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Original Article

Medication Adherence among Colorectal Cancer Patients Receiving Postoperative Adjuvant Chemotherapy : A longitudinal Study

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Abstract

Administration of oral agents is a standard postoperative adjuvant chemotherapeutic regimen in colorectal cancer patients. However, little is known about medication adherence of oral chemotherapy in Japanese patients. This study was aimed to elucidate the current status of medication adherence and identify the factors associated with low adherence to postoperative adjuvant chemotherapy in colorectal cancer patients. Among 81 enrolled patients receiving postoperative adjuvant chemotherapy, 61 patients (oral anticancer agents alone : 33, combination of oral anticancer agents and IV administration : 28) were analyzed. Medication adherence (MMAS-8), and anxiety and depression (HADS) were evaluated longitudinally at 3 time-points (1-2, 3-4, 5-6 months) using questionnaires. Factors associated with low adherence were analyzed by multivariate logistic regression. The median medication adherence score and anxiety and depression score did not change significantly over the 6-months of chemotherapy. At 1-2 months after initiation of treatment, low medication adherence was associated with treatment using oral anticancer agents alone (OR : 9.49) and depression (OR : 1.30). At 5-6 months, treatment with oral anticancer agents alone was also associated with low adherence (OR : 6.39).

To maintain adherence, health care professionals should focus on patients who have higher risk for low adherence by monitoring those receiving oral chemotherapeutic agents alone and patients with depression. Thus, continuous educational and emotional support tailored each patient should be considered from the initiation of chemotherapy.

Key words : colorectal cancer, medication adherence, MMAS-8, postoperative adjuvant chemotherapy, longitudinal study

Introduction

Colorectal cancer is one of the most common malignancies worldwide. In Japan, approximately 370,000 cancer-related deaths were recorded in 2016, with colorectal cancer being the second most common cause[1)]. Adjuvant chemotherapy is administered to patients with high-risk stage II and stage III colorectal cancer to prevent recurrence and improve postoperative prognosis. In general, adjuvant chemotherapy is recommended to start by 4 to 8 weeks after surgery and to continue for 6 months[2)]. This treatment schedule puts additional burden on patients as

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they receive the chemotherapy as a new treatment at outpatient clinics while also returning to the society after surgery.

There are three types of postoperative adjuvant chemotherapy : (1) oral administration only, (2) a combination of oral and intravenous (IV) administration, and (3) IV administration only[2]. This study focused on adherence to oral postoperative adjuvant chemotherapy in patients treated with oral administration only and a combination of oral and IV administration. Oral chemotherapy requires fewer hospital visits than intravenous therapy, entailing lesser lifestyle changes than the combination of oral and IV administration. To maintain high levels of medication adherence, patients need to not only comply with treatment requirements, but also proactively participate in the treatment. It has been reported that most patients undergoing anticancer treatment prefer oral to intravenous therapy[3]. Hence, as the oral chemotherapy is increasing, improvement of adherence in this group of patients will be a key issue in cancer care. Poor medication adherence and failure to reach the desired treatment goal could result in poor prognosis and increased medical costs[4].

Previous studies on medication adherence using a patient's self-reported data or a medication event monitoring system reported that the non-adherence rates for capecitabine treatment regimens ranged 9%-25%[5~7]. In Japan, a recent longitudinal study on 338 colorectal cancer patients treated by a combination therapy of oral and IV administration (CapeOX) reported that a median adherence rate was high (94% in the first cycle, and 98% in the final cycle)[8]. Another cross-sectional study reported compliance rate of 77% in 104 patients[9]. Poor adherence was reported to be associated with many factors such as the complexity of the treatment, side effects, inconvenience of visiting the hospital, cost, dissatisfaction with the treatment, forgetfulness, and depression[10~12]. Conversely, factors associated with high adherence included good relationship with healthcare providers, social support, milder adverse events, and adequate knowledge on medication[10]. Some studies suggested that adverse events did not necessarily lead to reduced medication adherence[11], however, results have been inconsistent[12].

Furthermore, regimens for postoperative adjuvant chemotherapy differ in Japan with those in other countries due to the differences in overall survival[2], health insurance system, and economic backgrounds. For example, in Japan, all citizens are covered by universal healthcare systems having unlimited access to standard medical cares. Thus, to develop a support program to improve adherence to postoperative adjuvant chemotherapy in patients with colorectal cancer, we first need to understand the current status of their adherence and identify the factors associated with poor medication adherence, particularly psychological conditions, social backgrounds, knowledge on the treatment, and complexity of the treatment.

The objectives of this study were to elucidate the status of adherence to postoperative adjuvant chemotherapies and to analyze factors associated with low medication adherence in patients with colorectal cancer.

Materials and Methods

1. Study design

This is a prospective longitudinal study based on self-report questionnaires administered during outpatient visits at two cancer centers and one general hospital in Japan. Patients were followed, and the questionnaires were handed out in the hospital or sent through mail. The surveys were conducted from October 2014 to March 2017 at 3 time points ; 1-2 months, 3-4 months, and 5-6 months after starting postoperative adjuvant chemotherapies. This study was approved by the Institutional Review Board of University of Occupational and Environmental Health, Japan (Approval number : H26-116) and that of all the collaborating institutions.

2. Participants

The inclusion criteria for our study was patients who (1) had clinical stage II or III disease who had started adjuvant chemotherapy with oral anticancer agents with/without intravenous administrations after curative surgery for colorectal cancer, (2) were aged 20 years and above, and (3) had the intellectual ability to fill out the self-administered questionnaire. After providing verbal and written information about the study, a written informed consent was obtained from all participants prior to enrollment. The standard treatment regimens for participants were either 1) oral treatment with uracil/tegafur with leucovorin (UFT + LV) that was administered only orally or 2) oral capecitabine plus intravenous oxaliplatin (CapeOX). In the UFT + LV regimen, one cycle consisted of 3 times a day oral administration for 28 days, followed by a week of off-drug period. In the CapeOX regimen, the anticancer agents were administered both orally (capecitabine) and intravenously (oxaliplatin). One cycle consisted of intravenous oxaliplatin on day 1 at an outpatient clinic and oral administration of capecitabine twice a day for 14 days followed by a week of off-drug period. It is recommended that these regimens continue for 6 months.

3. Questionnaires

1) Medication adherence

In this study, medication adherence was evaluated through a self-report questionnaire using Morisky Medication Adherence Scale-8 (MMAS-8)[13]. The MMAS-8 is a scale designed to evaluate the psychosocial characteristics of adherence, social support, and satisfaction with care related to medication adherence. A systematic review and meta-analysis showed that MMAS-8 had acceptable internal consistency and reproducibility[14] and it has been used in more than 200 studies since its development in 2009. The MMAS-8 score ranges from 0 to 8, where higher points indicate better adherence. Patients were classified into three groups for analysis based on their total adherence scores : the low adherence group comprised patients who scored less than 6 points ; the moderate adherence group, patients who scored from 6 points to less than 8 points ; and the high adherence group, 8 points. A Japanese translation of the MMAS-8 was developed by Dr. Morisky in collaboration with the Mapi Institute. A license agreement for the use of the copyrighted MMAS-8 is available from Donald E. Morisky.

2) Anxiety and depression

To evaluate the state of anxiety and depression of the patients, a Japanese version of the Hospital Anxiety and Depression Scale (HADS) for general outpatients (registration #13105116) was used[15]. HADS consists of 14 items : 7 items for anxiety (HADS-A) and 7 items for depression (HADS-D). Higher total scores indicate more severe depression and anxiety. Each item is scored from 0 to 3, and the total score ranges from 0 to 21 points. The patients were stratified into those with normal (≦ 7 points), mild (8 to ≦ 10 points), moderate (11 to ≦ 14 points), and severe (15 to ≦ 21 points) using the HADS. The validity and reliability of the Japanese version of HADS had been assessed previously[16][17] with calculated Cronbach's α of 0.73 to 0.81.

3) Adverse events

The occurrence of adverse events was surveyed using a 10-item questionnaire of the Japanese version of Common Terminology Criteria for Adverse Events v4.0 from the Japan Clinical Oncology Group[18]. The adverse events surveyed were fatigue, anorexia, altered taste, constipation, nausea, diarrhea, rash, fever, stomatitis, and hand-foot syndrome. Basic information on the patient's cancer (e.g., diagnosis, location, stage, duration, date when treatment was started, and regimen) was collected from electronic medical records.

4. Statistical analysis

Descriptive statistics were calculated in accordance with the MMAS-8 and HADS scoring

manuals. The Mann-Whitney U-test, chi-square test, and Fisher's exact test were used to compare the 2 groups. Repeated measures ANOVA were used to analyze the longitudinal changes in medication adherence during the treatment. In the analysis of factors associated with low levels of medication adherence, individuals with low and moderate MMAS-8 scores were grouped together and categorized as the low adherence group, following the method in a previous study[19]. The low adherence group and the high adherence group were used as dependent variables. Factors associated with low adherence at each time point were analyzed via logistic regression analysis. A univariate regression analysis was used to determine significant differences between the high and low adherence group for the following independent variables : age (≤ 65 years vs. > 65 years), sex, marital status, employment status, educational background (≤ high school vs. > high school), cancer location (colon vs. rectal), stage (stage II vs. stage III), stoma, administration route of adjuvant chemotherapy (oral vs. oral + IV), dose schedule (complex vs. simple), difficulty in each of the 4 items on the original questionnaire on the treatment experience and concerns on medication, depression (as assessed via HADS-D), and anxiety (as assessed via HADS-A). SPSS (Japanese version 22.0 for Windows, IBM Japan, Inc., Tokyo) was used for statistical analysis, and all tests used a 5% significance threshold.

Results

1. Demographic and clinical characteristics of the patients

A total of 81 patients were enrolled, of which data from 61 patients who completed the survey at 3 time points were analyzed. The demographic and clinical characteristics of the 61 patients are summarized in Table 1. The average age was 69.0 ± 8.1 (range, 44-83) years, and 67% of the participants were men. Thirty-three patients (54%) received oral chemotherapeutic agents only (the oral treatment group), whereas 28 patients (46%) received a combination of oral and IV chemotherapeutics (the oral + IV treatment group). In the oral treatment group, UFT/LV therapy was administered in 27 patients (44%), capecitabine in 4 patients (7%), and S-1 therapy in 2 patients (3%), while all 28 patients (46%) in the combination group were on CapeOX therapy. There were no significant differences in demographic and clinical characteristics between the oral treatment group and the oral + IV treatment group. However, the oral + IV treatment group tended to include more stage III patients (P = .06).

2. Medication adherence and anxiety and depression

The medication adherence as measured by MMAS-8 during the treatment period is summarized in Table 2. The mean MMAS-8 scores at 1-2 months, 3-4 months, and 5-6 months from the start of treatment were 7.0 ± 1.2, 6.8 ± 1.3, and 6.9 ± 1.3, respectively. A total of 16.4% -27.9% of patients had low medication adherence (MMAS < 6) during the study ; however, no significant differences were observed in MMAS-8 scores at different time points (F (2, 120) = 1.21, P = .30).

The anxiety and depression as measured by HADS during the treatment period is summarized in Table 2. Regarding anxiety, mild and moderate levels were observed in 1.6%-11.5% of the patients throughout the study period. Regarding depression, a total of 13.1%-16.4% of patients were mild or moderate level during the study period. No significant differences were observed in HADS-A (F (2, 180) = 0.29, P = .75) and HADS-D (F (2, 180) = 0.19, P = .83) at different time points.

The comparison of MMAS-8 scores according to different attributes is shown in Table 3. MMAS-8 scores were not significantly associated with age, sex, marital status, occupational status, educational level, location, or stage of cancer, or having stoma. However, the MMAS-8 score was

Table 1 Clinical Characteristics of the Patients

	Overall	Oral treatment group	Oral + IV treatment group	P-value
Number	61	33	28	-
Age, years	69.0 ± 8.1	70.0 ± 8.6	67.9 ± 7.5	.32
Men	41 (67.2)	23 (69.7)	18 (64.3)	.65
Married	47 (77.0)	26 (78.8)	21 (75.0)	.73
Employed	22 (36.1)	12 (36.4)	10 (35.7)	.96
Educational level				
Primary	8 (13.1)	2 (6.1)	6 (21.4)	
Secondary	39 (63.9)	23 (69.7)	16 (57.1)	.21
College	14 (23.0)	8 (24.2)	6 (21.4)	
Location of cancer				
Colon	41 (67.2)	23 (69.7)	18 (64.2)	.65
Rectum	20 (32.8)	10 (30.3)	10 (35.7)	
Clinical stage of cancer				
II	23 (37.7)	16 (48.5)	7 (25.0)	.06
III	38 (62.3)	17 (51.5)	21 (75.0)	
Patients with stoma	9 (14.8)	5 (15.2)	4 (14.3)	.92
Chemotherapy regimen				
UFT/LV	-	27 (44.3)	-	
Capecitabine	-	4 (6.6)	-	-
S-1	-	2 (3.3)	-	
CapeOX	-	-	28 (46.0)	

Abbreviations : Oral, patients with oral medications only ; Oral + IV, patients with oral and intravenous medications ; UFT, Uracil-tegafur ; LV, Leucovorin ; S-1, tegafur-gimeracil-oteracil ; CapeOX, capecitabine and oxaliplatin.
The UFT/LV therapy group included 2 patients on monotherapy, and the UFT/LV/protein-bound polysaccharide K group included 3 patients.

Data are displayed as mean ± SD or number (%).
We compared differences between patients with oral medications and patients with both oral and intravenous medications.

significantly lower ($P < .001$-$.01$) in the oral treatment group than in the oral + IV treatment group at all three time points. Compared with patients taking chemotherapeutics at similar doses ("Simple" in Table 3), those taking different doses of oral anticancer agents during the day (e.g., 2 tablets in the morning, 3 tablets at noon, and 2 tablets in the evening, "Complex" in Table 3) had significantly lower MMAS-8 scores at 5-6 months ($P = .02$) or tended to have lower MMAS-8 scores at 1-2 months and 3-4 months ($P = .051$-$.08$) after treatment.

Because there were significant differences in MMAS-8 scores between the oral group and oral + IV treatment group, the answers to each item of the MMAS-8 questions were compared to analyze whether there were certain items of MMAS-8 that were responsible for the differences (Table 4). Throughout the treatment period, the non-adherent answer to the question "Do you sometimes forget to take your pills?" was significantly higher in the oral treatment group than in the oral + IV treatment group ($P < .001$). Similarly, in the first 2 months of the treatment,

Table 2 MMAS-8 Score and HADS score at Each Phase

	1-2 Months (T1)	3-4 Months (T2)	5-6 Months (T3)	P-value
MMAS-8 score	7.0 ± 1.2	6.8 ± 1.3	6.9 ± 1.3	.30
MMAS-8 adherence level				
Low	10 (16.4)	17 (27.9)	12 (19.7)	
Medium	22 (36.1)	24 (39.3)	26 (42.6)	.40
High	29 (47.5)	20 (32.8)	23 (37.7)	
HADS-A score	2.9 ± 2.9	2.7 ± 2.4	3.1 ± 2.9	.75
HADS-A score ranges				
Normal	57 (93.4)	60 (98.4)	54 (88.5)	
Mild	3 (4.9)	1 (1.6)	7 (11.5)	.12
Moderate	1 (1.6)	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	
HADS-D score	3.9 ± 3.3	4.1 ± 3.2	3.7 ± 3.3	.83
HADS-D score ranges				
Normal	53 (86.9)	51 (83.6)	53 (86.9)	
Mild	5 (8.2)	8 (13.1)	5 (8.2)	.86
Moderate	3 (4.9)	2 (3.3)	3 (4.9)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	

Abbreviations : MMAS-8, Morisky Medication Adherence Scale-8.

Data are displayed as mean ± SD or number (%).

The patients were stratified into those with low adherence (< 6 points), medium adherence (6 to < 8 points), and high adherence (8 points) using the MMAS-8.

Abbreviations: HADS, Hospital Anxiety and Depression Scale

HADS-A; Anxiety scores from HADS, HADS-D; Depression scores from HADS

Data are displayed as mean ± SD or number (%).

The patients were stratified into those with normal (≦ 7 points), mild (8 to ≦ 10 points), moderate (11 to ≦ 14 points), and severe (15 to ≦ 21 points) using the HADS.

the non-adherent answer to the question "Thinking over the past two weeks, were there any days when you did not take your medicine?" and to the question "When you travel or leave home, do you sometimes forget to bring along your medication?" were also significantly higher in the oral treatment group than that in the oral + IV treatment group (P = .03 and .01, respectively). For the question "Do you ever feel hassled about sticking to your treatment plan?" the non-adherent answers were significantly higher in the oral treatment group than those in the oral + IV treatment group at 5-6 months of treatment (P = .049).

3. Adverse events

The most common adverse event throughout the treatment period was fatigue. A total of 39%, 56%, and 51% of the patients reported fatigue at 1-2, 3-4, and 5-6 months after starting treatment, respectively. The second most frequent adverse event was decrease in taste sensation that was reported by 34%, 43%, and 39% of the patients at 1-2, 3-4 months, and 5-6 months after starting treatment, respectively. There were no significant differences in MMAS-8 scores between patients with vs without adverse events.

Table 3 Differences in MMAS-8 Scores at Each Phase

	1-2 Months (T1)		3-4 Months (T2)		5-6 Months (T3)	
	MMAS-8 score	P-value	MMAS-8 score	P-value	MMAS-8 score	P-value
Age						
< 65 years old	7.3 ± 0.9	.71	6.5 ± 1.4	.42	6.7 ± 1.0	.28
≥65 years old	6.9 ± 1.3		6.9 ± 1.2		6.9 ± 1.4	
Sex						
Male	7.1 ± 1.0	.88	6.8 ± 1.3	.83	7.0 ± 1.1	.38
Female	6.9 ± 1.6		6.7 ± 1.3		6.5 ± 1.7	
Marital status						
Married	7.0 ± 1.2	.87	6.7 ± 1.3	.92	6.8 ± 1.4	.81
Single/divorced	7.0 ± 1.3		6.9 ± 1.1		7.0 ± 1.0	
Occupational status						
Employed	7.0 ± 1.3	.98	6.8 ± 1.5	.57	6.6 ± 1.5	.39
Unemployed	7.0 ± 1.2		6.8 ± 1.2		7.0 ± 1.2	
Educational level						
Primary	6.8 ± 1.1		6.8 ± 1.6		7.0 ± 0.9	
Secondary	7.0 ± 1.4	.64	6.8 ± 1.3	.92	6.8 ± 1.5	.99
College	7.3 ± 0.8		6.8 ± 0.9		7.0 ± 1.1	
Location of cancer						
Colon	7.0 ± 1.3	.92	6.8 ± 1.3	.86	6.6 ± 1.4	.11
Rectum	7.1 ± 1.2		6.8 ± 1.3		7.3 ± 1.0	
Clinical stage of cancer						
II	6.9 ± 1.4	.88	6.8 ± 1.4	.73	6.9 ± 1.6	.46
III	7.1 ± 1.2		6.8 ± 1.2		6.8 ± 1.2	
Stoma						
Yes	7.3 ± 0.9	.46	6.8 ± 1.0	.55	7.4 ± 0.9	.24
No	7.0 ± 1.3		6.8 ± 1.3		6.8 ± 1.4	
Route of administration						
Oral	6.5 ± 1.4	< .001	6.4 ± 1.3	.01	6.4 ± 1.5	< .001
Oral + IV	7.7 ± 0.6		7.2 ± 1.1		7.4 ± 0.9	
Dosage						
Simple	7.2 ± 1.1	.051	7.0 ± 1.1	.08	7.1 ± 1.0	.02
Complex	6.4 ± 1.6		6.2 ± 1.6		6.0 ± 1.8	

Abbreviations : MAAS-8, Morisky Medication Adherence Scale-8 ; Stoma, patients with stoma ; Oral, patients with oral medications ; Oral + IV, patients with both oral and intravenous medications.

Data are displayed as mean ± SD.

Table 4 Differences in Adherent Behavior Between the Oral Treatment Group and the Oral + IV Treatment Group

	1-2 Months (T1)				3-4 Months (T2)				5-6 Months (T3)			
	All	Oral	Oral + IV	P-value	All	Oral	Oral + IV	P-value	All	Oral	Oral + IV	P-value
1. Do you sometimes forget to take your pills? (Yes)	10 (16.4)	10 (30.3)	0 (0.0)	< .001	16 (26.2)	14 (42.4)	2 (7.1)	.003	14 (23.0)	13 (39.4)	1 (3.6)	.001
2. Over the past 2 weeks, were there any days when you did not take your medicine? (Yes)	9 (14.8)	8 (24.2)	1 (3.6)	.03	10 (16.4)	7 (21.2)	3 (10.7)	.32	11 (18.0)	9 (27.3)	2 (7.1)	.051
3. Have you ever cut back or stopped your medication without telling your doctor because you felt worse when you took it? (Yes)	3 (4.9)	3 (9.1)	0 (0.0)	.24	4 (6.6)	2 (6.1)	2 (7.1)	1.00	6 (9.8)	4 (12.1)	2 (7.1)	.68
4. When you travel or leave home, do you sometimes forget to bring along your medication? (Yes)	8 (13.1)	8 (24.2)	0 (0.0)	.01	6 (9.8)	5 (15.2)	1 (3.6)	.21	4 (6.6)	4 (12.1)	0 (0.0)	.12
5. Did you take your medication yesterday? (No)	4 (6.6)	4 (12.1)	0 (0.0)	.12	6 (9.8)	3 (9.1)	3 (10.7)	1.00	5 (8.2)	3 (9.1)	2 (7.1)	1.00
6. When you feel like health concern is under control, do you sometimes stop taking your medicine? (Yes)	1 (1.6)	1 (3.0)	0 (0.0)	1.00	1 (1.6)	1 (3.0)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	0 (0.0)	-
7. Do you ever feel hassled about sticking to your treatment plan for colon disease? (Yes)	19 (31.1)	12 (36.4)	7 (25.0)	.34	25 (41.0)	16 (48.5)	9 (32.1)	.20	21 (34.4)	15 (45.5)	6 (21.4)	.049
8. How often do you have difficulty remembering to take all your medicine?												
All the time	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)		1 (1.6)	1 (3.0)	0 (0.0)	
Usually	1 (1.6)	0 (0.0)	1 (3.6)		1 (1.6)	1 (3.0)	0 (0.0)		5 (8.2)	2 (6.1)	3 (10.7)	
Sometimes	4 (6.6)	4 (12.1)	0 (0.0)	.06	3 (4.9)	2 (6.1)	1 (3.6)	.37	3 (4.9)	2 (6.1)	1 (3.6)	.27
Once in a while	9 (14.8)	7 (21.2)	2 (7.1)		18 (29.5)	12 (36.4)	6 (21.4)		13 (21.3)	10 (30.3)	3 (10.7)	
Never/Rarely	47 (77.0)	22 (66.7)	25 (89.3)		39 (63.9)	18 (54.5)	21 (75.0)		39 (63.9)	18 (54.5)	21 (75.0)	

Abbreviations : Oral, patients with oral medications ; Oral + IV, patients with both oral and intravenous medications.

Data are displayed as number (%).

4. Factors associated with medication adherence

The results of logistic regression analyses are presented in Table 5. On univariate analysis, factors significantly associated with low adherence at 1–2 months of treatment were oral treatment only ($P < .001$) and depression ($P = .02$), while "knowing the names of medicines" was associated with high adherence ($P = .04$). Meanwhile, multivariate analysis showed that oral treatment (odds ratio (OR) : 9.49 ; 95% confidence interval (CI) : 2.63–34.23) and depression (OR : 1.30 ; 95% CI : 1.04–1.61) were significantly associated with low adherence at 1–2 months after starting treatment, whereas there were no factors significantly associated with low adherence at 3–4 months. At 5–6 months, oral therapy was significantly associated with low adherence on multivariate analysis ($P < .001$) with an OR of 6.39 (95% CI : 1.80–22.69).

Discussion

The present study aimed to analyze longitudinal changes in medication adherence and to identify the factors associated with low adherence in Japanese patients with colorectal cancer receiving oral adjuvant chemotherapy. In the present study, the MMAS-8 scores during the 6 months of adjuvant chemotherapy ranged from 6.8 to 7.0, which were similar to previous studies on adjuvant chemotherapy[19] and on patients with breast cancer patients under hormone therapy in Western countries[20]. Studies on medication adherence using the MMAS-8 in Japanese patients are limited in the studies of non-cancer patients such as type 2 diabetes (MMAS-8 scores of 5.9–6.2) and psoriasis (6.3)[21,22].

In general, patients with cancers are considered to be highly motivated to take their medication and have high adherence to chemotherapy because they understand the risks of not taking the medication and fear for potentially life-threatening disease[23]. The MMAS-8 scores in the patients with colorectal cancer in the present study are higher than those reported in Japanese patients with chronic diseases. Nevertheless, further improvement of medication adherence in patients with cancer is critical to achieve the treatment goal of postoperative adjuvant chemotherapy, i.e., to prevent recurrence and improve prognosis.

In the present study, depression as assessed by HADS-D was associated with low medication adherence at 1–2 months after starting the treatment. Regarding the types of therapy, treatment with oral anticancer agent alone was associated with low medication adherence at 1–2 and 5–6 months after starting treatment. The lower adherence in the oral treatment alone compared with the combination of oral + IV treatment was consistent with the results of previous studies[24,25] and suggested to be a common characteristic among patients receiving oral chemotherapeutics only.

One of the main reasons for these results could be the complexity of the oral chemotherapy regimen. It has been reported that the complexity of regimen such as the combination of different times and/or doses per day has a negative impact on medication adherence[10] and the schedule of medication is an important factor in adherence status[26]. Previous studies reported that the timing and times of oral administration affected adherence. One study reported that taking oral chemotherapy medication every 8 hours was significantly associated with non-adherence among patients with gastroenterological cancers[16]. UFT, the most commonly used drug in the present study, is taken every 8 hours, with recommendation to avoid taking the drug one hour before and after meals. Thus, compared with patients receiving capecitabine that is taken twice a day, patients on UFT have more concerns such as timing of taking the drug and eating meals and carrying the medication. This is consistent with our data that the patients on oral chemotherapy alone more frequently answered "Yes" to the questions "When you travel or leave home, do you

Table 5 Predictors for Low/moderate Medication Adherence

	1-2 Months (T1)				3-4 Months (T2)				5-6 Months (T3)			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
< 65 years old	1.05 (0.32-3.37)	.94	-	-	1.47 (0.40-5.36)	.56	-	-	1.29 (0.38-4.38)	.69	-	-
Men	0.86 (0.29-2.51)	.78	-	-	0.83 (0.26-2.62)	.75	-	-	0.84 (0.28-2.56)	.76	-	-
Married	0.88 (0.27-2.90)	.83	-	-	1.29 (0.35-4.77)	.70	-	-	0.76 (0.22-2.55)	.65	-	-
Employed	1.14 (0.40-3.25)	.81	-	-	0.57 (0.19-1.70)	.31	-	-	1.49 (0.50-4.48)	.48	-	-
Primary school	0.97 (0.42-2.27)	.95	-	-	1.53 (0.61-3.82)	.37	-	-	1.05 (0.44-2.53)	.91	-	-
Colon cancer	0.86 (0.29-2.51)	.78	-	-	0.58 (0.18-1.91)	.37	-	-	2.95 (0.98-8.95)	.06	-	-
Stage III of cancer	1.35 (0.45-3.81)	.57	-	-	1.58 (0.53-4.70)	.43	-	-	1.99 (0.68-5.77)	.21	-	-
Stoma	0.69 (0.17-2.85)	.60	-	-	-	-	-	-	0.42 (0.10-1.78)	.24	-	-
Oral medication	6.67 (2.17-20.48)	< .001	9.49 (2.63-34.23)	< .001	2.34 (0.79-6.99)	.13	-	-	6.96 (2.17-22.30)	< .001	6.39 (1.80-22.69)	< .001
Simple medication	0.40 (0.12-1.33)	.14	-	-	0.91 (0.27-3.10)	.88	-	-	0.46 (0.13-1.64)	.23	-	-
Depression	1.20 (1.00-1.42)	.045	1.30 (1.04-1.61)	.02	1.16 (0.96-1.40)	.11	-	-	1.05 (0.89-1.23)	.58	-	-
Anxiety	1.07 (0.89-1.28)	.47	-	-	1.15 (0.91-1.45)	.25	-	-	1.05 (0.87-1.26)	.63	-	-

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval.

sometimes forget to bring along your medication?" and "How often do you have difficulty remembering to take all your medicine?" due to simple forgetting. Therefore, it was suggested that early educational intervention focusing on the complexity of treatments was necessary for patients receiving treatment with oral anticancer agents alone.

Another reason for the low adherence in the oral treatment group may arise from shorter time spent with health professionals aside from visiting a doctor than that of combination therapy. Jacob Arriola et al reported a significant correlation between the frequency of patients' communication with medical professionals and medication adherence[27]. Collectively, these results suggested that limited communication with medical professionals may be one of the reasons causing low medication adherence in patients receiving oral chemotherapy alone. Patients on oral chemotherapy typically receive a prescription from the hospital, bring it to a local pharmacy, and consume the drugs as prescribed. Meanwhile, oral + IV chemotherapy patients usually spend more time with health professionals as they need to stay in the infusion room and interact with health professionals when the drug is administered intravenously. Patients on oral chemotherapy alone have less opportunity for communication to get information and for consulting with nurses, pharmacists, and other health professionals compared with those on oral + IV chemotherapy. In a survey of 397 cancer institutions in Japan, the patients with oral anticancer agent alone received less medication information from pharmacists compared to the patients treated with intravenous chemotherapeutics[28].

In the present study, depression at 1–2 months after starting chemotherapy was associated with low medication adherence during the same period. Depression in patients with cancer is not only caused by psychological problems, but also by physical symptoms and the adverse effects of chemotherapy, among others. Anxiety and depression in addition to physical symptoms such as fatigue and abdominal symptoms during the postoperative period were also reported among patients with colorectal cancer[17].

On the other hand, 1–2 months after starting postoperative adjuvant chemotherapy, patients try to return to their social life while adjusting to their altered gastrointestinal function and handling adverse events of chemotherapy. Depression along with physical and psychological instability may be a reason for the low medication adherence during this period.

As an increased use of oral chemotherapy is predicted, intervention for patients at high risk for poor adherence, such as those receiving oral chemotherapy or those with depression is necessary. For this purpose, methods to evaluate medication adherence at outpatient clinics, where time and manpower are limited, are necessary. Medication adherence is defined by the World Health Organization as the extent to which a person's behavior – taking medications, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider[29]. Seal et al reported the usefulness of MMAS-8 as a method to briefly and effectively evaluate medication adherence[25]. Evaluating adherence from the viewpoint of patients is also important, although measuring adherence via self-report has a risk for overestimation of the actual adherence status[23].

Our data indicate that "simple forgetting" is one of the main reasons for low adherence, which suggests that factors like remembering the time to take medications and carrying the drugs are obstacles to maintaining adherence. Patients on postoperative adjuvant chemotherapy struggle to add medication management as a new daily routine, and this issue may lead to low adherence. Thus, nurses will need to identify problems in taking medication in individual patients and provide success stories from other patients to solve problems, such as suggesting methods for simple packing of medication to carry, using the

reminder function in mobile phones, and obtaining support from family members.

The limitations of the present study include the small number of patients recruited in a few medical facilities. As such, comparison with previously published data on the association of demographic factors with adherence was incomplete. Additionally, the statistical power was low due to the small number of subjects, which might lead to failure in achieving statistical significance. Another limitation is the relatively short surveillance period, which is set to 6 months based on the length of the standard postoperative adjuvant chemotherapy. However, the treatment period can be extended in certain patients, and clinical trials with longer treatment period are ongoing. Thus, the surveillance period has to be extended corresponding to each treatment period and follow-up studies will be necessary to address these issues. Furthermore, establishing a support program to help medication adherence in patients receiving oral chemotherapy, according to the setting of medical practice would be possible by accumulating data on medication adherence in Japan.

Conclusions

Medication adherence of the patients with colorectal cancer who received postoperative adjuvant chemotherapy was longitudinally evaluated by questionnaire survey. The results suggested that treatment with oral chemotherapeutic agent alone and depressive state were significantly associated with low medication adherence. Thus, additional attention might be given to these patients who are at a high risk of low medication adherence, and nurses in collaboration with other medical professionals would need to develop individualized patient education programs and provide emotional intervention to improve medication adherence in this patient population. However, the generalization of the results needs to be evaluated by future studies because they were based on the small number-survey at only three facilities.

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References

1) National Cancer Center Japan Cancer Information Service. Cancer Registry and Statistics. 2017. Retrieved from https : //ganjoho.jp/reg_stat/statistics/stat/summary.html.
2) Japanese Society for Cancer of the Colon and Rectum : Japanese classification of colorectal carcinoma Guidelines 2016 for the treatment of colorectal cancer. pp. 28-29, Kanehara & Co Tokyo, 2016.
3) Fallowfield L, Atkins L, Catt S, Cox A, Coxon C, Langridge C, Morris R and Price M : Patients' preference for administration of endocrine treatments by injection or tablets results from a study of women with breast cancer. Annals of Oncology. 17 : 205-210, 2015.
4) McDonald HP, Garg AX and Haynes RB : Interventions to enhance patient adherence to medication prescriptions : scientific review. JAMA. 288 : 2868-2879, 2002.
5) Bhattacharya D, Easthall C, Willoughby KA, Small M and Watson S : Capecitabine non-adherence : exploration of magnitude, nature and contributing factors. J. Oncol. Pharm. Pract. 18 : 333-342, 2012.
6) Partridge AH, Archer L, Kornblith AB, Gralow J, Grenier D, Perez E, Wolff AC, Wang X, Kastrissios H, Berry D, Hudis C, Winer E and Muss H : Adherence and persistence with oral adjuvant chemotherapy in older women with early-stage breast cancer in CALGB 49907 : Adherence companion study 60104. J. Clin. Oncol. 28 : 2418-2422, 2010.
7) Winterhalder R, Hoesli P, Delmore G, Pederiva S, Bressoud A, Hermann F, von Moos R and SAEDA Investigators Group (Swiss prospective cohort group) : Self-reported compliance with

capecitabine : findings from a prospective cohort analysis. Oncology. 80 : 29–33, 2011.
8) Kawakami K, Yokokawa T, Kobayashi K, Sugisaki T, Suzuki K, Suenaga M, Inoue A, Machida Y, Yamaguchi T and Hama T : Self-reported adherence to capecitabine on XELOX treatment as adjuvant therapy for colorectal cancer. Oncology Research, 25, 1625–1631, 2017.
9) Tashiro J, Yamaguchi S, Ishii T, Suzuki A, Kondo H, Morita Y, Hara K and Koyama I : Inferior oncological prognosis of surgery without oral chemotherapy for stage III colon cancer in clinical settings. World. J. Surg. Oncol. 12 : 145, 2014.
10) Mathes T, Pieper D, Antoine SL and Eikermann M : Adherence influencing factors in patients taking oral anticancer agents : systematic review. Cancer. Epidemiol. 38 : 214–226, 2014.
11) Verbrugghe M, Verhaeghe S, Lauwaert K, Beeckman D and Van Hecke A : Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs : A systematic review. Cancer. Treat. Rev. 39 : 610–621, 2013.
12) Irwin M and Johnson LA. Factors influencing oral adherence : qualitative metasummary and triangulation with quantitative evidence. Clin. J. Oncol. Nurs. 19 : 6–30, 2015.
13) Morisky DE, Ang AK, Krousel-Wood M and Ward HJ : Predictive validity of a medication adherence measure in an outpatient setting. J. Clin. Hypertens. 10 : 348–354, 2008.
14) Moon SJ, Lee W-Y, Hwang JS, Hong YP and Morisky DE : Accuracy of a screening tool for medication adherence : A systematic review and meta-analysis of the Morisky Medication Adherence Scale-8. PLoS ONE. 12 : e0187139, 2017.
15) Zigmord AS and Snaith RP : The Hospital Anxiety and Depression Scale. Acta. Psychiatr. Scand. 67 : 361–370, 1983.
16) Hirao C, Mikoshiba N, Shibuta T, Yamahana R, Kawakami A, Tateishi R, Yamaguchi H, Koike K and Yamamoto-Mitani N : Adherence to oral chemotherapy medications among gastroenterological cancer patients visiting outpatient clinic. Japanese Journal of Clinical Oncology. 47 : 786–794, 2017.
17) Tsunoda A, Nakao K, Hiratsuka K, Yasuda N, Shibusawa M and Kusano M : Anxiety, depression and quality of life in colorectal cancer patients. Int. J. Clin. Oncol. 10 : 411–417, 2005.
18) Japan Clinical Oncology Group. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Available at http : //ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 Published : May 28, 2009 (v4.03 : Jun. 14, 2010)
19) Berry DL, Blonquist TM, Hong F, Halpenny B and Partridge AH : Self-reported adherence to oral cancer therapy : relationships with symptom distress, depression, and personal characteristics. Patient. Prefer. Adherence. 4 : 1587–1592, 2015.
20) Kesmodel SB, Goloubeva OG, Rosenblatt PY, Heiss B, Bellavance EC, Chumsri S, Bao T, Thompson J, Nightingale G, Tait NS, Nichols EM, Feigenberg SJ and Tkaczuk KH : Patient-reported adherence to adjuvant aromatase inhibitor therapy using the morisky medication adherence scale : an evaluation of predictors. Am. J. Clin. Oncol. 41 : 508–512, 2018.
21) Sugita H, Shinohara R, Yokomichi H, Suzuki K and Yamagata Z : Effect of text messages to improve health literacy on medication adherence in patients with type 2 diabetes mellitus : A randomized controlled pilot trial. Nagoya. J. Med. Sci. 79 : 313–321, 2017.
22) Ichiyama S, Ito M, Funasaka Y, Abe M, Nishida E, Muramatsu S, Nishihara H, Kato H, Morita A, Imafuku S and Saeki H : Assessment of medication adherence and treatment satisfaction in Japanese patients with psoriasis of various severities. J. Dermatol. 45 : 727–731, 2018.
23) Osterberg L and Blaschke T : Adherence to medication. N. Engl. J. Med. 353 : 487–497, 2005.
24) Shimada Y, Hamaguchi T, Mizusawa J, Saito N, Kanemitsu Y, Takiguchi N, Ohue M, Kato T, Takii Y, Sato T, Tomita N, Yamaguchi S, Akaike M, Mishima H, Kubo Y, Nakamura K, Fukuda H and Moriya Y : Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection : final results of JCOG0205. Eur. J. Cancer. 50 : 2231–2240, 2014.
25) Seal BS, Anderson S and Shermock KM : Factors associated with adherence rates for oral and intravenous anticancer therapy in commercially insured patients with metastatic colon cancer. J. Manag. Care. Spec. Pharm. 22 : 227–235, 2016.
26) Claxton AJ, Cramer J and Pierce C : A

systematic review of the associations between dose regimens and medication compliance. Clin. Ther. 23 : 1296–1310, 2001.
27) Jacob Arriola KR, Mason TA, Bannon KA, Holmes C, Powell CL, Horne K and O'Regan R : Modifiable risk factors for adherence to adjuvant endocrine therapy among breast cancer patients. Patient. Educ. Couns. 95 : 98–103, 2014.
28) Matsuo K, Iihara H, Iwamoto T, Ogata K, Kawakami K, Kumihashi Y, Kuroda J, Hayashi T, Hioki M, Yoshimura T and Yonemura M : Academic Committee Academic 3rd Small Committee Report, Investigation and research on the business development of the pharmacists in outpatient chemotherapy. Journal of the Japan Society of Hospital Pharmacists. 49 : 796–800, 2013. (In Japanese)
29) World Health Organization. Adherence to long–term therapies : Evidence for action. Geneva, Switzerland : World Health Organization. 2003. Available at http : //apps.who.int/iris/bitstream/10665/42682/1/9241545992.pdf. Accessed February 22, 2017.

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（和文抄録）

術後補助化学療法中の大腸がん患者の服薬アドヒアランスに関する縦断調査

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大腸がんの術後補助化学療法として経口抗がん剤を使用した療法は標準治療の一つとなっているが，日本において経口抗がん剤を用いた術後補助化学療法中の服薬アドヒアランスに関する報告は僅かである．

本研究の目的は，経口抗がん剤を使用する術後補助化学療法を受ける大腸がん患者の服薬アドヒアランスの実態と服薬アドヒアランスの低下に関連する要因を明らかにすることである．61 名の患者（経口抗がん剤単独群 33 名，経口抗がん剤に静注薬併用群 28 名）を対象として，6ヶ月間の術後補助化学療法の治療開始から 3 時点（1〜2，3〜4，5〜6ヶ月後）において服薬アドヒアランス（MMAS-8 scores），不安と抑うつ（HADS）に関する質問紙調査を実施した．アドヒアランス低下に関連する要因の解析はロジスティック回帰分析を使用した．

MMAS-8 scores によるアドヒアランスや HADS による不安と抑うつの術後 6ヶ月間の経時的有意な変化は無かった．服薬アドヒアランスの低下に関連する要因は，治療開始 1〜2ヶ月は経口抗がん剤単独による治療（OR：9.49）と抑うつ（OR：1.30）であった．治療開始 5〜6ヶ月は経口抗がん剤単独治療（OR：6.39）が関与していた．

本調査結果から，アドヒアランスを維持するためには，医療者はアドヒアランスの低下のリスクが高い経口抗がん剤単独治療を受ける患者や抑うつに焦点を当て，治療開始初期から継続的に教育的，精神的な支援を検討する必要があることが示唆された．

キーワード：大腸がん，服薬アドヒアランス，MMAS-8，術後補助化学療法，縦断調査