RESEARCH ARTICLE

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Validation of Steroid-Sparing Therapy in Patients Receiving Oxaliplatin-based Chemotherapy: A before-and-after Prospective Observational Study

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Abstract

Background and Objective: Although steroids are useful antiemetics, various moderate-to-severe chemotherapy-induced adverse events are observed. Although steroid-sparing antiemetic therapy is beneficial for moderate emetic risk, studies on only oxaliplatin-based regimen have not been fully evaluated. Therefore, this prospective observational study aimed to assess the usefulness of steroid-sparing antiemetic therapy for the second and subsequent courses of chemotherapy. **Methods:** Eligible patients who received a moderate emetic risk oxaliplatin-based chemotherapy regimen at Komaki City Hospital between January 2019 and March 2022 were switched to steroid-sparing antiemetic therapy after the second course. Steroid-sparing antiemetic therapy consisted of switching from granisetron to palonosetron on day 1 and discontinuing steroids on days 2–3. Complete response (CR; no emesis and no rescue medication), nausea and vomiting incidence, rescue use, and food intake were recorded by a pharmacist before the next chemotherapy session and compared before and after steroid-sparing antiemetic therapy. **Results:** In total, 10 patients were included with a median age of 74 years; six were male. CR rate was 70.0% before and 80.0% after steroid-sparing antiemetic therapy, with no significant difference between the two groups. None of the patients experienced worsening nausea or vomiting after steroid-sparing antiemetic therapy. The nausea was transient in all patients with nausea and was managed via abortive rescue treatment with oral administration of metoclopramide. There was no increase in side effects after steroid sparing. **Conclusion:** Based on the proven efficacy and safety in this patient population, we recommend the implementation of steroid-sparing therapy after the second course.

Keywords: Chemotherapy-induced nausea and vomiting- Dexamethasone- Moderately emetogenic chemotherapy

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a major adverse event during chemotherapy that affects the patient's quality of life and directly impacts the continuation of chemotherapy, making its prevention pertinent [1-2].

Chemotherapeutic agents are classified into four groups according to emetic risk, and various guidelines have recommended antiemetic regimens for each group [3-6]. Particularly, moderate emetic chemotherapy (MEC) regimens are defined as those presenting with a risk of nausea and vomiting in 30–90% of patients. A 5-hydroxytryptamine 3 (5-HT3) receptor antagonist plus dexamethasone (DEX) is recommended for prevention of acute (within 24 h of chemotherapy administration) emesis and DEX alone for at least 2 days to control delayed (>24 h after administration) emesis [3-6].

Corticosteroids such as DEX have long been used as effective antiemetics [7]; however, medical experts have expressed concerns regarding the adverse effects of repeated dosing because of their side effects, including elevated blood sugar and insomnia [8]. Recently, antiemetic therapies involving steroid conservation on days 2–3 by intensifying non-steroidal antiemetic therapy have been assessed and introduced into routine clinical practice [9]. Komatsu et al. evaluated the benefit of steroid-sparing antiemetic therapy on days 2–3 by switching from granisetron, a first-generation 5-HT3 receptor, to palonosetron, a second-generation 5-HT3 receptor, for MEC regimen and reported non-inferiority of the steroid-sparing antiemetic therapy [10]. Palonosetron has a higher selective affinity and longer half-life than first-generation 5-HT3 antagonists [11], indicating its potential to control late-onset CINV. However, although the study included a large number of patients on oxaliplatin-based regimens,

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there was a mix of patients on irinotecan-based regimens and carboplatin, which is known to be more emetogenic and has been reclassified as a highly emetogenic risk regimen in foreign guidelines.

Moreover, only a few studies have examined steroid-sparing antiemetic therapies, including oxaliplatin-based regimens [10,12]. However, no reports have focused exclusively on oxaliplatin-based regimens. Thus, the evidence regarding benefits of steroid-sparing therapy appears to be insufficient. Therefore, we switched to day 2–3 steroid-sparing antiemetic therapy by replacing granisetron with palonosetron for all patients on oxaliplatin-based MEC-risk regimens at our institution starting from April 2022.

Consequently, this prospective observational study aimed to implement steroid-sparing antiemetic therapy for the second and subsequent courses of chemotherapy and evaluate its usefulness.

Materials and Methods

Study patients and design

This was a single-center, prospective, observational study of patients who received steroid-sparing antiemetic therapy during the second and subsequent courses of chemotherapy. With the consensus of gastroenterologists and surgeons, since April 2022, we have introduced steroid-sparing antiemetic therapy in oxaliplatin-based MEC regimens for gastrointestinal cancer, excluding patients with severe CINV and those receiving antiemetic therapy not compliant with clinical guidelines. In addition, for patients who had already been receiving oxaliplatin-based regimens prior to April 2022, the antiemetic regimen was changed to a steroid-sparing approach after the second course. We planned this study based on the rationale that evaluating the impact of modifying the antiemetic regimen within the same patient would provide valuable insights.

All patients eligible for a change to steroid-sparing antiemetic therapy received an explanation from a hospital pharmacist assigned to the outpatient chemotherapy unit regarding the standardized change in antiemetic regimen. The steroid-sparing regimen was administered only to those who provided informed consent. Exclusion criteria included patients who did not consent to the change to steroid-sparing antiemetic therapy, those receiving antiemetic treatment not compliant with clinical guidelines, age < 18 years, and those experiencing nausea or vomiting due to organic causes such as brain metastasis, tumor infiltration of the bowel, or other gastrointestinal abnormalities.

The following patient background data were collected from medical records at the time of data analysis: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), cancer type, regimen, history of diabetes, relative dose intensity of anticancer drugs, concomitant medications that may affect antiemetic efficacy (anxiolytics, antipsychotics, and antihistamines), and laboratory data. The relative dose intensity of the anticancer drugs was calculated by excluding molecular-targeted drugs.

This study was conducted in accordance with The Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects issued by the Japanese government after approval by the Institutional Review Board of Komaki City Hospital (Approval No. 221002).

Antiemetic treatment

Before April 2022, patients were administered guideline-recommended antiemetic therapy comprising 9.9 mg of injectable DEX and 2 mg of oral granisetron before chemotherapy administration (day 1) and 8 mg DEX orally on days 2–3 [6]. In our hospital, we use a single dose of 2 mg oral granisetron, a less expensive 5-HT3 receptor antagonist, because it provides total antiemetic control comparable to that via intravenous ondansetron (32 mg) in patients receiving highly emetogenic cisplatin-based chemotherapy [13]. The steroid-sparing antiemetic therapy received 9.9 mg dexamethasone i.v. and 0.75 mg palonosetron i.v. on day 1, and no DEX on days 2–3. Metoclopramide 5 mg was prescribed as a rescue medication, one pill, up to three times a day, at a time if symptoms remained.

Evaluation of the control of CINV

Pharmacists were responsible for providing drug information and safety precautions and monitoring adverse drug reactions, including CINV, to patients in our outpatient chemotherapy center. They interviewed patients using a checklist on the next course of chemotherapy to determine if they had post-chemotherapy-related events, such as nausea and vomiting, food intake, constipation, and hiccups, which were recorded. Nausea was rated on a 4-point Likert scale (no, mild, moderate, or severe) according to the examination checklist, and anorexia was used to determine whether the patient consumed more than half of his or her food intake. Vomiting and adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. The primary efficacy endpoint was set at the complete response rate (CR). Additionally, the following efficacy endpoints were collected: incidence of nausea and vomiting in the acute (within 0-24 hours), delayed (after 24 h to 120 h), and overall phases, use of relief medication with the expectation of antiemetic effects, and presence of anorexia. The CR rate was defined as the percentage of patients who did not have an emetic event and did not receive antiemetic medication.

Statistical analysis

This study was based on the hypothesis that there is no clinically significant difference in the CR rate between the standard antiemetic doublet regimen of granisetron and DEX and the steroid-reducing regimen consisting of palonosetron and single-day DEX, both administered in the context of L-OHP-based chemotherapy. Previous studies have reported CR rates for both regimens ranging from 64.9% to 82.5% [10,12]. Based on this, we set a non-inferiority margin of 10% and used a within-subjects comparison to test the hypothesis. According to a sample size calculation using McNemar's test with a two-sided significance level of 0.05 and a power of 80%, a minimum of 10 patients was required. Fisher's exact probability

test, χ^2 test, and paired t-test were used to analyze patient characteristics for each group. The CR rate and incidence of nausea, which are indicators of efficacy, were analyzed using the χ^2 test. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics. All reported p-values were two-sided, with a value of $p < 0.05$ considered statistically significant [14].

Results

Patients

During the study period, 13 patients who received an oxaliplatin-based MEC regimen as first-line chemotherapy underwent steroid-sparing from the second course onward. The final analysis included 10 patients with colorectal cancer, excluding 3 patients who underwent a reduction in chemotherapy dosage simultaneously with the steroid-sparing antiemetic therapy. The median number of courses in which steroid-sparing therapy was initiated was 7 (2–33). The baseline patient characteristics are presented in Table 1. Of the 10 patients, six were males (60.0%) with a median age of 74 (62–78) years. None of the patients received anxiolytics (including those used to treat insomnia), antipsychotics such as olanzapine, or antihistamines such as diphenhydramine. One patient had a history of diabetes mellitus and a recent HbA1c level of 6.7%. There were no significant differences in laboratory data before and after steroid sparing, except for total bilirubin (Table 2).

Table 1. Patient's Characteristics

Characteristics (n=10)	All patients
Age, years	74 (62–78)
Sex, (male/female)	6/4
Performance Status	
0–1	7 (70)
2	3 (30)
Tumor type	
Colorectal cancer	9 (90)
Gastric cancer	1 (10)
Chemotherapy regimen	
CAPOX	3 (30)
CAPOX + Bev	4 (40)
SOX + Bev	1 (10)
SOX + Her	1 (10)
mFOLFOX + Bev	1 (10)
Concomitant medications	
Aprepitant	0
Anxiolytics	0
Antipsychotics	0
Antihistamines	0
RDI at the start of steroid sparing, %	
L-OHP	85 (60–100)
5-FU based treatment	100 (50–100)

Relative dose intensity: L-OHP, oxaliplatin; 5-FU, fluorouracil. Data are presented as n (%) or medians (min–max).

Changes in antiemetic effect due to steroid-sparing

The overall CR rate was 70% before steroid-sparing and 80% after steroid sparing (Figure 1) (p=1). Table 3 shows the items evaluated other than nausea before and after steroid-sparing therapy. Vomiting did not occur before or after steroid sparing. Two patients experienced mild nausea, whereas one presented with a moderate degree of nausea before steroid sparing. The nausea was transient in both patients and was managed using abortive rescue treatment with oral administration of metoclopramide. These patients were satisfied with the results and did not request additional antiemetic treatment; therefore, steroid-sparing was implemented. After steroid sparing treatment, in the first patient, mild nausea including anorexia completely resolved, whereas the second patient maintained a consistent level of nausea comparable to that observed before steroid sparing.

Steroid-related adverse events, insomnia, and elevated blood glucose levels remained unchanged after steroid-sparing therapy. In addition, hiccups and agitation did not occur before steroid sparing treatment. Constipation, a 5-HT3-related adverse event, remained unchanged after steroid sparing.

Discussion

Our results reaffirm that steroid sparing during the

Table 2. Patient's Laboratory Data before and after Steroid Sparing

Characteristics (n=10)	Before steroid sparing	After steroid sparing	p-value
Baseline Laboratory Data			
Serum albumin, g/dL	3.75 (3.4 – 4.5)	3.8 (3.4 – 4.6)	0.44
Serum creatinine, mg/dL	0.83 (0.56 – 1.47)	0.89 (0.64 – 1.37)	0.28
AST, U/L	23.4 (14.7 – 62.0)	26.7 (17.2 – 74.3)	0.15
ALT, U/L	14.1 (7.8 – 55.4)	17.2 (8.2 – 64.8)	0.21
Total bilirubin, mg/dL	0.65 (0.3 – 1.5)	1.1 (0.3 – 2.1)	< 0.01
Casual blood sugar, mg/dL	106.0 (72.1 – 175.5)	107.4 (76.1 – 167.9)	0.84
Serum sodium, mEq/L	141.5 (136.5 – 144.5)	142.4 (136.0 – 147.1)	0.65

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Data are presented as median (min–max).

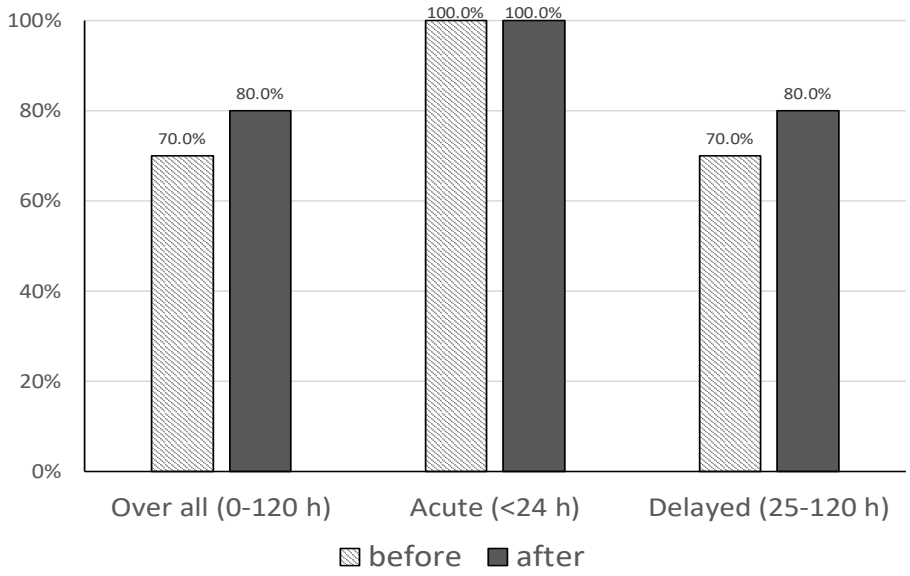

Figure 1. CR rate before and after Steroid-Sparing

Table 3. Secondary Efficacy Endpoints and Adverse Events before and after Steroid Sparing

Characteristics (n=10)	Before steroid sparing	After steroid sparing	p-Value
Secondary efficacy endpoints			
Vomiting	0	0	1
Nausea, Likert scale			
No	7 (70)	8 (80)	1
Mild	2 (20)	1 (10)	
Moderate	1 (10)	1 (10)	
Severe	0	0	
Anorexia	3 (30)	2 (20)	1
Salvage therapies			
Metoclopramide for rescue medication	3 (30)	2 (20)	-
Others	0	0	
Adverse events			
Constipation	7 (70)	7 (70)	1
Hiccup	0	0	1
Insomnia	5 (50)	5 (50)	1
Agitation	0	0	1

Data are numbers (%).

course of the study may not affect CINV in patients without severe nausea and vomiting receiving oxaliplatin-based MEC regimens for gastrointestinal cancer. These results support previously reported results [10,12] and indicate that similar results may be obtained with oxaliplatin-based regimens alone. Unfortunately, owing to the limited number of patients, we were unable to confirm the benefits of steroid sparing in reducing elevated blood glucose, improving insomnia, or improving stuttering; however, we believe that the avoidance of repeated steroid administration may reduce future adverse effects. Patients receiving cumulative steroid doses may experience more severe adverse events, which highlights the potentially harmful effects of short-term prophylactic DEX administration in patients receiving consecutive emetogenic chemotherapy courses [15-16]. Thus, effective approaches to reduce patient exposure to corticosteroids have become a hot topic in clinical research on CINV. From a healthcare economics perspective, the reduction in drug costs from steroid sparing is very low; however, if steroid-induced diabetes and steroid-induced insomnia can be prevented, healthcare costs can be significantly reduced. Therefore, implementation of this program is of importance from a healthcare economics perspective.

A notable aspect of this study was the tapering of antiemetic therapy after the second course. Although the advent of new antiemetic agents has made it possible to administer several combinations of antiemetic agents, overmedication has become a problem in terms of adverse events and medical economics. Therefore, we believe that

establishing a method to reduce the dose of antiemetic drugs after the second course, should be focused on in future studies.

This study had a high CR rate and a low incidence of nausea, and we intended the text to represent these results as superior to those previously reported. However, we discovered that this was not the intended outcome. We propose a change to the text below. Please review it. "Both the Complete Response (CR) rate and the incidence of nausea in this study demonstrated superior outcomes compared to those previously reported [10, 12, 17], which may be because the study included patients without severe nausea or vomiting. Moreover, L-OHP-based regimens, which are considered MEC-risk regimens, can cause severe nausea and vomiting in some patients. Therefore, in such patients and in those with multiple known emetic risk factors, such as female sex and age [5-6], we do not recommend the steroid-sparing approach to replace granisetron with palonosetron. Instead, steroid sparing with olanzapine or aprepitant, as is done in regimens with high emetogenic risk, could be considered for such patient populations. However, further studies are needed to determine whether these practices are justified.

Nevertheless, the current study had several limitations. First, the median number of steroid-sparing courses was seven, indicating that the patient population was relatively accustomed to receiving the same chemotherapeutic regimen. This may indicate that many patients in this population are accustomed to the pattern of adverse anticancer drug events and do not have high anxiety about these events, including nausea and vomiting. Thus, it is important to consider patients' concerns and provide explanations when implementing steroid sparing in the early stages. Second, this study had a small sample size and the results were from a single center, which may limit the generalizability of the findings. The sample size calculated based on a within-subjects comparison of pre- and post-treatment measures was 10 patients. Although the sample size is small, we believe that the results obtained in this study hold significant value. However, future studies should address variations in factors such as the use of the targeted agent bevacizumab and cancer types. To further validate these findings, a multicenter observational study designed to provide a more consistent set of background factors would be desirable. Third, this study included patients who had received at least one course of an L-OHP-based regimen, excluding those who had experienced severe CINV prior to the implementation of steroid sparing. Therefore, further studies are needed to evaluate whether steroid sparing can be implemented for patients whose CINV is not sufficiently controlled after the first course of treatment. Third, this study included patients with controlled CINV after the administration of an L-OHP-based regimen. Therefore, future studies are required to determine whether similar preservation methods are acceptable when this regimen is administered starting with the first course.

In conclusion, in patients who do not exhibit severe nausea and vomiting on oxaliplatin-based MEC regimens, steroid sparing by switching from granisetron to palonosetron may not affect CINV outcomes. Furthermore, we suggest that the introduction of steroid-sparing therapy be considered in this patient population even after the second course because antiemetic therapy with steroids causes certain side effects. Based on our results, we hope that further studies will be conducted to evaluate the tapering of antiemetic therapy after the second course to accumulate further evidence.

Author Contribution Statement

YY and NW contributed to the study conception and design. AG, HH, TF, and YD conducted the acquisition of data. The first draft of the manuscript was written by YY. NW and AG helped to draft the manuscripts. All authors read and approved the final manuscript.

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Ethical Declaration

This study was designed and conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Komaki City Hospital (Approval No. 221002). Information about the study was provided during the opt-out period, and all patients were given an opportunity to decline participation.

Availability of data

The datasets generated and analyzed during the current study are not publicly available because of privacy and ethical restrictions.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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