Optimal Dose Period for Indisetrone Tablets for Preventing Chemotherapy-Induced Nausea and Vomiting with Modified FOLFOX6: A Randomized Pilot Study

Hiroshi Nakatsumi^{a,b} Yoshito Komatsu^d Satoshi Yuki^b Susumu Sogabe^h
Miki Tateyamaⁱ Shuichi Muto^j Mineo Kudo^g Kanji Kato^k Takuto Miyagishima^h
Minoru Uebayashi^l Takashi Meguro^e Koji Oba^f Masahiro Asaka^c

^aDepartment of Internal Medicine, Wakkanai City Hospital, Wakkanai, Departments of ^bGastroenterology, and ^cCancer Preventive Medicine, Hokkaido University Graduate School of Medicine, ^dDepartment of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, ^eDepartment of Internal Medicine, Hokkaido Gastroenterology Hospital, ^fTranslational Research and Clinical Trial Center, Hokkaido University Hospital, Hokkaido University, and ^gDepartment of Gastroenterological Medicine, Sapporo Hokuyo Hospital, Sapporo, ^hDepartment of Internal Medicine, Kushiro Rosai Hospital, Kushiro, ⁱDepartment of Internal Medicine, Tomakomai Nissho Hospital, and ^jDepartment of Gastroenterological Medicine, Tomakomai City Hospital, Tomakomai, ^kDepartment of Internal Medicine, Iwamizawa Municipal General Hospital, Iwamizawa, and ^lDepartment of Gastroenterological Medicine, Japanese Red Cross Kitami Hospital, Kitami, Japan

Key Words

Indisetrone hydrochloride · Chemotherapy-induced nausea and vomiting · FOLFOX · Colorectal cancer

Abstract

Background: Indisetrone is a serotonin (5-hydroxytryptamine type 3) receptor antagonist that also antagonizes 5-hydroxytryptamine type 4 receptors. We designed a pilot study in order to explore the optimal dosing period for indisetrone during modified FOLFOX6 (mFOLFOX6). **Patients and Methods:** Forty-two chemotherapy-naïve patients with advanced colorectal cancer scheduled to receive mFOLFOX6 were randomly assigned to either a 1- or 3-day indisetrone regimen arm. The primary endpoint was complete protection from vomiting. **Results:** Proportions of patients with complete protection from vomiting were 85.7% [95% confidence inter-

val (CI) 63.7–97.0] with the 3-day regimen and 81.0% (95% CI 58.1–94.6) with the 1-day regimen. Proportions of patients with complete protection from nausea were 47.6% in each arm (95% CI 25.7–70.2). No rescue therapy rates were 66.7% (95% CI 43.0–85.4) versus 57.1% (95% CI 34.0–78.2). No severe adverse events were observed in either arm. **Conclusion:** Both 1- and 3-day indisetrone regimens were feasible for preventing nausea and vomiting induced by mFOLFOX6.

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most feared adverse events and can reduce the physical and mental status of patients, which may result in deteriorated quality of life or withdrawal from fur-

ther chemotherapy. CINV is commonly classified as acute (occurring within 24 h after initiation of chemotherapy), delayed (occurring between days 2 and 5) or anticipatory (occurring before the next chemotherapy cycle and resulting from a previous experience of CINV) [1]. Intravenously administered chemotherapeutic agents are divided into four levels of emetogenicity: high, >90% of patients experience acute vomiting without antiemetic prophylaxis; moderate, 30–90% experience acute vomiting; low, 10–30% experience acute vomiting; and minimal emetic risk, <10% experience acute vomiting [2]. The emetogenic potential of a chemotherapeutic agent is the strongest predictor of CINV [3]. Thus, antiemetic guidelines have defined antiemetic regimens based on the emetic risk of chemotherapeutic regimens. Many antiemetic guidelines have recommended the combination of a serotonin (5-hydroxytryptamine type 3, 5-HT₃) receptor antagonist and corticosteroid for the prevention of CINV induced by moderately emetogenic chemotherapy [3, 4]. This combination controls approximately 80% of acute CINV, but delayed CINV remains problematic [5, 6].

FOLFOX, a combination regimen of bolus and infusional 5-fluorouracil (5-FU), leucovorin and oxaliplatin, is a standard chemotherapeutic regimen for patients with advanced colorectal cancer. Oxaliplatin is moderately emetogenic, while 5-FU shows low emetogenicity [7]. Previous phase III trials have shown that 64–72.2% of patients receiving FOLFOX experienced nausea, while 39–54.2% experienced vomiting [8–11]. These clinical trials did not indicate any prophylactic regimen for preventing CINV induced by FOLFOX, and no large clinical trials have evaluated antiemetic agents for preventing CINV by the FOLFOX regimen.

Indisetrone hydrochloride (Sinseron tablet®; Kyorin/Yakult, Tokyo, Japan) is an oral 5-HT₃ receptor antagonist that has recently been developed in Japan [12] and also shows 5-HT₄ antagonistic activity in pharmacological profiles. Based on the hypothesis that 5-HT₄ receptors are partially responsible for CINV [13, 14], this characteristic is expected to contribute to the further efficacy of preventing CINV. A phase III trial in Japan showed the non-inferiority of indisetrone tablets compared to ondansetrone tablets in terms of efficacy for preventing CINV induced by a cisplatin-based regimen [15]. The Pharmaceuticals and Medical Devices Agency in Japan approved indisetrone tablets for sale in Japan in 2004. However, some limitations were present in the study. First, dexamethasone was not administered for antiemetic prophylaxis, as the agent was not indicated for

that use in Japan at the time. Thus, the efficacy and safety of indisetrone in combination with dexamethasone was unclear. Second, the study endpoint was not complete response, which is widely used as the primary endpoint in clinical trials of antiemetic agents. Furthermore, nausea and vomiting were only assessed for 24 h. Therefore, the study did not assess delayed CINV. The efficacy of indisetrone in combination with dexamethasone has remained unclear, particularly for the prevention of delayed CINV. The Pharmaceuticals and Medical Devices Agency has not recommended multiple-day use of indisetrone for preventing delayed emesis because of these limitations.

Data regarding the antiemetic efficacy of indisetrone during FOLFOX are lacking, and no recommendations have been made regarding the optimal dose period for indisetrone. Therefore, to explore the optimal dose period for the indisetrone-based antiemetic regimen during FOLFOX, this pilot study evaluated the efficacy of 1- and 3-day regimens of indisetrone.

Patients and Methods

Trial Design

This study was a pilot, multicenter, randomized, open-label, comparative trial. The study was conducted in accordance with the World Medical Association Helsinki Declaration. All clinical protocols for this study project were approved by the Institutional Review Board of Hokkaido University and the protocol committees of the Hokkaido Gastrointestinal Cancer Study Group (HGCSG). Eight hospitals belonging to the HGCSG participated in this study. The study protocol was approved by the institutional review board of each participating hospital.

Eligibility

Chemotherapy-naïve patients with advanced colorectal cancer who were scheduled to receive the first cycle of modified FOLFOX6 (mFOLFOX6), with or without administration of molecular targeted agents, were considered eligible for the study. Other eligibility criteria included: age 20–80 years; Eastern Cooperative Oncology Group performance status 0–2; and acceptable hematologic, hepatic and renal functions. Patients were considered ineligible if they had any known central nervous system malignancy; had any seizure disorder needing anticonvulsants; had active gastrointestinal ulcers or obstruction; had any other organic cause of nausea or vomiting unrelated to chemotherapy; were scheduled to undergo radiotherapy; were pregnant or nursing women; or had any history of drug hypersensitivity. All eligible patients provided written informed consent prior to participation in the study.

Treatment Course

The mFOLFOX6 regimen comprised oxaliplatin 85 mg/m² and L-leucovorin 200 mg/m² given as a 2-hour infusion followed by bolus 5-FU 400 mg/m² and a 46-hour infusion of 5-FU 2,400

mg/m², with or without a 60-min infusion of bevacizumab at 5 mg/kg every 2 weeks. Eligible patients were randomized to either a 3-day or a 1-day regimen arm. On day 1, indisetron 8 mg was administered orally and dexamethasone 8 mg was administered intravenously 30–120 min before administration of oxaliplatin. In the 3-day regimen arm, indisetron 8 mg was administered orally in the morning on days 2–3. In the 1-day regimen arm, no prophylactic medications were taken on days 2–3. Rescue medication including dexamethasone and/or metoclopramide for the treatment of breakthrough CINV was permitted on an as-needed basis. The follow-up period was 5 days from the start of chemotherapy.

Efficacy Parameters

The primary endpoint was complete protection from vomiting, defined as no vomiting for 5 days after initiation of chemotherapy. Secondary endpoints were complete protection from nausea (no nausea for 5 days after chemotherapy), no use of rescue therapy (no rescue therapy to treat breakthrough CINV for 5 days after chemotherapy) and tolerability. Nausea, vomiting and other adverse events were evaluated using Common Terminology Criteria for Adverse Events, version 3.0 [16]. The exploratory endpoint is complete response, defined as no vomiting and no use of rescue therapy for 5 days after initiation of chemotherapy.

Sample Size

In this pilot study, 20 patients were required for each regimen arm to estimate the proportion of patients with complete protection from vomiting within $\pm 17.5\%$, with a 95% confidence interval (CI) when the expected proportion was 80%.

Statistical Analyses

Demographic data of patients were reported using descriptive statistics. Baseline characteristics of patients in each arm were compared using the χ^2 or Fisher's exact tests for categorical data and 2-sided, 2-sample t tests for continuous data. To assess the primary endpoint, the proportion of patients with complete protection from vomiting in each of the two regimen arms was calculated based on an exact 95% CI [17]. The proportion of patients with complete protection from nausea, those with no use of rescue therapy and those with complete response was also calculated based on an exact 95% CI. The designed level of statistical significance was $p < 0.05$.

Results

Patient Characteristics

Patients were enrolled between 9 January 2008 and 4 September 2009. Of the 45 patients randomized to receive treatment, 2 patients in the 3-day regimen arm and 1 patient in the 1-day regimen arm did not receive study treatment. As a result, 42 patients (21 patients in each arm) remained. All patients received mFOLFOX6. Characteristics of patients in each group were balanced except for the primary site (table 1).

Table 1. Patient characteristics

	3-day regimen (n = 21)	1-day regimen (n = 21)	p
Sex			
Male	10 (47.6)	14 (66.7)	0.212 ^a
Female	11 (52.4)	7 (33.3)	
Age, years			0.360 ^b
Median	60	67	
Range	42–80	37–77	
Primary site			0.013 ^a
Colon	16 (76.2)	8 (42.9)	
Rectum	5 (23.8)	13 (57.1)	
ECOG PS			1.000 ^c
0	18 (85.7)	18 (85.7)	
1	2 (9.5)	3 (14.3)	
2	1 (4.8)	0	

Figures in parentheses are percentages. ECOG PS = Eastern Cooperative Oncology Group performance status.

^a χ^2 test.

^b Two-sample t test.

^c Fisher's exact test.

Primary Endpoint

The proportion of patients with complete protection from vomiting was 85.7% (95% CI 63.7–97.0) in the 3-day regimen arm and 81% (95% CI 58.1–94.6) in the 1-day regimen arm. Proportions of patients with no vomiting during days 1–5 are shown in figure 1.

Other Endpoints and Safety

The proportion of patients with complete protection from nausea was 47.6% in each arm (95% CI 25.7–70.2). In the acute phase, the proportion of patients with no nausea was 100% in the 3-day and 95.2% in the 1-day regimen arm. The proportion of delayed complete protection from nausea was similar between the two treatment arms (fig. 2). No rescue therapy rates were 66.7% (95% CI 43.0–85.4) in the 3-day regimen and 57.1% (95% CI 34.0–78.2%) in the 1-day regimen. In the acute phase, the proportion of patients with no rescue therapy was 100% in each regimen arm. The proportion of patients with no rescue therapy in the delayed phase was 66.7% in the 3-day regimen and 57.1% in the 1-day regimen arm (fig. 3). Severity of nausea and vomiting based on the worst grade was similar between the 3- and 1-day regimens (table 2).

The proportion of patients with complete response was 66.7% (95% CI 43.0–85.4) in the 3-day regimen and 57.1% (95% CI 34.0–78.2) in the 1-day regimen. In the

Fig. 1. Percentage of patients with no vomiting during days 1-5.

Fig. 2. Percentage of patients with no nausea during days 1-5.

Fig. 3. Percentage of patients with no rescue therapy during days 1-5.

Table 2. Severity of CINV using Common Terminology Criteria for Adverse Events version 3.0

Worst grade:	3-day regimen (n = 21)				1-day regimen (n = 21)			
	1	2	3	all grades	1	2	3	all grades
Vomiting	4 (19.0)	0	0	4 (19.0)	2 (9.5)	1 (4.8)	0	3 (14.3)
Nausea	5 (23.8)	6 (28.6)	0	11 (52.4)	8 (38.1)	2 (9.5)	1 (4.8)	11 (52.4)

Figures in parentheses are percentages.

acute phase, the proportion of patients with complete response was 100% in the 3-day regimen and 95.2% (95% CI 76.2–99.9) in the 1-day regimen arm. The proportion of patients with complete response in the delayed phase was 66.7% in the 3-day regimen and 57.1% in the 1-day regimen arm.

No severe drug-related adverse events were observed in either arm. Only 2 patients experienced constipation (grade 1) in the 3-day regimen arm, while 1 patient in the 1-day regimen arm had a headache (grade 1).

Discussion

The findings of this pilot study suggest that the efficacy of 3- and 1-day indisetron regimen arms are sufficient for preventing CINV induced by mFOLFOX6. Indisetron in combination with dexamethasone 8 mg provided protection against emesis in approximately 80% of patients receiving mFOLFOX6.

The present pilot study found that the efficacy of both the 3- and 1-day regimen arms was feasible with respect to the proportion of patients with complete protection from vomiting. Similar efficacy was also apparent in the prevention of acute and delayed phases of nausea and vomiting between the two arms. The 3-day regimen did not appear to offer any benefits in alleviating the severity of nausea or vomiting. In this study, the proportion of patients with nausea was 52.4% in both 1- and 3-day regimen arms, while the proportion of patients with vomiting was 14.3% with the 1-day regimen and 19.0% with the 3-day regimen. These findings resemble those of other clinical trials evaluating FOLFOX for patients with colorectal cancer [10, 11, 18], which did not mention antiemetic regimens, but conventional regimens of a first-generation 5-HT₃ receptor antagonist (i.e. granisetron, ondansetron, tropisetron, or dolasetron) plus dexamethasone might have been applied.

In our study, the proportion of patients with complete response was 66.7% in the 3-day regimen and 57.1% in the 1-day regimen, which was the same result as of those with no rescue therapy. The result was not very different from that of other first-generation 5-HT₃ receptor antagonists for preventing CINV induced by moderate emetogenic chemotherapy [19–21], but seemed to be less than that of the control arm (ondansetron plus dexamethasone) in the study investigating the NK-1 receptor antagonist capsoitant for the prevention of oxaliplatin-induced emesis, in which the complete response was 85% [22]. This difference may be a result of the small sample size of our study

or some risk factors of CINV such as alcoholic use or motion sickness that were not assessed in our study.

Indisetron, as with first-generation 5-HT₃ receptor antagonists, did not improve the efficacy of preventing delayed CINV. Although the 3-day regimen might have a placebo effect because of this open-label trial, the 3-day regimen did not show significant differences in efficacy with the 1-day regimen, especially against delayed emesis. It might be due to small sample size and some biases, but the meta-analysis evaluating other 5-HT₃ receptor antagonists in preventing delayed CINV showed similar results [23]. We suggest that multiple-day use of 5-HT₃ receptor antagonists might not be effective, especially for preventing delayed CINV. In order to prevent delayed CINV, we might have to block other neurotransmitter pathways such as the NK-1 receptor pathway. However, the second-generation 5-HT₃ receptor antagonist, palonosetron, a potent and highly selective 5-HT₃ receptor antagonist with strong binding affinity to the receptor and a long plasma elimination half-life (about 40 h), has shown efficacy in preventing acute and delayed CINV induced by moderately or highly emetogenic chemotherapy [24, 25]. Further evaluations about the prevention of delayed CINV are warranted.

In conclusion, both 3- and 1-day indisetron regimen arms were feasible in terms of preventing nausea and vomiting induced by mFOLFOX6. Multiple-day use of 5-HT₃ receptor antagonists might not be effective for prevention of delayed nausea and vomiting. Future studies need to evaluate indisetron-containing regimens or a second-generation 5-HT₃ receptor antagonist in terms of the prevention of delayed nausea and vomiting induced by a mFOLFOX6 regimen.

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Disclosure Statement

The authors declare that there are no conflicts of interest.

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