

Thalidomide improves prevention of chemotherapy-induced gastrointestinal side effects following a modified FOLFOX7 regimen: results of a prospective randomized crossover study

Yunpeng Liu, Jingdong Zhang, Yuee Teng, Lingyun Zhang, Ping Yu, Bo Jin, Mingfang Zhao, Jing Shi, Shizhou Liu, Na Song, and Zhi Li

Department of Medical Oncology, the First Hospital, China Medical University, Shenyang City, China

ABSTRACT

Aims and background. Thalidomide was firstly evaluated for the control of chemotherapy-induced gastrointestinal side effects following a modified FOLFOX7 (mFOLFOX7) regimen.

Methods and study design. Chemotherapy-naive patients with malignant tumors were randomized into two groups: A-B group (A, 0.3 mg of ramosetron plus 10 mg of dexamethasone on day 1, was given intravenously in the first cycle, and B, 0.3 mg of ramosetron plus 10 mg of dexamethasone on day 1 intravenously plus 150 mg orally twice daily of thalidomide on days 2 through 5, in the second cycle) and B-A group (those drugs were given in the reverse sequence). The primary end point was the efficacy of thalidomide in controlling delayed (days 2 through 5) chemotherapy-induced nausea and vomiting (CINV). The secondary end point was the safety of thalidomide.

Results. Of 52 patients enrolled, 50 patients (96%) were assessable. Complete response rates of delayed nausea (no nausea) were higher with group B than group A (52% vs 24%, $P = 0.004$ on day 2; 58% vs 24%, $P = 0.001$ on day 3; and 60% vs 36%, $P = 0.016$ on day 4). Complete response rates of delayed emesis (no emetic episodes, no rescue therapy) for group B and A also showed significance (86% vs 66%, $P = 0.019$ on day 2 and 76% vs 56%, $P = 0.035$ on day 3). Complete response rates on anorexia for group B were higher than those for group A on days 2 through 5. More patients in group B reported sedation or dizziness than in group A (42% vs 9.6%; $P = 0.000$).

Conclusions. Thalidomide improves prevention of chemotherapy-induced gastrointestinal side effects following the mFOLFOX7 regimen. It is a safe, effective antiemetic.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common side effects of cancer chemotherapy. Clinical consequences of CINV such as malnutrition, acid-base and electrolyte changes, and patient refusal to continue chemotherapeutic cycles decrease health-related quality of life¹ and compromise treatment efficacy. In the meantime, CINV has a considerable economic impact². During the last 20 years, many agents have been studied to establish their efficacy in controlling CINV. Antiemetic agents include serotonin (5-HT₃) receptor antagonists (ondansetron, granisetron, ramosetron and dolasetron), NK-1 receptor antagonist (eg, aprepitant), dexamethasone, phenothiazines and antihistamines. Most patients receiving moderately (e.g., oxaliplatin >75 mg/m²) to highly (e.g., cisplatin ≥50 mg/m²) emetogenic chemotherapy³ will not experience acute emesis (which occurs within 24 h postchemotherapy) with the combination of a 5-HT₃ receptor antagonist and corticosteroids.

Key words: chemotherapy-induced nausea and vomiting (CINV), ramosetron, thalidomide.

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Correspondence to: Professor Yunpeng Liu, Department of Medical Oncology, the First Hospital, China Medical University, NO.155, North Nanjing Street, Heping District, 110001, Shenyang City, China.
Tel +86-24-81018401;
fax +86-24-83282543;
e-mail liuyunpeng@medmail.com.cn;
cmuliyunpeng@yahoo.cn

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teroids. However, 5-HT₃ antagonists and corticosteroids control less than 50% of delayed CINV episodes, which occur 24 h or more after the start of chemotherapy⁴.

Among those antiemetic agents, dexamethasone is clearly effective in preventing emesis in both acute and delayed phases⁵. A recent meta-analysis of randomized controlled trials found that adding a 5-HT₃ antagonist to dexamethasone did not improve the antiemetic effect of dexamethasone in preventing delayed emesis. The introduction of aprepitant and palonosetron represented an important advance in the prevention of delayed CINV⁶⁻⁸. Nevertheless, the control of delayed CINV was still not satisfactory. Therefore, further progress depends on innovative approaches and agents.

Thalidomide, a derivative of glutamic acid, was introduced in Europe in 1954 as a sedative/hypnotic agent and was used to ameliorate nausea in pregnancy. Although thalidomide was well tolerated, a large increase in the incidence of limb malformations in newborn children was observed as a result of thalidomide use during pregnancy. Thalidomide was withdrawn from the market in Europe by the end of 1961. Since that time, new studies and uses for the drug have emerged, including the treatment of erythema nodosum leprosum⁹, aphthous ulcers of Behçet's disease¹⁰, wasting and oral ulcers associated with the human immunodeficiency syndrome^{11,12}, and graft-versus-host disease¹³. Moreover, thalidomide has already become part of the standard therapy for the treatment of patients with relapsed and refractory multiple myeloma^{14,15}. It has also been found to have varying degrees of benefit in various other malignancies¹⁶.

However, it is not clear whether or not thalidomide is effective in controlling delayed CINV. We thus undertook a prospective randomized crossover controlled study to evaluate thalidomide in controlling of chemotherapy-induced gastrointestinal side effects following a mFOLFOX7 regimen. The primary hypothesis was that addition of thalidomide to a ramosetron plus dexamethasone regimen would be superior to ramosetron plus dexamethasone in controlling delayed CINV.

Patients and methods

Patients

Chemotherapy-naïve patients in our institution with histological or cytological confirmed malignancies who were scheduled to receive chemotherapy were randomized into the A-B group and B-A group. Other inclusion criteria were age between 18 and 70 years, ECOG (Eastern Cooperative Oncology Group) performance status of 0-2, and anticipated survival of more than 3 months. Patients were excluded if they were unable to understand or cooperate with study procedures. Other

exclusion criteria were as follows: primary CNS malignancy or brain metastases, known seizure disorder, clinically significant neuromuscular disorder or degenerative disorder of the nervous system, clinically significant endocrine abnormalities not controlled with current therapy, history of thrombosis, history of significant hypersensitivity to thalidomide or the 5-HT₃ receptor antagonist, use of any other medication with potential antiemetic action within 24 hr of chemotherapy, radiation therapy to the abdominal or pelvic areas within 48 hr before the study period, and pregnancy or lactation. Fertile patients had to be using effective contraception. The study was confirmed by the local Ethics Committee.

Chemotherapy regimen

The patients were scheduled to receive a moderately emetogenic mFOLFOX7 regimen (oxaliplatin, 100-130 mg/m² intravenously over 2 hr on day 1; leucovorin, 200 mg/m² intravenously over 2 hr on day 1; followed by 46-hr 2,400 mg/m² 5-fluorouracil continuous infusion, every 3 weeks).

Study design

The primary end point was the efficacy of thalidomide in controlling delayed CINV. The secondary end point was the safety of thalidomide. A prospective, randomized, open, crossover design was used. All patients were randomized into two groups: A-B group (group A, ramosetron plus dexamethasone on day 1 was given in the first cycle; and group B, the same antiemetic regimen as group A on day 1 plus thalidomide on days 2 through 5 in the second cycle) and B-A group (the same drugs were given in the reverse sequence). All the patients received ramosetron (0.3 mg intravenously) combined with dexamethasone (10 mg intravenously) 30 min prior to chemotherapy on day 1 for prophylaxis against acute emesis. In group B, additional thalidomide was given as 150 mg orally twice a day on days 2 through 5. Chemotherapy drug usage and dosage were consistent in the two consecutive periods.

Patients in both groups were permitted to receive an intravenous rescue dose of dexamethasone (10 mg) if vomiting occurred more than 2 times (National Cancer Institute Common Terminology Criteria for Adverse Events V2.0¹⁷, NCI-CTCAE V2.0 grade 2) within 24 hr. Patients who required rescue therapy were to receive enough supportive therapy if still troubled by vomiting of more than 5 times within 24 hr (NCI-CTCAE V2.0 grade 3 or 4).

Patients were withdrawn from the study if they were not satisfied with the antiemetic treatment, or the chemotherapy was changed for the reason of uncontrolled side effects. The study was conducted according to the Declaration of Helsinki, and each patient gave a written informed consent before any study-related procedures were performed.

Evaluation methods

Pretreatment evaluations included a complete medical history, physical examination, ECG and clinical laboratory profile within 1 week of the start of chemotherapy. An emetic episode was defined as one occurrence of vomiting or a sequence of occurrences in very close succession not relieved by a period of relaxation of at least 1 min, any number of episodes of unproductive emesis (retches) in a unique 5-min period, or an episode of retching of <5 min duration combined with vomiting not relieved by a period of relaxation of 1 min.

The observation period was 5 days. Patients recorded daily episodes of vomiting (number and time) and degree of nausea and anorexia. They also recorded side effects such as peripheral neurology, sedation, hot flushing, headache, dry mouth and rash. The side effects were graded by the investigator according to NCI-CTCAE V2.0.

Response criteria

Nausea score No nausea (-); slight nausea but no influence on food intake (+); obvious nausea, influence on food intake (++); serious nausea, no intake of food and patient bedridden (+++).

Antiemetic efficacy Complete response, no emetic episodes and no rescue therapy; partial response, 1-2 emetic episodes; minor response, 3-5 emetic episodes; treatment failure, >5 emetic episodes.

Anorexia score Normal food intake (-); intake of a little solid food (+); liquid diet (++); no food intake (+++).

The complete response rate was calculated as the percentage of complete response for vomiting, and the percentage of (-) for nausea and anoxia. The effective rate was calculated as the percentage of complete response and partial response for vomiting and the percentage of [(-) + (+)] for nausea and anorexia¹⁸.

Statistical analysis

Chi-squared and Fisher's exact test were applied for analysis of categorical variables. If the expected frequency in table cells was under 5 or total sample size was under 20, Fisher's exact test was used. All *P* values were based on two-sided tests. *P* < 0.05 was considered statistically significant. Statistical analysis was performed using statistical software (SPSS for Windows, Ver: 13.0).

Results

Patient characteristics

A total of 52 patients were enrolled from October 2006 to December 2007. All patients completed the study except for 2 patients in group A-B who did not receive the second cycle for bad compliance, and side effects were

moderate in both patients. Fifty patients were evaluated for efficacy, and all 52 patients were included in the toxicological evaluation. Demographic data and patient characteristics are presented in Table 1.

Efficacy on acute nausea

The complete response rates and effective rates of group B for acute nausea (on day 1) were similar to those of group A; differences were not statistically significant (Table 2).

Efficacy on delayed nausea

The complete response rates and effective rates of group B on days 2 through 4 were higher than those of group A (Table 2), and the differences were statistically significant. The complete response rates and effective rates for both groups on day 5 were high and showed no significance.

Table 1 - Demographic characteristics of the two groups (n = 52)

	A-B (n = 26)	B-A (n = 26)
Sex		
Male	18	17
Female	8	9
Median age, yr (range)	55.5 (28-69)	54 (31-70)
ECOG performance status		
0	15	12
1	11	14
Primary tumor		
Gastric cancer	8	13
Colorectal cancer	16	11
Others	2	2

Table 2 - Efficacy of both groups on nausea

Observation period	Group	Nausea score				CRR		ER	
		-	+	++	+++	%	<i>P</i>	%	<i>P</i>
Day 1	A	34	10	6	0	68.0	0.373	88.0	0.505
	B	38	8	4	0	76.0		92.0	
Day 2	A	12	21	17	0	24.0	0.004	66.0	0.009
	B	26	18	5	1	52.0		88.0	
Day 3	A	12	20	16	2	24.0	0.001	64.0	0.005
	B	29	15	4	2	58.0		88.0	
Day 4	A	18	17	12	3	36.0	0.016	70.0	0.053
	B	30	13	7	0	60.0		86.0	
Day 5	A	27	12	10	1	54.0	0.309	78.0	0.050
	B	32	14	4	0	64.0		92.0	

CRR complete response rate, calculated as the percentage of no nausea (-); ER, effective rate, calculated as the percentage of sum of no nausea (-) and slight nausea but no influence on food intake (+), namely [(-) + (+)].

Efficacy on acute vomiting

As shown in Table 3, there was no significant difference between the two groups for the complete response rates and effective rates on day 1.

Efficacy on delayed vomiting

The complete response rates for group B on delayed vomiting were higher than those for group A, as shown in Table 3, and the differences were statistically significant on days 2 and 3. The complete response rates for group B on days 4 and 5 were higher than those for group A, but the differences were not statistically significant.

Efficacy on anorexia

Table 4 shows that the complete response rates on anorexia for group B were higher than those for group A

Table 3 - Efficacy of both groups on vomiting

Observation period	Group	Antiemetic efficacy				CRR		ER	
		CR	PR	MR	F	%	P	%	P
Day 1	A	44	5	1	0	88.0	0.485	98.0	1.000*
	B	47	2	1	0	94.0		98.0	
Day 2	A	33	12	5	0	66.0	0.019	90.0	0.433*
	B	43	5	2	0	86.0		96.0	
Day 3	A	28	14	7	1	56.0	0.035	84.0	0.110
	B	38	9	3	0	76.0		94.0	
Day 4	A	33	11	5	1	66.0	0.068	88.0	0.505
	B	41	5	4	0	82.0		92.0	
Day 5	A	43	5	1	1	86.0	0.182	96.0	1.000*
	B	47	2	1	0	94.0		98.0	

CR, complete response; PR, partial response; MR, minor response; F, treatment failure; CRR, complete response rate; ER, effective rate, the percentage of (CR+PR).

*Continuity correction.

Table 4 - Efficacy of both groups on anorexia

Observation period	Group	Anorexia score				CRR		ER	
		-	+	++	+++	%	P	%	P
Day 1	A	33	12	5	0	66.0	0.271	90.0	0.712*
	B	38	9	3	0	76.0		94.0	
Day 2	A	15	25	10	0	30.0	0.009	80.0	0.084
	B	28	18	3	1	56.0		92.0	
Day 3	A	12	19	17	2	24.0	0.001	62.0	0.000
	B	29	17	2	2	58.0		92.0	
Day 4	A	12	24	11	3	24.0	0.004	72.0	0.022
	B	26	19	5	0	52.0		90.0	
Day 5	A	20	18	11	1	40.0	0.046	76.0	0.004
	B	30	18	2	0	60.0		96.0	

CRR, complete response rate, the percentage of anorexia score (-); ER, effective rate, the percentage of anorexia score [(-)+(+)].

*Continuity correction.

on days 2 through 5, and the differences were statistically significant.

Additional antiemesis drug administration

On day 1 of the two cycles, 3 patients in group A and 2 patients in group B received an additional administration of dexamethasone (10 mg) due to unsatisfactory control. After 24 hr, 14 patients in group A and 6 in group B were administered a rescue dose of dexamethasone ($P = 0.046$). Two patients in group A and 1 patient in group B received metochlopramide/prochlorperazine and support treatment.

Adverse effect

Adverse events occurring in 5% or more of patients in either treatment group are shown in Table 5. Generally, adverse effects were mostly mild to moderate (grade 1-2, NCI-CTC V2.0), and there was no grade 3-4 toxicity in any of the chemotherapy cycles. There was no significance difference in the adverse events of the two treatment groups except for frequency of the sedation, which occurred more frequently in group B than in group A.

Discussion

Development of the 5-HT₃ receptor antagonists represents a significant advance in antiemetic therapy in controlling CINV¹⁹. Preclinical studies have shown that the pharmacological action of ramosetron was long lasting^{20,21}. Moreover, ours and another previous clinical study found that ramosetron showed longer-lasting effects than granisetron^{22,23}.

Although both palonosetron and aprepitant have been shown to be effective to some degree in preventing delayed emesis, lack of adequate CINV control continues to trouble cancer patients. Moreover, neither of the two drugs is commercially available in China, so delayed CINV is still bothersome for Chinese patients.

Even though thalidomide was withdrawn from the market following reports of teratogenicity for pregnant women, its availability in a well-tolerated oral form and its importance of angiogenesis in development, growth,

Table 5 - Summary of adverse events occurring in 5% or more of patients in the two treatment groups [no.(%)]

	Group A (n = 52)	Group B (n = 50)	P
Constipation	12 (23.1)	10 (20)	0.706
Headache	6 (11.5)	5 (10)	0.802
Peripheral neurology	11 (21.2)	9 (18)	0.688
Hot flushing	9 (17.3)	8 (16)	0.859
Sedation/dizziness	5 (9.6)	21 (42)	0.000

In parenthesis, percentage.

and metastasis of malignant tumors prompted the initiation of thalidomide clinical trials in the treatment of cancer. Based on the satisfactory efficiency of thalidomide in controlling nausea and vomiting in pregnant women, we hypothesized that thalidomide may be effective in controlling delayed CINV in cancer patients. This is the first randomized crossover controlled study in which thalidomide was evaluated for the control of chemotherapy-induced gastrointestinal side effects, and the results confirmed our hypothesis.

Our study was aimed to observe the efficiency of thalidomide in controlling delayed CINV. Therefore, on day 1, antiemetic regimens for both groups were the same, and there was no significant difference between two groups in incidence of acute CINV. In group B, rates of delayed CINV were obviously lower than those in group A on days 2 through 4. Addition of thalidomide increased 34% of complete response rates of delayed nausea and 20% of complete response rates of delayed emesis on day 3. The rates of anorexia were significantly lower for group B than for group A on days 2 through 5. The result was encouraging and showed that addition of thalidomide to ramosetron plus dexamethasone could control delayed CINV satisfactorily and also improve the quality of life. Actually, the chemotherapeutic regimen consisted of 46-hr 5-fluorouracil continuous infusion, so, the gastrointestinal side effects on days 2-3 may also result from acute CINV from 5-fluorouracil. The finding also indicates that thalidomide may also be effective in controlling acute CINV.

On day 1, 3 patients in group A and 2 in group B required additional antiemetic drug administration, which indicated the high efficacy of both regimens on acute nausea and vomiting. However, on days 2 through 5, 14 and 6 patients in group A and B, respectively, received additional antiemetic therapy. The difference between the two groups was significant, which further supported that thalidomide could improve control of delayed CINV.

Most of the clinical trials in cancer have used thalidomide doses of 200 to 800 mg/d¹⁶. In our study, the thalidomide dose of 150 mg orally twice a day was shown to be tolerated in cancer patients. The adverse effects were mostly mild, and there was no grade 3-4 toxicity in any of the chemotherapy cycles. The main complaint was sedation/dizziness (21/50, 42%). In general, thalidomide is a safe, effective antiemetic drug.

In our study, a crossover design was used instead of a parallel design. It is well known that in a crossover study, dropouts tend to occur frequently and a carryover effect is the main shortcoming of a crossover design. Nevertheless, crossover designs have been widely used in antiemetic studies. The dropout rate in our study was low (3.8%, 2/52), and the washout period was long enough to avoid the presence of a carryover effect. Thus, the efficacy of cycles 1 and 2 could be combined for analysis.

Additional larger randomized, double-blind, multicenter trials are indicated to confirm the clinical value of thalidomide in the control of delayed CINV.

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