ประสิทธิผลของการปรับสูตรยานำก่อนให้เคมีบำบัดต่อการเกิดปฏิกิริยาภูมิไวเกิน ในผู้ป่วยมะเร็งลำไส้ใหญ่และลำไส้ตรงที่ได้รับยาเคมีบำบัดสูตร FOLFOX: การศึกษานำร่อง
Effectiveness of Modified Premedication Regimen on Hypersensitivity Reactions in Colorectal Cancer Patients Receiving FOLFOX Chemotherapy: A Pilot Study

นิพนธ์ต้นฉบับ

สมชาย เป็กเตปิน[1], พัทธมน สนิท[1], วีรวรรณ พรหมคำ[1], ทิพย์เนตร มหามิตร[2], ภาณุวัฒน์ ไตรธรรม[3], ณัฐ นาเอก[4] และ นทพร ชัยพิชิต[4]*

[1] นิสิตหลักสูตรเภสัชศาสตรบัณฑิต สาขาวิชาบริบาลเภสัชกรรม
[2] กลุ่มงานเภสัชกรรม
[3] แผนกศัลยกรรม
[4] สาขาวิชาบริบาลเภสัชกรรม
[1 และ 4] คณะเภสัชศาสตร์ มหาวิทยาลัยพะเยา อ.เมือง จ.พะเยา 56000
[2 และ 3] โรงพยาบาลพะเยา อ.เมือง จ.พะเยา 56000

* **Corresponding author:** natapohn.ch@up.ac.th

Original Article

Somchai Pektepin[1], Pattamon Sanit[1], Weerawan Promkam[1], Tipnet Mahamit[2], Panuwat Traitham[3], Nat Na-Ek[4] and Natapohn Chaipichit[4]*

[1] Student in Doctor of Pharmacy Program in Pharmaceutical Care
[2] Pharmacy Department
[3] Surgery Department
[4] Department of Pharmaceutical Care
[1 and 4] School of Pharmaceutical Sciences, University of Phayao, Phayao, 56000, Thailand
[2 and 3] Phayao Hospital, Muang, Phayao, 56000, Thailand

* **Corresponding author:** natapohn.ch@up.ac.th

บทคัดย่อ

วัตถุประสงค์: การศึกษานำร่องนี้มีวัตถุประสงค์เพื่อศึกษาความชุกและปัจจัยเสี่ยงของการเกิดปฏิกิริยาภูมิไวเกิน และเพื่อเปรียบเทียบประสิทธิผลของการให้ยานำก่อนให้เคมีบำบัดระหว่างสูตรดั้งเดิมและสูตรที่มีการปรับปรุง **วิธีการศึกษา:** ผู้วิจัยได้ทำการศึกษาเชิงสังเกตย้อนหลัง เก็บข้อมูลผู้ป่วยโรคมะเร็งลำไส้ใหญ่และลำไส้ตรงจำนวน 58 คน ที่มีอายุ 20 ปีขึ้นไปและได้รับยาเคมีบำบัดสูตร FOLFOX-4 หรือ mFOLFOX-6 ณ โรงพยาบาลพะเยา ตั้งแต่เดือนมกราคม พ.ศ. 2560 ถึงมกราคม พ.ศ. 2563 ยานำก่อนให้เคมีบำบัดสูตรดั้งเดิม (สูตร 1) ประกอบด้วยยา dexamethasone 8 - 12 mg ยานำสูตรปรับปรุง (สูตร 2) ประกอบด้วยยา dexamethasone 20 mg ร่วมกับยา ranitidine 50 mg และ chlorpheniramine maleate 10 mg **ผลการศึกษา:** ความชุกของการเกิดปฏิกิริยาภูมิไวเกินโดยรวมของยาทั้งสองสูตรมีค่าประมาณ 31.0% โดยส่วนใหญ่ (38.9%) เกิดเพียงครั้งเดียว และมักเป็นความรุนแรงในระดับปานกลาง (ระดับ 2) ผู้ป่วยที่ได้รับยานำเคมีบำบัดสูตร 2 มีอัตราการเกิดปฏิกิริยาภูมิไวเกินน้อยกว่าการได้รับยานำสูตร 1 ถึง 85% อย่างมีนัยสำคัญทางสถิติ (Incidence Rate Ratio 0.15; 95% CI 0.05 to 0.42; *P*-value <0.001) การมีอายุน้อยกว่า 60 ปี เป็นเพศหญิง มีประวัติได้รับยาเคมีบำบัดแพลทินัมรุ่น 3 และการได้รับยาเคมีบำบัดสูตร mFOLFOX-6 มีแนวโน้มที่จะสัมพันธ์กับการเกิดปฏิกิริยาภูมิไวเกินแต่ไม่มีนัยสำคัญทางสถิติ **สรุป:** การเพิ่มขนาดยา dexamethasone ร่วมกับการให้ยา ranitidine และ chlorpheniramine maleate ลดอัตราการเกิดปฏิกิริยาภูมิไวเกิน ทั้งนี้ด้วยขนาดตัวอย่างที่เล็ก จึงยังต้องทำงานวิจัยที่มีขนาดตัวอย่างใหญ่ขึ้นเพื่อใช้ยืนยันผลการศึกษาดังกล่าวต่อไป

คำสำคัญ: มะเร็งลำไส้ใหญ่และลำไส้ตรง, ปฏิกิริยาภูมิไวเกิน, ยาเคมีบำบัด, ยานำก่อนให้เคมีบำบัด

Abstract

Objective: To examine the prevalence of and factors associated with hypersensitivity reactions (HSRs) and to compare the effectiveness of traditional chemotherapy premedication to a modified preventive regimen. **Method:** In this retrospective observational study, we used data from 58 colorectal cancer patients aged 20 years or older receiving FOLFOX-4 or mFOLFOX-6 at Phayao Hospital from January 2017 and January 2020. The traditional premedication (Regimen 1) consisted of dexamethasone 8 - 12 mg. The modified premedication (Regimen 2) consisted of dexamethasone 20 mg plus ranitidine 50 mg and chlorpheniramine maleate 10 mg. **Results:** The prevalence of HSR in both preventive regimens was approximately 31.0%. Most of HSR incidences (38.9%) occurred only once with moderate severity (Grade 2). Rate of HSR with Regimen 2 was 85% lower than that of Regimen 1 with statistical significance (incidence rate ratio = 0.15; 95% CI = 0.05 to 0.42; *P*-value < 0.001). Age less than 60 years, being female, having a history of receiving third-generation platinum chemotherapy, and receiving mFOLFOX-6 chemotherapy tended to be related to HSR. However, the associations did not reach statistical significance. **Conclusion:** Increasing dexamethasone dosage while adding ranitidine and chlorpheniramine maleate into the regimen may reduce the HSR rate. Due to the small sample size, a larger study is required to confirm these findings.

Keywords: colorectal cancer, hypersensitivity reaction, chemotherapy, premedication

Journal website: http://ejournals.swu.ac.th/index.php/pharm/index

Introduction

Colorectal cancer was the third most common cancer reported in Thailand by the National Cancer Institute in 2017.[1] There are three main methods of treating cancer, including surgery, radiation, and chemotherapy. Chemotherapy can cause non-serious side effects, e.g., nausea and vomiting, which might diminish patients' quality of life.[2] Moreover, there are serious side effects that could be life-threatening. For example, hypersensitivity reactions (HSRs), which are unexpected toxicity reactions, are common in patients receiving chemotherapy containing platinum, taxanes, asparaginase, procarbazine, monoclonal antibodies, and epipodophyllotoxins.[3]

Oxaliplatin is a derivative of the divalent oxalate salt–platinum compound. It forms a covalent bond with purine, a

DNA base, and inhibits DNA synthesis leading to cancer cells' death.[4] In the United States of America, oxaliplatin is indicated for adjuvant treatment of stage III colon cancer with 5-fluorouracil (5-FU) and leucovorin (this combination is known as a FOLFOX regimen) in patients who have undergone complete resection of their primary tumor and for treatment of advanced colorectal cancer.[5,6] In Thailand, oxaliplatin is also indicated for the use with FOLFOX regimens, which are approved for patients younger than 75 years old who have been diagnosed with stage III colorectal cancer and have Eastern Co-operative Oncology Group (ECOG) performance status of 0 - 1.[7] Recommendations for dosage and administration of oxaliplatin is similar for FOLFOX-4 and mFOLFOX-6 regimens.[8] These treatment methods are effective, and the cancer-free rate at three years after chemotherapy was 5.3% higher when oxaliplatin was combined with FOLFOX-4 than when oxaliplatin was not used.[9] The response rate of patients receiving an mFOLFOX-6 and oxaliplatin regimen as first-line therapy was 33.3%.[10]

Although oxaliplatin is an effective treatment, the incidence rate of HSRs associated with oxaliplatin is high. Between 8.9% and 22.2% of patients treated with oxaliplatin develop HSRs.[11-15] HSRs are most common between the third[11] and eighth cycles of chemotherapy.[14,15] Importantly, recurrent HSRs can be life-threatening and are associated with an increased risk of death.[16] 10.3% of patients treated with FOLFOX-4 exhibit HSRs, of which 2.9% are severe.[9] In patients receiving the mFOLFOX-6 regimen, the HSR rate is higher with 19.5% of patients exhibiting HSRs, of which 4.5% are severe.[10] The Health Product Vigilance Center (HPVC) of Thailand reported that the cumulative count of adverse drug events (ADEs) associated with oxaliplatin from 1984 to 2019 was 1,246. Of these events, 150 ADEs were probable HSRs.[17] A single-site study in Thailand reported an HSR-rate of 8.3% in patients receiving the FOLFOX-4 or XELOX regimens. Reactions commonly occurred between the second and eighth chemotherapy cycles. Patients received dexamethasone (4 - 10 mg/dose) and ondansetron or metoclopramide as premedication before chemotherapy.[18]

Several factors are associated with increased oxaliplatin-related HSRs including female sex[11-13], history of atopic diseases[13], age younger than 60 years old[19], not receiving premedication before chemotherapy[14], receiving less than 12 mg/dose of dexamethasone[15], serum albumin level higher than 4.1 g/dL[20], and low levels of lactate dehydrogenase and monocyte.[13] Even with a general agreement that premedication to prevent HSRs is necessary, it has been difficult to separate the impacts of these factors.

Particular interest has been on the role of corticosteroids (e.g., dexamethasone). Corticosteroids with or without antihistamines are commonly administered to patients before receiving oxaliplatin to prevent HSRs. Higher corticosteroid doses may lower HSR incidence.[20] In one study, the prevalence of HSRs in patients receiving high dose dexamethasone (20 mg) was 7%. By contrast, patients receiving only 8 mg of dexamethasone exhibited a prevalence of 20%.[21]

The efficacy and safety of premedication to prevent HSRs during FOLFOX chemotherapy has never been reported for Thai populations. In March 2019, the dexamethasone dose used for premedication at Phayao Hospital was raised from 12 mg to 20 mg. In addition, ranitidine 50 mg and chlorpheniramine maleate (CPM) 10 mg were added to the premedication regimen. All premedications were administered 30 minutes before receiving the FOLFOX regimen. This pilot study aimed to examine the efficacy of premedication and investigate factors associated with HSRs in colorectal cancer patients receiving FOLFOX chemotherapy regimens.

Methods

Patient selection

This retrospective observational cohort study collected HSR data from colorectal cancer patients who received FOLFOX regimens at Phayao Hospital between January 2017 and January 2020. Eligible patients were those 20 years old or older and received at least one cycle of the FOLFOX-4 or mFOLFOX-6 regimen.

This study was approved by the University of Phayao Human Ethics Committee (Study number 2-167-62) and the Phayao Hospital Human Ethics Committee (Study number 62-01-027).

Chemotherapy and premedications

Patients received HSR preventive medications administered 30 minutes before chemotherapy in each cycle. There were two preventive regimens as follows. The traditional premedication (Regimen 1) was administered to patients receiving chemotherapy from January 2017 to February 2019. In Regimen 1, dexamethasone 8 - 12 mg was diluted in 5%

dextrose (D5W) 100 ml and administered by intravenous infusion for 30 minutes.

The modified premedication (Regimen 2) was administered to patients receiving chemotherapy since March 2020. Patients received similar preventive medications as in Regimen 1 in the initial chemotherapy cycles. However, in the late chemotherapy cycles, individuals received dexamethasone 20 mg plus ranitidine 50 mg diluted in D5W 100 ml and administered by intravenous infusion for 15 minutes. Then, chlorpheniramine maleate 10 mg was also administered by intravenous infusion. This modification was initiated at the sixth cycle in patients receiving chemotherapy from March to August 2019 and at the fifth cycle in those receiving chemotherapy since September 2019.

Data collection

Data were collected from the pharmaceutical care database of chemotherapy patients at Phayao Hospital. This database included the patient's general information (gender, age, body mass index, body surface area, underlying disease, history of drug allergy, and treatment history with third generation platinums), cancer information (type and staging), chemotherapy regimen and preventive medications, hypersensitivity reactions in each cycle (signs and symptoms, physical examinations, and laboratory tests), and management of hypersensitivity reaction in each cycle.

Definition of hypersensitivity reactions and outcome evaluation

Hypersensitivity reactions were identified when patients presented with at least one sign or symptom after receiving FOLFOX chemotherapy. These were transient flushing, transient rash, urticaria, fever, difficulty breathing, abnormal blood pressure, shiver, nausea, vomiting, and edema caused by allergy. The study outcome was the HSR rate during 12 cycles of chemotherapy.

The severity of hypersensitivity reactions was evaluated according to the National Cancer Institute's standard terminology criteria for adverse events (NCI-CTCAE) version 4.03.[22] Five severity gradings include Grade 1: mild symptoms; intervention not indicated, Grade 2: moderate or localized symptoms; intervention or infusion interruption indicated, Grade 3: severe or prolonged symptoms following initial improvement; hospitalization indicated for clinical

sequelae, Grade 4: life-threatening consequences; urgent intervention indicated, and Grade 5: death (Table 1).

Table 1 The evaluation criteria of the severity of hypersensitivity reactions according to the NCI CTCAE v4.03.

Grade	Hypersensitivity reaction	Anaphylaxis
1	o Transient flushing	-
	o Transient rash	
	o Drug fever (body temperature < 38 °C)	
	o Intervention not indicated	
2	o Intervention or infusion interruption indicated	-
	o Responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics)	
	o Prophylactic medications indicated for less than 24 hours	
3	o Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion)	o Symptomatic bronchospasm, with or without urticaria
	o Recurrence of symptoms following initial improvement	o Parenteral intervention indicated
	o Hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	o Allergy-related edema/angioedema o Hypotension
4	o Life-threatening consequences	o Life-threatening consequences
	o Urgent intervention indicated	o Urgent intervention indicated
5	o Death	o Death

Data analysis

Frequency and percentage were calculated for population characteristics and prevalence of HSRs. Mean, standard deviation or median and interquartile range (IQR) were calculated for continuous variables according to data distribution. Differences in baseline characteristics between those receiving regimen 1 and 2 were tested using chi-squared, Fisher's exact test, or independent t-tests as appropriate. A Kaplan-Meier graph was plotted to analyze the cumulative incidence of the first episode of HSR and compare the incidences between regimens using a log-rank test.

Factors associated with HSR were analyzed using univariate zero-inflated poisson (ZIP) regression analysis. ZIP regression was used because most patients did not exhibit HSRs for most chemotherapy cycles (5% of cycles). These factors, which were reported in previous studies[12,13,19,23], included sex, age, body mass index, body surface area, underlying disease, history of drug allergy, history of taking the third-generation platinum analogs, absolute neutrophil count (ANC), type and stage of the cancer, chemotherapy regimen, history of postponing chemotherapy for at least one cycle, and mean oxaliplatin dose and mean dexamethasone dose per each chemotherapy cycle.

The effectiveness of the modified preventative regimen in reducing the prevalence and rate of HSRs was compared to

the traditional preventative regimen using ZIP regression analysis. After initial analysis, the model was further adjusted for age, gender, cancer staging, history of drug allergy, and chemotherapy regimen. Because ZIP models are a combination of both a logistic regression model and a poisson regression model, these analyses yielded two sets of parameter estimates. One set of parameters associated with the logistic regression predicted whether or not a patient would have any HSRs. This estimate was interpretable as an odds ratio (OR). The other set of parameters associated with the poisson regression predicted how many HSRs a patient would have per cycle given that they had any. This estimate was interpretable as an incidence rate ratio (IRR). The statistical analysis was performed based on a complete-case analysis using STATA version 14 (StataCorp LP), and the two-sided significance level was set as 0.05 (5%).

Results

Patient characteristics and the prevalence of hypersensitivity reactions

From January 2017 to January 2019, 58 colorectal cancer patients received FOLFOX treatment at Phayao Hospital. The number of male and female patients was equal (50.0% each). Their average age was 55.7 ± 12.8 years old. Pretreatment Regimen 1 and Regimen 2 were administered to 42 patients (72.4%) and 16 patients (27.6%), respectively. The proportion of patients reporting previous drug allergies was higher for patients receiving Regimen 1 than Regimen 2 (21.4% vs. 0.0%, P-value = 0.05). Patients in receiving Regimen 2, which was defined as those patients receiving increased dexamethasone in later chemotherapy cycles did receive a higher mean dose of dexamethasone than patients receiving the traditional pretreatment (10.90 ± 1.79 vs. 015.72 ± 1.42 mg, respectively, P-value < 0.001). Other characteristics were not different between groups (Table 2).

The prevalence of at least one HSR during across all chemotherapy cycles was 31% (18 patients). The prevalence between treatment regimens was not different (Regimen 1 = 31.0% vs. Regimen 2 = 31.2%; P-value = 0.98). The median cycle at which HSR occurred in Regimen 1 and Regimen 2 patients were 9 (8,11) and 6 (5,9), respectively. Most patients experienced only one episode of HSR (38.9%), and most of these (73.0%) had grade 2 severity (Table 3). Most HSR involved skin (37.8%) and respiratory systems (15.6%). In

general, patients in both regimens tended to experience between zero and two episodes of hypersensitivity reactions (Table 3).

Table 2 Patient characteristics classified by the preventive regimen.

| Patient characteristics	N (%)		All patients (n= 58)	P-value
	Regimen 1 (n = 42)	Regimen 2 (n = 16)		
Gender				
Male	22 (52.4)	07 (43.8)	29 (50.0)	0.56*
Age (years)				
Mean ± SD	54.81 ± 13.12	58.00 ± 11.98	55.69 ± 12.79	0.40$
Median	57.50	53.50	55.00	0.36†
(IQR)	(27.00 - 84.00)	(42.00 - 76.00)	(27 - 84)	
Proportion of patients age < 60-year-old	23 (54.8)	9 (56.2)	32 (55.2)	0.92*
Body mass index (kg/m^2), mean ± SD	20.50 ± 3.40	21.17 ± 2.49	20.68 ± 3.17	0.47*
Body surface area (m^2), mean ± SD	01.51 ± 0.21	01.51 ± 0.12	01.51 ± 0.19	0.92#
Presence of underlying disease	15 (35.7)	05 (31.2)	20 (34.5)	0.75*
History of drug allergy	09 (21.4)	00 (0.0)	09 (15.5)	0.05Ψ
Presence of the third-generation platinum history	01 (2.4)	02 (12.5)	03 (5.2)	0.12*
Mean ANC (log scale), mean ± SD	07.85 ± 0.37	07.90 ± 0.51	07.86 ± 0.41	0.71*
Cancer types				0.59Ψ
Colon cancer	25 (59.5)	9 (56.2)	34 (58.6)	
Rectal cancer	15 (35.7)	05 (31.2)	20 (34.5)	
Colorectal cancer	02 (4.8)	02 (12.5)	04 (6.9)	
Cancer staging				0.70Ψ
Stage 2	14 (33.3)	07 (43.8)	21 (36.2)	
Stage 3	18 (42.9)	05 (31.2)	23 (39.7)	
Stage 4	10 (23.8)	04 (25.0)	14 (24.1)	
Receiving FOLFOX-4	40 (95.2)	14 (87.5)	54 (93.1)	0.30*
Postpone receiving chemotherapy ≥ 1 cycle	27 (64.3)	07 (43.8)	34 (58.6)	0.16*
Number of chemotherapy cycle				0.70*
< 12 cycles	7 (16.7)	2 (12.5)	9 (15.5)	
12 cycles	35 (83.3)	14 (87.5)	49 (84.5)	
Dose, mean ± SD				
Mean oxaliplatin dose (mg/cycle)	128.88 ± 27.80	127.93 ± 13.21	128.62 ± 24.53	0.86#
Cumulative dose of oxaliplatin (mg)	1,384.62 ± 403.02	1,468.44 ± 272.39	1,407.75 ± 371.20	0.45*
Mean dexamethasone dose (mg/cycle)	010.90 ± 1.79	015.72 ± 1.42	012.23 ± 2.75	< 0.001$

* Chi-squared test, $ Independent t-test with equal variance, † Wilcoxon-rank sum test, # Independent t-test with unequal variance, and Ψ Fisher's exact test

Table 3 The prevalence and severity of hypersensitivity reactions.

Hypersensitivity reactions (HSR)	N (%)		All patients (n = 58)	P-value
	Regimen 1 (n = 42)	Regimen 2 (n = 16)		
Number of affected patients	13 (31.0)	05 (31.2)	18 (31.0)	0.98*
Median cycles (Interquartile range)	9 (8 - 11)	6 (5,9)6 (5,9)		
Number of HSR episode				> 0.99$
1	5 (38.5)	2 (40.0)	7 (38.9)	
2	4 (30.8)	1 (20.0)	5 (27.8)	
3	2 (15.4)	2 (40.0)	4 (22.2)	
4	2 (15.4)	0 (00.0)	2 (11.1)	
Severity grading of HSR, number				0.70†
Grade 1	1 (3.7)	0 (0.0)	1 (2.7)	
Grade 2	20 (74.1)	7 (70.0)	27 (73.0)	
Grade 3	6 (22.2)	3 (30.0)	9 (24.3)	
Symptoms of HSR				
Transient rash	7 (25.9)	1 (05.6)	8 (17.8)	
Urticaria	5 (18.5)	4 (22.2)	9 (20.0)	
Breathing difficulty	4 (14.8)	3 (16.7)	7 (15.6)	
Transient flushing	4 (14.8)	0 (0.0)	4 (8.9)	
Flushing	3 (11.1)	2 (11.1)	5 (11.1)	
Hypotension	2 (7.4)	2 (11.1)	4 (8.9)	
Shivering	1 (3.7)	2 (11.1)	3 (6.7)	
Nausea	1 (3.7)	1 (5.6)	2 (4.4)	
Vomiting	0 (0.0)	2 (11.1)	2 (4.4)	
Edema from allergy	0 (0.0)	1 (5.6)	1 (2.2)	

* Chi-squared test, $ Fisher's exact test (Grades 3 and 4 combined), † Fisher's exact test (Grades 1 and 2 combined)

Across patients, the first HSR episodes in Regimen 1 and Regimen 2 were found in cycles 5 and 4 of chemotherapy, respectively (*P*-value = 0.94). The peak incidence of HSRs in Regimen 1 and Regimen 2 were found in cycles 9 and 5, respectively. In Regimen 1, the HSR occurrences were commonly found in cycle 5 - 11. Similarly, the HSR occurrences in regimen 2 were found in cycles 4, 5, 9, and 11 (Figure 1).
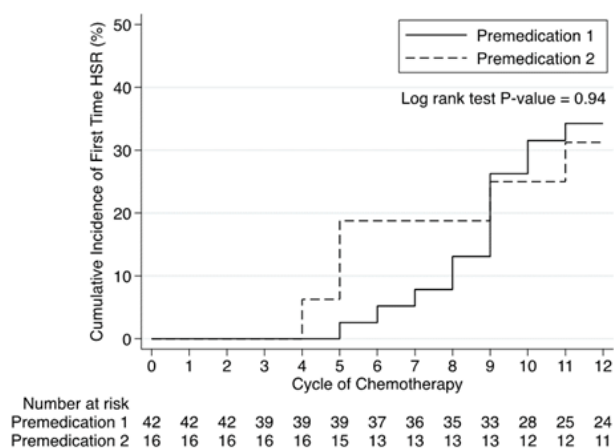
Figure 1 The cumulative incidence of the first episode of hypersensitivity reactions in patients receiving Regimen 1 and Regimen 2 preventive medications (N = 58).

Factors associated with hypersensitivity reactions

Univariate exploration of factors possibly associated with HSR yielded no significant results (Table 4). No differences were found in ANC between patients who developed HSRs and those who did not (Figure 2).
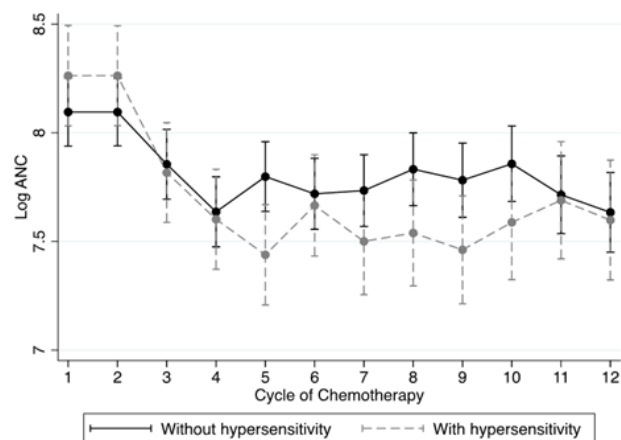
Figure 2 Mean absolute neutrophil count (logarithmic scale) in patients with and without hypersensitivity reactions varying by chemotherapy cycles (N = 58).

Table 4 Univariate analysis of factors associated with hypersensitivity reactions (N = 58).

Factors	OR (95%CI)*	IRR (95%CI)[†]	*P*-value[§]
Age (year)	1.01 (0.96 to 1.06)	1.00 (0.99 to 1.03)	0.85
60 years and older	1.00 (Reference)	1.00 (Reference)	0.94
Younger than 60	0.64 (0.16 to 2.52)	1.03 (0.44 to 2.40)	
Gender			
Male	1.00 (Reference)	1.00 (Reference)	0.63
Female	0.52 (0.13 to 2.10)	1.23 (0.52 to 2.88)	
Body mass index (kg/m²)	0.85 (0.67 to 1.07)	1.01 (0.91 to 1.12)	0.82
Body surface area (m²)	0.08 (0.00 to 12.24)	0.54 (0.03 to 8.58)	0.66
Presence of underlying disease			
No	1.00 (Reference)	1.00 (Reference)	0.87
Yes	0.56 (0.13 to 2.50)	0.93 (0.40 to 2.17)	
History of drug allergy			
No	1.00 (Reference)	1.00 (Reference)	0.86
Yes	3.87 (0.31 to 47.88)	0.85 (0.13 to 5.44)	
Presence of the third-generation platinum history			
No	1.00 (Reference)	1.00 (Reference)	0.30
Yes	0.83 (0.05 to 14.70)	2.17 (0.60 to 7.91)	
Mean ANC (log scale)	2.15 (0.33 to 13.87)	0.62 (0.23 to 1.67)	0.35
Cancer types			
Colon cancer	1.00 (Reference)	1.00 (Reference)	0.18
Rectal cancer	2.99 (0.57 to 15.54)	0.74 (0.24 to 2.28)	
Colorectal cancer	N/A	0.24 (0.05 to 1.01)	
Cancer staging			
Stage 2	1.00 (Reference)	1.00 (Reference)	0.22
Stage 3	0.81 (0.13 to 4.96)	1.18 (0.38 to 3.64)	
Stage 4	1.46 (0.23 to 9.24)	2.33 (0.78 to 6.98)	
Chemotherapy regimen			
FOLFOX-4	1.00 (Reference)	1.00 (Reference)	0.59
mFOLFOX-6	0.11 (0.00 to 4.63)	1.36 (0.47 to 3.98)	
Postpone receiving chemotherapy ≥ 1 cycle			
No	1.00 (Reference)	1.00 (Reference)	0.10
Yes	1.57 (0.26 to 9.37)	2.22 (0.80 to 6.17)	
Mean oxaliplatin dose (mg/cycle)	1.00 (0.90 to 1.12)	1.01 (0.92 to 1.12)	0.80
Mean cumulative dose of oxaliplatin (per 100 mg)	0.94 (0.74 to 1.20)	0.95 (0.81 to 1.11)	0.54
Mean dexamethasone dose (mg/cycle)	1.11 (0.87 to 1.42)	1.01 (0.87 to 1.16)	0.91

Note: N/A = not applicable
* Odds ratio (OR) of never had hypersensitivity reactions.
[†] Incidence rate ratio (IRR) of hypersensitivity reaction rate.
[§] *P*-value from the likelihood ratio statistic comparing between each model and an empty model using Zero-inflated poisson regression.

The effectiveness of the preventive medications

The HSR prevalence for regimen 1 was 31.0%, and the HSR rate for Regimen 2 was 31.2% (*P*-value = 0.98). The overall incidence was 0.055 HSR episodes per chemotherapy cycle in Regimen 1 and 0.053 HSR episodes per chemotherapy cycle in Regimen 2. ZIP regression revealed that the odds ratio (95%CI) and the incidence rate ratio (95%CI) were 0.84 (0.20 to 3.57) and 1.15 (0.46 to 2.86), respectively. An adjusted model found that Regimen 2 was associated with HSR reduction when comparing with Regimen 1 (incidence rate ratio (95%CI) = 0.15 (0.05 to 0.42), *P*-value < 0.001). However, the odds ratio was not different from 1 (Table 5).

Table 5 Effectiveness of the preventive medications (N = 58).

Preventive medications	OR (95%CI), *P*-value of hypersensitivity reactions	
	Unadjusted model	Fully adjusted model*
Regimen 1	1.00 (Reference) 0	1.00 (Reference)
Regimen 2	0.84 (0.20 to 3.57), *P*-value = 0.81	1.00 X 10^{16}†, *P*-value = 0.99

Preventive medications	IRR (95%CI), *P*-value of hypersensitivity reaction rate	
	Unadjusted model	Fully adjusted model*
Regimen 1	1.00 (Reference)	1.00 (Reference)
Regimen 2	1.15 (0.46 to 2.86), *P*-value = 0.77	0.15 (0.05 to 0.42), *P*-value < 0.001

Note: CI: Confidence interval, OR: Odds ratio, IRR: Incidence rate ratio,

* Fully adjusted model was adjusted for age, gender (60 years and older), cancer staging, history of drug allergy, and chemotherapy regimen (FOLFOX-6 or mFOLFOX-6).

† OR of the fully adjusted model = 1.00 X 10^{-16} (95% CI e$^{-22568.1}$ to e$^{22494.42}$).

Discussions and Conclusion

We reported a pilot study of 58 colorectal cancer patients treated with FOLFOX regimens at Phayao Hospital from January 2017 to January 2020. The prevalence of hypersensitivity reactions was 31.0%, many of which (38.9%) occurred only once and had moderate severity, requiring symptomatic treatment or abrupted chemotherapy infusion (Grade 2). Patients should be closely monitored to prevent HSR. In our data, there were no particular risk factors that predicted increased risk for HSRs. The overall rate of HSRs was not different between patients treated with high doses of dexamethasone plus ranitidine and CPM compared to patients receiving dexamethasone monotherapy.

In the present study, 31.0% of all patients in both preventive regimens experienced at least one episode of hypersensitivity reactions during their chemotherapy treatment. This prevalence was higher than in previous studies. In patients who received oxaliplatin-based chemotherapy, including the FOLFOX or XELOX regimen, the overall incidence of HSR was 13.4% when low-dose dexamethasone (10 mg) and chlorpheniramine maleate 10 mg injection was given before the oxaliplatin administration.[14] The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC), the largest trial of the FOLFOX-4 regimen, reported that 10.3% of all patients given oxaliplatin-based chemotherapy had experienced allergic reactions.[9]

Past studies have found that differences in the prevalence of HSR and its onset may be related to the preventive medications and the chemotherapy regimen. A retrospective study by Kidera et al reported that patients receiving the mFOLFOX-6 regimen reported that HSRs occurred in 20% of subjects receiving low-dose dexamethasone (8 mg), whereas only 7% of patients developed HSRs after receiving high-dose dexamethasone (20 mg) with diphenhydramine 50 mg and famotidine 20 mg.[21] In the present study, chlorpheniramine maleate and ranitidine were administered to patients. Nonetheless, the efficacy of different antihistamines in HSR prevention has not been reported. Most patients in the present study were given the FOLFOX-4 regimen. By contrast, Kidera et al's patients were given the mFOLFOX-6 regimen[21], and the FOLFOX or XELOX regimens were used in one study that reported a 13.4% rate of HSRs.[14] These differences in chemotherapy treatments may explain why patients in the present study exhibited higher levels of HSRs.

The timing of HSRs observed in the present study was earlier than has been observed elsewhere. The first cycles in which HSRs occurred in regimens 1 and 2 were the fifth and fourth cycles, respectively, and the median timing of HSRs occurred at cycle 9 (IQR = 8 - 11) and 6 (IQR = 5 - 9), respectively. A previous report found that the eight cycle is the median time to develop HSR in patients receiving dexamethasone 10 mg and chlorpheniramine 10 mg.[14] The early onset of HSR in Regimen 2 patients might be associated with the delayed administration of antihistamines, which were initiated after cycle five (in Regimen 1 group) and cycle 4 (in Regimen 2 group). The increased prevalence of HSR and the occurrence of hypersensitivity reported in earlier cycles of chemotherapy reflect the need to develop a more effective premedication regimen. Additionally, genetic variants may have influenced the differences in HSRs.[20,23] The HSR prevalence in Asian patients given the FOLFOX-4 regimen ranged between 4.0% and 25.0%, whereas the prevalence in four Western studies ranged between 6.3% and 10.0%.[24] Further studies should investigate factors associated with HSRs in the Thai population.

Our results were disconcordant with a previous study by Kidera et al.[21] While Kidera et al found that high-dose dexamethasone was associated with a significant decrease in both the overall prevalence of HSRs and the incidence of HSRs per chemotherapy cycle, we did not find differences in either measure as a function of pretreatment regimen. However, a zero-inflated poisson regression model using several patient characteristics as covariates did find that there was an 85% reduction in the incidence rate ratio of HSRs per chemotherapy cycle as a result of the high-dose dexamethasone and antihistamines treatment. This result must be interpreted with caution as it is not clear why the set of covariates used yielded a significant result when models

using other sets of covariates did not always yield significant results. One reason for the lack of significant results may be the small sample size in the present study compared with Kidera et al (58 patients vs. 181 patients, respectively). The present study also employed different statistical analyses.[21] Another difference was the chemotherapy regimen. All patients in the previous study were given the mFOLFOX-6 regimen,[21] while over 94.0% of patients in this study were given the FOLFOX-4 regimen. Also, differences in adverse events reporting were documented between the two regimens.[25]

Previous reports have shown associations between HSRs and various factors, including being younger than 60-year-old, being female, having a drug allergy history, receiving the stop-and-go regimen, and undergoing salvage therapy.[12,13,19,23] In our data, none of these associations were apparent, but this may have been due to a low sample size. Previous studies have also found HSRs to be associated with neutrophil, monocyte, lactate dehydrogenase[13], and serum albumin.[20] In the present study, absolute neutrophil count (ANC) was not different between patients with and without HSRs. A previous report demonstrated that neutrophils were more stimulated in HSR patients. The mechanism of this reaction, however, remains unclear.[26]

This is the first study reporting the efficacy of the premedication to prevent chemotherapy-related hyper-sensitivity reactions in Thai patients given the FOLFOX regimen. There were some limitations worth mentioning. First, even though Phayao Hospital is a relatively large general hospital with 400 beds, only 58 cancer patients were eligible in the present study. Consequently, it was found that only 10% of statistical power was achieved. Second, we retrospectively collected data from the pharmaceutical care records that were not explicitly designed for research purposes. Therefore, some laboratory results were missing during HSRs. For example, monocyte, lactate dehydrogenase[13] and serum albumin[20] were not available.

As this is only a pilot study, it may be limited in its clinical application. However, the statistical analysis in our study helps determine a method for selecting a model to analyze data with excessive zero-values (i.e., no events). We also calculated the sample size required to have at least 80% statistical power to detect differences based on the effect size of 1.15, we found that 350 patients would be required. Extension of the study period and increasing the number of study settings can help achieve the sample size.

The incidence rates of hypersensitivity reactions were not different between traditional and modified preventive medications. However, increasing the dose of dexamethasone combined with ranitidine and chlorpheniramine maleate as the preventive medication tended to be more beneficial than the lower dose of dexamethasone premedication in the decrease of HSR frequency and HSR rate in the later cycle of chemotherapy. Nonetheless, a larger study is needed to confirm our findings.

References

1. Saengkrajang S, Laowahutanon P, Sangariyavanich E, Phetcharit W. Hospital-based cancer registry 2017. Bangkok. Pornsup Printing, 2018: p. 2. (in Thai)

2. Oudomphon N, Rat-inthong P. Study of hematological effects from using oxaliplatin in combination with other anticancer drugs in in-patients with colorectal cancer of the national cancer institute of Thailand. *Thai Cancer J* 2008;28(1):34-2843. (in Thai)

3. Zanotti KM, Markman M. Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Saf* 2001;24(10):767-779.

4. Gammon D, Bhargava P, McCormick MJ. Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist* 2004;9(5):546-549.

5. Pagani M, Bonadonna P. Skin test protocol for the prevention of hypersensitivity reactions to oxaliplatin. *Anticancer Res* 2014;34(1):537-540.

6. Price TJ, Segelov E, Burge M, et al. Current opinion on optimal treatment for colorectal cancer. *Expert Rev Anticancer Ther* 2013;13(5):597-611.

7. The National Committee on Drug System Development. National list of essential medicines. 2017. (Accessed on May. 29, 2020, at http://dmsic. moph.go.th/index/download/782) (in Thai)

8. National Health Security Office. Manual of cancer treatment guideline in adults 2018 for obtaining health service fee in the National Health Security System. Nonthaburi. Sahamitr Printing and Publishing, 2018: pp. 87-88. (in Thai)

9. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; 350(23):2343-2351.

10. Matsumoto S, Nishimura T, Kanai M, et al. Safety and efficacy of modified FOLFOX6 for treatment of metastatic or locally advanced colorectal cancer. A single-institution outcome study. *Chemotherapy* 2008;54(5):395-403.

11. Parel M, Ranchon F, Nosbaum A, et al. Hypersensitivity to oxaliplatin: clinical features and risk factors. *BMC Pharmacol Toxicol* 2014;151-156.

12. Kim BH, Bradley T, Tai J, Budman DR. Hypersensitivity to oxaliplatin: an investigation of incidence and risk factors, and literature review. *Oncology* 2009;76(4):231-238.

13. Seki K, Senzaki K, Tsuduki Y, et al. Risk factors for oxaliplatin-induced hypersensitivity reactions in Japanese patients with advanced colorectal cancer. *Int J Med Sci* 2011;8(3):210-215.

14. Shen Y, Li C, Liu W, et al. Clinical Analysis of Hypersensitivity Reactions to Oxaliplatin Among Colorectal Cancer Patients. *Oncol Res* 2018;26(5): 801-807.

15. Yamauchi H, Goto T, Takayoshi K, et al. A retrospective analysis of the risk factors for allergic reactions induced by the administration of oxaliplatin. *Eur J Cancer Care* 2015;24(1):111-116.

16. Park HJ, Lee JH, Kim SR, et al. A New practical desensitization protocol for oxaliplatin-induced immediate hypersensitivity reactions: A necessary and useful approach. *J Investig Allergol Clin Immunol* 2016;26(3):168-176.

17. Health Product Vigilance Center, FDA. Spontaneous report of adverse drug reaction 2019. Bangkok. Aksorn Graphic and Design Publishing Limited Partnership, 2019: pp. 3674-3680. (in Thai)

18. Uitrakul S, Aksornwong S. Oxaliplatin hypersensitivity reaction: Case analysis from Maharaj Nakhon Sri Thammarat Hospital. *Thai Cancer J* 2012;32(3).104-110. (in Thai)

19. Mori Y, Nishimura T, Kitano T, et al. Oxaliplatin-free interval as a risk factor for hypersensitivity reaction among colorectal cancer patients treated with FOLFOX. *Oncology* 2010;79(1-2):136-143.

20. Nishihara M, Nishikura K, Morikawa N, Yokoyama S. Factors Influencing the Appearance of Oxaliplatin-Induced Allergy. *Biol Pharm Bull* 2017; 40(12):2105-2109.

21. Kidera Y, Satoh T, Ueda S, et al. High-dose dexamethasone plus antihistamine prevents colorectal cancer patients treated with modified FOLFOX6 from hypersensitivity reactions induced by oxaliplatin. *Int J Clin Oncol* 2011;16(3):244-249.

22. National Cancer Institute Cancer Therapy Evaluation Program (CTEP). Common Terminology Criteria for Adverse Events (CTCAE)v4.03. 2010. (Accessed on Aug. 10, 2019, at https://ctep.cancer.gov/protocol Development/electronic_applications/ ctc.htm#ctc_40) (in Thai)

23. Makrilia N, Syrigou E, Kaklamanos I, Manolopoulos L, Saif MW. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. *Met Based Drugs* 2010;2010207084.

24. Sugihara K, Ohtsu A, Shimada Y. Safety analysis of FOLFOX4 treatment in colorectal cancer patients: a comparison between two Asian studies and four Western studies. *Clin Colorectal Cancer* 2012;11(2):127-137.

25. Kashi ASY, Razzaghdoust A, Rakhsha A. A comparative study of treatment toxicities between FOLFOX 4 and modified FOLFOX 6 in iranian colorectal cancer patients. *Iran J Cancer Prev* 2017;(1)e9429.

26. Francis A, Bosio E, Stone SF, Fatovich DM, Arendts G, Nagree Y, et al. Neutrophil activation during acute human anaphylaxis: analysis of MPO and sCD62L. *Clin Exp Allergy* 2017;47(3):361-370.