

Retrospective Analysis of Chemotherapy-Induced Nausea and Vomiting (CINV) in Colorectal Cancer Patients Treated with Antiemetics

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Abstract

Purpose: The aim of this retrospective study was to clarify the effect of the antiemetics for chemotherapy-induced nausea and vomiting associated with FOLFOX chemotherapy.

Methods: Fifty patients were given FOLFOX as chemotherapy for colorectal cancer, and granisetron were used as first-line antiemetics. The severity of CINV was evaluated using (1) questioning, (2) Common Terminology Criteria for Adverse Events version 4.0, and (3) Multinational Association of supportive care in cancer method for patient self-assessment. When a patient indicated that another antiemetic was desired, granisetron was switched to palonosetron.

Results: Forty two patients did not express a desire for another antiemetic, but eight patients expressed a desire for it. They were evaluated as Grade 2 according to the CTCAE 4.0. The MAT method identified a score of 6 points or more. Granisetron was switched to palonosetron as a second-line antiemetic. The severity of CINV decreased to Grade 1 or less, while the MAT method score decreased to 0 points in 3 patients and ≤ 4 points in 5 patients. None of the 8 patients expressed a desire for another antiemetic.

Conclusion: Granisetron/palonosetron can be thought to have improved the patients' QOL, relieved their anxiety, and contributed to continuation of the chemotherapy.

Keywords: Colorectal cancer; Chemotherapy; Chemotherapy-induced nausea and vomiting; Antiemetic; Palonosetron; Granisetron

Abbreviations: QOL: Quality of Life; CTCAE: Common Terminology Criteria for Adverse Events; CINV: Chemotherapy-Induced Nausea and Vomiting

Introduction

The last 10 years have seen striking advances in chemotherapy for unresectable, advanced, recurrent colorectal cancer. In the early 2000s, the Median Survival Time (MST) was about 14-17 months [1,2], whereas survival has been steadily extended since then, recently reaching approximately 30 months [3,4]. However, conversely, chemotherapy-related adverse reactions due to chemotherapy have become an issue, and it is not unusual for such reactions to decrease patients' Quality of life (QOL). Nausea and vomiting rank high on the list of such chemotherapy-related adverse reactions that especially impact on the daily life of patients and cause anxiety [5,6]. Granisetron is a first-generation 5-HT₃ receptor antagonist and commonly used as a first-line antiemetic. Palonosetron is a second-generation 5-HT₃ receptor antagonist that has recently (April, 2010) gone on the market in Japan. Compared with the first-generation antiemetic, granisetron, palonosetron is characterized by stronger affinity for the 5-HT₃ receptor and a plasma half-life that is 40 hours longer [7]. For these reasons, palonosetron is said to show both acute (up to 24 hours postchemotherapy) and delayed (after 24 hours postchemotherapy) antiemetic activity. However, there have not yet been any reports of studies that investigated the efficacy of palonosetron, the second-generation 5-HT₃ receptor antagonist, in colorectal cancer patients who did not respond sufficiently to the first-generation antiemetic, granisetron. The present retrospective study aimed to clarify the efficiency of the antiemetics.

Materials and Methods

Prior to being given FOLFOX as chemotherapy for unresectable,

advanced, recurrent colorectal cancer, 50 patients were given granisetron (0.75 mg, intravenous) and dexamethasone (4 mg, intravenous) as first-line antiemetics to suppress Chemotherapy-Induced Nausea and Vomiting (CINV). On days 2-4 after starting the chemotherapy, dexamethasone (4 mg) was administered orally (Figure 1). Following the chemotherapy, the following were done: (1) the patient was questioned (i.e., asked whether another antiemetic was desired), (2) the severity of nausea and/or vomiting was evaluated using CTCAE version 4.0 (CTCAE 4.0), and (3) the Multinational Association of supportive care in cancer (MAT) method developed by Multinational Association of Supportive Care in Cancer (MASCC) was used for patient self assessment and recording of the severity of nausea and vomiting [8].

Results

Forty-two patients did not express a desire for another antiemetic. The CTCAE 4.0 classification of nausea/vomiting was Grade 1 or less. The MAT method showed that nausea/vomiting was a score of 3 points or less. Eight patients expressed a desire for another antiemetic (Table 1). Using the CTCAE 4.0, nausea was rated as Grade 2 in all 8 patients, while vomiting was rated as Grade 2 in 3 patients, Grade 1 in 4 patients,

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and Grade 0 in 1 patient. In addition, using the MAT method, the same patients each showed a score of 6 points or higher.

Subsequently, the medication was switched from granisetron to palonosetron as a second-line antiemetic. The CTCAE 4.0 classification of nausea/vomiting decreased to Grade 1 or less in all 8 patients, while the MAT method showed that nausea/vomiting was completely suppressed to a score of 0 points in 3 patients and to a score of 4 points or less in the remaining 5 patients. None of the 8 patients expressed a desire for another antiemetic. There were no serious antiemetic-related adverse effects that were considered to have been caused by palonosetron (Table 2).

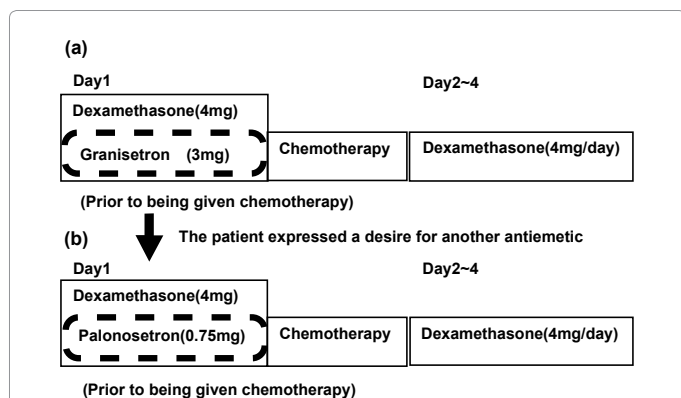


Figure 1: a) Prior to being given chemotherapy, the patients were given granisetron (0.75 mg, intravenous) and dexamethasone (4 mg, intravenous) as first-line antiemetics. On days 2-4 after starting the chemotherapy, dexamethasone (4 mg) was administered orally. b) When the patients expressed a desire for another antiemetic, the medication was switched from granisetron to palonosetron as a second-line antiemetic.

| Age | Sex (grade)* | Granisetron | | Palonosetron | |
|-----|--------------|--------------------|----------------|--------------------|-------|
| | | Nausea/vomit score | **MAT (grade)* | Nausea/vomit score | **MAT |
| 57 | M | (G2)/(G1) | 7 | (G0)/(G0) | 1 |
| 61 | M | (G2)/(G1) | 6 | (G1)/(G0) | 0 |
| 49 | M | (G2)/(G0) | 8 | (G1)/(G0) | 0 |
| 51 | F | (G2)/(G2) | 8 | (G1)/(G0) | 3 |
| 56 | M | (G2)/(G2) | 10 | (G1)/(G0) | 4 |
| 54 | F | (G2)/(G1) | 8 | (G1)/(G0) | 4 |
| 69 | M | (G2)/(G1) | 9 | (G0)/(G0) | 0 |
| 52 | F | (G2)/(G2) | 7 | (G1)/(G0) | 1 |

*CTCAE 4.0 grade

**Maximum: acute and delayed CIMV

Table 1: The results of eight patients expressed a desire for another antiemetic (Forty-two patients did not express a desire for another antiemetic).

| | Grade 1-2 | Grade 3-4 |
|---|-----------|-----------|
| Constipation | 0 (0%) | 0 (0%) |
| Headache | 0 (0%) | 0 (0%) |
| Increased AST concentration | 0 (0%) | 0 (0%) |
| Prolonged ECG QTc | 0 (0%) | 0 (0%) |
| Increased ALT concentration | 0 (0%) | 0 (0%) |
| Angiopathy | 0 (0%) | 0 (0%) |
| Protein urine present | 0 (0%) | 0 (0%) |
| Increased blood bilirubin concentration | 0 (0%) | 0 (0%) |
| Increased gamma-GTP concentration | 0 (0%) | 0 (0%) |
| Constipation | 0 (0%) | 0 (0%) |

Table 2: Toxicity (CTCAE v4.0).

Discussion

The efficacy rates of the mainstay FOLFOX chemotherapy regimen, which consist of combinations of 5-fluorouracil, Oxaliplatin, and leucovorin, in the treatment of unresectable, advanced, recurrent colorectal cancer are generally said to be in the range of about 50-60% [9,10]. Moreover, in recent years, molecularly targeted drugs such as bevacizumab, cetuximab, and panitumumab have been added to the therapeutic arsenal, and the survival rate has been prolonged [3,4,11-13]. However, chemotherapy-related adverse reactions have become an issue, and, in particular, it is said that 70-80% of patients undergoing CINV [14]. Moreover, the patients themselves rank CINV as top issues causing misgivings regarding their cancer chemotherapy [5,6]. In addition, CINV can not only exert bad effects, such as anorexia and malnutrition, but it can also lead to a marked decrease in the patient's QOL and interfere with continuation of the cancer chemotherapy.

In consideration of that situation, the National Comprehensive Cancer Network (NCCN) and American Society for Clinical Oncology (ASCO) have prepared guidelines for antiemetic therapy. In these guidelines, the FOLFOX regimens for unresectable, advanced, recurrent colorectal cancer are classified as Moderate Emetic Risk (MER) in the emesis risk classification. In Japan, many institutions administer granisetron and dexamethasone as first-line antiemetics. However, it is said that these agents are unable to control CINV in some patients. Nevertheless, to date, there have been few reports of studies aimed at identifying effective antiemetics for colorectal cancer patients. The objective of the present study was to generate data in regard to this important aspect of patient care.

Our findings indicated that 84% of patients did not express a desire for another antiemetic, but 16% of patients expressed a desire for it. Control of CINV was poor in 16% of colorectal cancer patients undergoing chemotherapy and that a back-up strategy was needed for management of CINV in such cases. Palonosetron, the second-generation 5-HT₃ receptor antagonist that was used in this study, is characterized by stronger affinity for the 5-HT₃ receptor and a plasma half-life that is 40 hours longer in comparison with granisetron, which is a first-generation antiemetic [7]. Prior to this, Saito et al. performed a comparative study of palonosetron and granisetron as first-line antiemetics for acute and delayed CINV caused by high-emetic-risk chemotherapy in breast cancer patients. They reported that palonosetron was significantly more effective than granisetron in suppressing CINV [15].

The present study focused on 50 patients who received the FOLFOX regimen, which are classified as MEC in the emesis risk classification, to treat unresectable, advanced, recurrent colorectal cancer. CINV for 8 patients was not effectively controlled by granisetron and dexamethasone as first-line antiemetics. However, when palonosetron was given as a second-line antiemetic, replacing granisetron, it was found to safely control CINV in all patients.

Granisetron/palonosetron can be thought to have improved the patients' QOL, relieved their anxiety, and contributed to continuation of the chemotherapy.

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