cycle, but only one patient required intervention in the second cycle, which showed the efficacy of the rescue intervention. In general, 20/30 patients (66.7%) met the criteria for Complete response (defined as no vomiting and no rescue antiemetics), and 12/30 patients (40%) met the criteria for Complete control (defined as no emesis, nau-

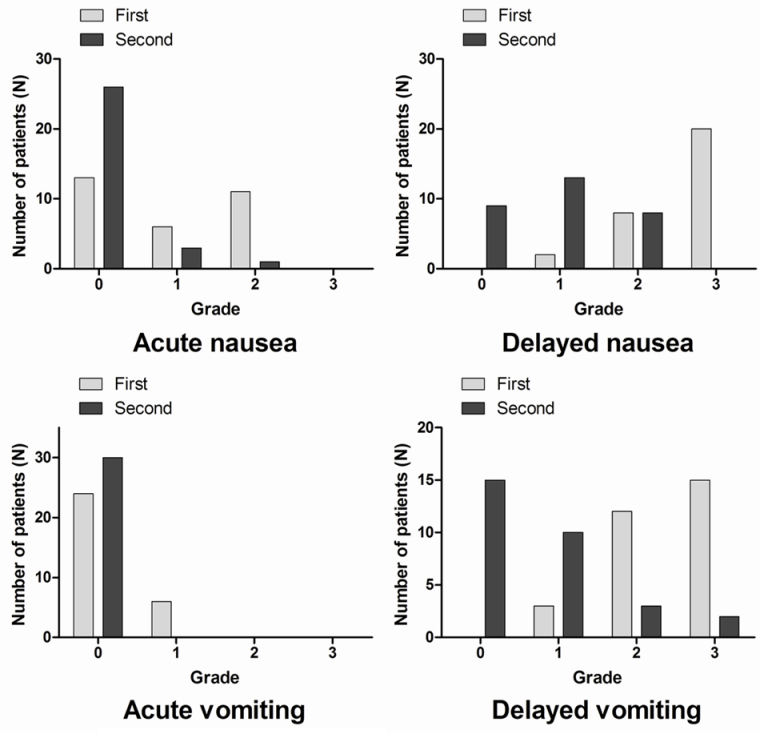

Figure 1. The severity of CINV assessed by NCI-CTCAE v4.0 during the first and second cycles.

Table 3. Adverse events in two cycles in cancer patients receiving aprepitant as rescue therapy

Responses	First cycle N (%)	Second cycle N (%)	*P* value
Dry mouth	9 (30.0)	11 (36.7)	0.584
Headache	4 (13.3)	4 (13.3)	1.000
Insomnia	7 (23.3)	6 (20.2)	0.754
Fever	2 (6.7)	0 (0.0)	0.150
Abdominal pain	3 (10.0)	1 (3.3)	0.301
Bloating	10 (33.3)	9 (30.0)	0.781
Constipation	24 (80.0)	22 (73.3)	0.542
Diarrhea	3 (10.0)	2 (6.7)	0.640

sea, emetic episodes, or rescue antiemetics) in the second trial.

Adverse events during two cycles in cancer patients used aprepitant as rescue medication were shown in **Table 3**. The rates of dry mouth, headache, insomnia, fever, abdominal pain, bloating, constipation and diarrhea were not significantly different between the first and the second cycle (P>0.05). Aprepitant did not increase the incidence of adverse events in the second cycle, which suggested aprepitant was not associated with additional adverse events. Furthermore, no patient experienced treatment interruption resulted from these adverse events, and no treatment-related mortality occurred during the trial.

Discussion

It is obvious to all that the availability and convenience of XELOX chemotherapy in anticancer treatment. XELOX was proved to be more convenient result from the use of an oral fluoropyrimidine instead of injectable fluorouracil [15]. In the clinical observation for a long time, most patients have expressed a preference for XELOX over conventional intravenous 5-fluorouracil [16]. More importantly, XELOX is an attractive regimen for use in anticancer chemotherapy on account of only 1 day of cytotoxic treatment. Therefore, XELOX is regarded as a standard combination partner with other antemetics [4].

Recently the application of XELOX in gastrointestinal cancers has made progress at an unprecedented rate [17, 18]. Borner et al. [4] added cetuximab to standard XELOX [15, 19] in colon cancer patients, leading to higher response rates, which seemed to achieved remarkable effect in potentially resectable metastases. Both colon and gastric cancer patients were enrolled in the present study to assess the emetic reflex of digestive cancers.

As we all know, XELOX chemotherapy-induced adverse effect CINV is among the most tormenting symptoms [20, 21]. It is a well-established phenomenon that nausea and emesis following anticancer chemotherapy [14]. The impact of CINV on patients' daily function and lives is a clinically relevant to therapeutic effect [22]. CINV is commonly classified as acute and delayed one according to time of onset. From **Table 2** we can see that all thirty digestive cancers patients experienced delayed CINV in the

first cycle, which indicated the 5-HT3 receptor antagonists and dexamethasone lost efficacy occurring more than 24 h post chemotherapy. Similar with the result, the acute phase is highly susceptible to resist by 5-HT3 receptor antagonists and the delayed one is generally more resistant [23]. This result was also consistent with previous outcomes of [10, 11]. Meanwhile, it is investigated that peaks of CINV intensity appeared on 48-72 h post chemotherapy in colon and gastric cancer patients (data not show), which was consistent with [24, 25].

Primary endpoint was the rate of Complete response (no emetic episodes or rescue therapy) during chemotherapy. Previous reports revealed the addition of aprepitant to a 5-HT3 antagonist, dexamethasone, and metoclopramide enhanced the control of CINV in lung cancer patients, with 16% rate of Complete response [21]. It is investigated that aprepitant has been added to 5-HT3 receptor antagonist and dexamethasone for 7 days after high-dose chemotherapy for stem cell transplantation with Complete response rate of 42.9% [26]. Complete response rate in the present study was 20% during the second cycle added aprepitant. The result showed a moderate prevention of CINV among gastrointestinal cancer patients receiving aprepitant.

In summary, our studies with 5-HT3 receptor antagonists and dexamethasone in colon and gastric cancer patients demonstrated a crucial role of aprepitant in the emetic reflex post chemotherapy.

Disclosure of conflict of interest

None.

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