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Aprepitant Relieves Chemotherapy-induced Inappetance in Colorectal Cancer Patients in the Acute Phase of Moderate Emetogenic Chemotherapy: An Observational Study Based on Self-report Diaries

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Abstract **Background:** The novel drugs aprepitant (APR) and palonosetron are recommended for the treatment of chemotherapy-induced nausea and vomiting. Here, we assessed the effects of these antiemetics using a self-report diary.
Methods: This was a retrospective observational study based on data from 87 patients prospectively collected in 222 self-report diaries. We assessed the effect of vomiting and nausea on the patients' quality-of-life, and food and water intake. A "no event" was treated as a favorable outcome. We compared the rates of no event between the first course of chemotherapy and subsequent courses, as well as among the different emetogenic risks and post-chemotherapy phases. We also studied the effect of APR in a subgroup of colorectal cancer patients receiving moderate emetogenic chemotherapy.
Results: Nearly 90% of patients reported that the vomiting and nausea did not affect their quality-of-life; however, the rate of normal food intake was only 30%-40%. Colorectal cancer patients receiving APR demonstrated a significantly higher rate of normal food intake during the first chemotherapy course than those who did not receive this drug.
Conclusions: APR could relieve this chemotherapy-induced inappetance in colorectal cancer patients in the first course and acute phase of moderate emetogenic chemotherapy.

Key words: antiemesis, palonosetron, food intake, water intake

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a serious problem in cancer patients receiving chemotherapy.[1,2] The guidelines for antiemetics define emetogenic risk by individual chemotherapy agents into high, moderate, low, and minimal emetogenic chemotherapy categories (HEC, MEC, LEC, and MinEC, respectively).[3-5] In a clinical setting, the use of antiemetic therapies is often recommended when HEC and MEC are used. Serotonin receptor antagonists (5-HT_3) and dexamethasone (DEX) have been used routinely as antiemetics, but novel drugs have recently been approved, including aprepitant (APR), a neurokinin-1 antagonist, and palonosetron (PALO), a second-generation 5-HT_3 antagonist. Oral APR and PALO began commercial clinical use in Japan in 2009 and 2010, respectively.

Our hospital first used APR and PALO for patients receiving HEC and MEC in 2010, and at the same time we instigated a self-report diary of emesis and food and water intake, to assess the effectiveness of the new antiemesis drugs.

Current antiemesis guidelines (2011-2012) recommend APR with 5-HT_3 and DEX for HEC and an anthracycline + cyclophosphamide (AC) regimen, and PALO with DEX for MEC.[3-5] However, from 2010 to 2011, our department protocol was to use APR with 5-HT_3 and DEX for both HEC and MEC patients; PALO was used for HEC and AC patients instead of first generation 5-HT_3, and PALO was also used in MEC patients in cases of uncontrollable emesis. This was in the line with the former guidelines.

CINV is divided into two phases of emesis: the acute phase (0-24 h) and the delayed phase (25-120 h). Some trials have shown that both APR and PALO can prevent CINV in both phases.[6-9] In the present study, we studied the antiemesis effect of APR and PALO, based on the self-report diary of chemotherapy patients. APR was used by 35% of chemotherapy patients and PALO by 9%. Unfortunately, because of the small sample size and biases in the group, the PALO data could not be analyzed.

Materials and Methods

Study design

This study was based on a prospective self-report diary collected from chemotherapy patients. The diary was distributed for a year, from October 2010 to October 2011, to patients with cancer of the digestive system (esophageal, gastric, colorectal, or pancreatic), breast, or lung. During this period, our center treated 1664 chemotherapies of cancer patients as inpatients or outpatients, and 222 kept the diary (collection rate: 13.3%). We analyzed the diary data as a retrospective observational study. The variables included the use of APR, the chemotherapy regimen (high, moderate, low, and minimal emetogenic risk), the chemotherapy course (first or subsequent), and the phase of emesis (early or delayed).

Patients and treatment

From October 2010 to October 2011, all chemotherapy patients received a self-report diary. At the time of collection, the hospital ID, age, sex, cancer origin, chemotherapy regimen, and antiemesis drugs used were added to the diary by the medical staff.

We collected 222 diaries, containing the details of 87 patients receiving chemotherapy. The patients' characteristics are shown in Table 2. The most common cancer among them was colorectal cancer (34 of 87 patients and 105 of 222 diaries). Therefore, we analyzed colorectal cancer patients as a subgroup. APR was used in 69% of colorectal cancer patients receiving MEC, so we were able to analyze the antiemetic effect of APR in the subgroup; however, we could not similarly analyze PALO because of insufficient patient numbers.

APR was used for 3 days (day 1: 125 mg and days 2-3: 80 mg). PALO was used at 0.75 mg on day 1, instead of granisetron. The patients receiving HEC and MEC who were not prescribed PALO all used granisetron, and DEX was also used in all cases of HEC and MEC. We did not use a placebo in place of APR; all patients knew that they were receiving additional antiemetic therapy.

Assessments

Each term in the diary was assessed as an event or no event, and each no event ("no effect on quality-of-life", "normal food intake", and "water intake possible") was treated as a favorable outcome. We also recorded the number of vomitings in 5 days (within 120 h). If one diary entry were blank, the medical staff consulted the patient and usually recorded a favorable outcome, because, for most of the cases, a blank meant that there was no problem.

Statistical analyses

Continuous variables were analyzed using the Student's t-test and categorical variables were analyzed using the χ^2 test. The threshold of significance was set at $P < 0.05$.

Results

The structure of the self-report diary is

shown in Table 1. From day 1 to day 7, the patients could record their symptoms of CINV in a multiple-choice format. In addition, the diary had a large blank space for the patient to record the details.

Table 2 shows the characteristics of the 87 patients who completed diaries. The mean age was 67.4 years, 42.2% were male, and 66.3% received chemotherapy as an outpatient. The patients kept, on average, 2.6 diaries each. Their cancer origins were colorectal (39%), gastric (24%), breast (13%), esophagus (8%),

Table 1 Structure of the self-report diary

	Day 1	Day 2	—	Day 7
Date	____/____	____/____		____/____
Vomitings (*n* / day)	____/ day	____/ day		____/ day
Effect of vomiting on quality-of-life	□strong □weak □almost none □none	□strong □weak □almost none □none		□strong □weak □almost none □none
Effect of nausea on quality-of-life	□strong □weak □almost none □none	□strong □weak □almost none □none	—	□strong □weak □almost none □none
Food intake	□none □little □over half □normal	□none □little □over half □normal		□none □little □over half □normal
Water intake	□impossible □normal	□impossible □normal		□impossible □normal

Days 3-6 have been omitted in this Table for simplicity.

Table 2 Chemotherapy patient characteristics

	Patients (*n* = 87)
Age (years)	67.4 ± 8.4
Male (*n*, %)	35 (42.2%)
Chemotherapy received as outpatient (*n*, %)	55 (66.3%)
Number of diaries completed (*n* per patient)	2.6 ± 2.4
Cancer origin (*n*, %)	
Colorectal	34 (39%)
Gastric	21 (24%)
Breast	11 (13%)
Esophagus	7 (8%)
Pancreatic	4 (5%)
Lung	2 (2%)
Undescribed	8 (9%)

The age and number of diaries data are shown as mean ± SD.

pancreatic (5%), lung (2%), and undescribed (9%).

Table 3 shows the details of the chemotherapy and antiemesis regimens among the 222 diaries. The number of the different emetogenic risks was as follows: HEC, 16 (7%); MEC, 105 (47%); LEC, 72 (32%); and MinEC, 29 (13%). The antiemesis drugs used were as follows: APR, 78 (35%); PALO, 20 (9%); DEX, 192 (86%); and granisetron, 172 (77%).

Table 4 shows the CINV outcomes collated from the diaries. The number of vomitings over 5 days, and the proportion experiencing no vomiting and nausea (effect on quality-of-life was checked as none in the diaries), and normal food and water intake (checked as normal in the diaries) are shown according to the emetogenic risk, chemotherapy course (first or subsequent), and post-chemotherapy phase (early or delayed). When comparing the first course of chemotherapy with subsequent courses, there were significantly fewer

Table 3 Chemotherapy and antiemesis regimens

	Total chemotherapies (n = 222)
Chemotherapy regimens (n, %)	
High emetogenic chemotherapy	16 (7%)
CDDP-related regimen (+S-1: 9)	10
FEC (5FU+epirubicin+cyclophosphamide)	4
FP (5FU+CDDP)	2
Moderate emetogenic chemotherapy	105 (47%)
mFOLFOX6-related regimen (+Bmab: 19, +Cmab: 6, +Pmab: 1)	64
FOLFIRI-related regimen (+Bmab: 3, +Cmab: 8, +Pmab: 2)	20
irinotecan-related regimen (+Cmab: 3)	12
Docetaxel+nedaplatin	3
5FU+nedaplatin	5
Paclitaxel+cyclophosphamide	1
Low emetogenic chemotherapy	72 (32%)
Paclitaxel	63
Gemcitabin	7
Docetaxel	1
S-1	1
Minimally emetogenic chemotherapy	29 (13%)
Cmab	15
Vinorelbine	11
Trastuzumab	3
Antiemesis drugs used (n, %)	
Aprepitant	78 (35%)
Palonosetolon	20 (9%)
Dexamethason	192 (86%)
Granisetron	172 (77%)

CDDP: cysplatin, mFOLFOX6: modified FOLFOX6, FOLFIRI: modified FOLFIRI, Bmab: bevacizumab, Cmab: cetuximab, Pmab: panitumumab.

vomitings in first-course patients receiving HEC ($P = 0.01$), and a significantly lower proportion of first-course MinEC patients with no nausea in the delayed phase ($P = 0.04$).

Table 5 shows the subgroup analysis of colorectal cancer patients receiving MEC. The data were compared between those receiving or not receiving APR. In addition to significant differences in the chemotherapy regimens between the groups, there was a significantly higher rate of normal food intake in the early phase of first-course patients receiving APR ($P = 0.04$).

Discussion

In general, our data did not reveal significant differences except for a few variables in

Table 4 CINV-related outcomes

Variables	First course	Subsequent courses	*P* value
High risk (*n*, %)	13	3	
Aprepitant	12 (92%)	2 (67%)	0.23
Palonosetolon	8 (62%)	1 (33%)	0.38
Vomitings (*n* / 5 days)	0.4 ± 0.9	3.0 ± 3.0	**0.01**
No vomiting	12 (92%) / 11 (85%)	3(100%) / 1 (33%)	0.62 / 0.06
No nausea	8 (62%) / 8 (62%)	3 (100%) / 0 (0%)	0.20 / 0.06
Normal food intake	5 (38%) / 3 (23%)	0 (0%) / 0 (0%)	0.20 / 0.36
Normal water intake	13 (100%) / 13 (100%)	3 (100%) / 3 (100%)	- / -
Moderate risk	45	60	
Aprepitant	22 (49%)	38 (63%)	0.14
Palonosetolon	6 (13%)	5 (8%)	0.41
Vomitings (*n* / 5 days)	0.8 ± 3.3	0.0 ± 0.3	0.09
No vomiting	42 (93%) / 40 (89%)	55 (92%) / 55 (92%)	0.75 / 0.63
No nausea	30 (67%) / 24 (53%)	44 (73%) / 31 (52%)	0.46 / 0.87
Normal food intake	31 (69%) / 13 (29%)	40 (67%) / 23 (38%)	0.81 / 0.31
Normal water intake	45 (100%) / 43 (96%)	59 (98%) / 56 (93%)	0.38 / 0.63
Low risk	26	46	
Aprepitant	1 (4%)	0 (0%)	0.18
Palonosetolon	0 (0%)	0 (0%)	-
Vomitings (*n* / 5 days)	0.6 ± 1.9	0.2 ± 0.9	0.25
No vomiting	22 (85%) / 24 (92%)	44 (96%) / 44 (96%)	0.10 / 0.55
No nausea	18 (69%) / 17 (65%)	31 (67%) / 30 (65%)	0.87 / 0.99
Normal food intake	13 (15%) / 11 (42%)	22 (48%) / 17 (37%)	0.86 / 0.66
Normal water intake	24 (92%) / 25 (96%)	46 (100%) / 46 (100%)	0.06 / 0.18
Minimal risk	6	23	
Aprepitant	0 (0%)	0 (0%)	-
Palonosetolon	0 (0%)	0 (0%)	-
Vomitings (*n* / 5 days)	0.0 ± 0.0	0.0 ± 0.0	-
No vomiting	6 (100%) / 6 (100%)	23 (100%) / 23 (100%)	- / -
No nausea	5 (83%) / 4 (67%)	22 (96%) / 22 (96%)	0.29 / **0.04**
Normal food intake	4 (67%) / 4 (67%)	21 (91%) / 19 (83%)	0.12 / 0.39
Normal water intake	6 (100%) / 6 (100%)	23 (100%) / 23 (100%)	- / -

The data for the number of vomitings are presented as mean ± SD. The first and second sets of data refer to the acute phase and the delayed phase, respectively.
No vomiting: effect of vomiting on quality-of-life was none,
No nausea: effect of nausea on quality-of-life was none,
Normal food intake: food intake was normal,
Normal water intake: water intake was normal.

Table 5 CINV-related outcomes in colorectal cancer patients receiving moderate emetogenic chemotherapy

Variables	With aprepitant	Without aprepitant	*P* value
First course (*n*, %)	21	13	
Chemotherapy regimen			
mFOLFOX6-related	19 (90%)	6 (46%)	**0.02**
FOLFIRI-related	2 (10%)	6 (46%)	
Irinotecan-related	0 (0%)	1 (8%)	
Palonosetolon	5 (24%)	0 (0%)	0.06
Vomitings (*n* / 5 days)	0.4 ± 2.0	0.2 ± 0.6	0.63
No vomiting	20 (95%) / 19 (90%)	12 (92%) / 13 (100%)	0.72 / 0.25
No nausea	17 (81%) / 11 (52%)	9 (69%) / 8 (62%)	0.43 / 0.60
Normal food intake	17 (81%) / 7 (33%)	6 (46%) / 3 (23%)	**0.04** / 0.52
Normal water intake	0 (0%) / 20 (95%)	0 (0%) / 13 (100%)	- / 0.43
Subsequent courses (*n*, %)	38	14	
Chemotherapy regimen			
mFOLFOX6-related	32 (84%)	7 (50%)	**0.01**
FOLFIRI-related	6 (16%)	5 (36%)	
Irinotecan-related	0 (0%)	2 (14%)	
Palonosetolon	5 (13%)	0 (0%)	0.15
Vomitings (*n* / 5 days)	0.0 ± 0.0	0.1 ± 0.5	0.10
No vomiting	34 (89%) / 34 (89%)	13 (93%) / 13 (93%)	0.71 / 0.71
No nausea	27 (71%) / 19 (50%)	11 (79%) / 6 (43%)	0.59 / 0.65
Normal food intake	24 (63%) / 14 (37%)	9 (64%) / 3 (21%)	0.94 / 0.29
Normal water intake	37 (97%) / 34 (89%)	14 (100%) / 14 (100%)	0.54 / 0.21

mFOLFOX6: modified FOLFOX6, FOLFIRI: modified FOLFIRI, The data for the number of vomitings are presented as mean ± SD. The first and second sets of data refer to the acute phase and the delayed phase, respectively.
No vomiting: effect of vomiting on quality-of-life was none, No nausea: effect of nausea on quality-of-life was none, Normal food intake: food intake was normal, Normal water intake: water intake was normal.

the post-chemotherapy phase. Actually, there was an only trend for each emetogenic risk group towards worse nausea and vomiting in the first course of chemotherapy compared with in the subsequent courses, however, more than 80-90% of the patients in each group reported that the vomiting had no effect on their quality-of-life. One explanation for this is that most of the cases in MEC and HEC groups had already received APR and/or PALO therapy (88% of HEC patients were treated with APR and 56% with PALO; 57% of MEC patients were treated with APR and 10% with PALO). These antiemesis drugs probably suppressed the CINV events, therefore, anticipatory nausea and vomiting could be also suppressed, and improved quality-of-life.[3]

APR has been shown to prevent CINV in cases of HEC and MEC.[10-16] However, when CINV has been assessed in previous studies, a favorable outcome is usually defined as “no emetic episodes” or “no administration of rescue therapy”. In this study, we added food and water intake to the diary, because these factors could indicate CINV even without overt episodes of emesis. In fact, even the patients who reported no effect on their quality-of-life did show suppressed food intake (only 30-40% reported normal intake); on the

other hand, water intake was not affected by CINV. We believe that the assessment of food intake in a self-report diary is a useful tool to improve the analysis of CINV in cases of no emesis and/or no use of rescue drugs.

Similarly, in our study subgroup of colorectal cancer patients receiving MEC, the vomiting and nausea did not affect the patients' quality-of-life, but food intake in the acute phase of the first course was reduced (P = 0.04). In this subgroup (acute phase of the first course), there were five cases of PALO usage among those who received APR; however, if these PALO cases were removed, food intake was still significantly different between those who did and did not receive APR (normal food intake with APR: 81% vs. without APR: 46%, P = 0.048; data not shown). Therefore, although the current guidelines do not recommend APR for patients receiving MEC,[3-5] it is possible that APR could relieve the inappetance in the acute phase. Because chemotherapy is now often performed as an outpatient procedure, the symptoms experienced during the acute phase of the first chemotherapy course are of great importance to the patient, who is understandably nervous. Giving APR to relieve CINV and stimulate appetite could be very useful in this situation.

Our data did not show a significant antiemetic effect of APR in the delayed phase. However, this may be because of the significant differences among the chemotherapy regimens (most of the patients who were given APR were receiving FOLFOX-related chemotherapy).

This study has some limitations. Firstly, it is based on self-reported diaries; therefore, the records contain a degree of subjectivity and the CINV symptoms could be under- or over-assessed. Secondly, the diary did not record the administration of rescue drugs, and as such, the CINV symptoms were possibly masked in some cases. Thirdly, APR was assessed in only colorectal cancer patients; the other subgroups had insufficient sample sizes.

Conclusions

This observational study, based on self-report diaries, demonstrated chemotherapy-induced inappetance with or without chemotherapy-induced emesis. Aprepitant could relieve this chemotherapy-induced inappetance in colorectal cancer patients in the first course and acute phase of moderate emetogenic chemotherapy.

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Conflict of Interest

The authors state no conflict of interest.

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