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Self-Reported Adherence to Capecitabine on XELOX Treatment as Adjuvant Therapy for Colorectal Cancer

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Adherence has become an important issue in modern oncology treatment. Most studies have included heterogeneous target tumor types, regimens, and therapy settings. Our study focused on capecitabine during capecitabine plus oxaliplatin (XELOX) treatment as an adjuvant therapy for colorectal cancer. The main aims of this study were to evaluate real-life adherence to capecitabine and to investigate candidate factors that might decrease adherence. We studied 338 consecutive patients who received XELOX treatment between December 1, 2011, and April 30, 2015, at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. Our study assessed adherence to capecitabine through patient-reported treatment diaries and interviewed nonadherents to determine the reasons for not taking capecitabine at a pharmaceutical outpatient clinic. We calculated the adherence rate in a cycle as: number of times the patient took capecitabine/28. Relative dose intensities and factors associated with deteriorating adherence to capecitabine were retrospectively surveyed from electronic patient records. Uni- and multivariate logistic regression analyses were used to investigate factors associated with optimal adherence. The study covered 282 patients who received 2,055 cycles of XELOX. Median adherence rate was 94.0% in the first cycle, and median relative dose intensity of capecitabine was 77.8%. The most common reasons for nonadherence were nausea/vomiting and diarrhea. The presence of the following factors was not significantly associated with adherence: ECOG performance status ≥ 1 ($p=0.715$), clinical stage ($p=0.408$), primary tumor site ($p=0.576$), age ≥ 70 years at study entry ($p=0.757$), female gender ($p=0.504$), and not living alone ($p=0.579$). The adherence rate from this study was significantly higher than the adherence from metastatic settings. Adherence-enhancing interventions for capecitabine in XELOX treatment as adjuvant therapy comprised management of nausea/vomiting and diarrhea.

Key words: Capecitabine; Adherence; XELOX treatment; Pharmaceutical outpatient clinic; Oral anticancer drugs

INTRODUCTION

The use of oral anticancer therapy is increasing every year. In particular, cytotoxic agents and, more recently, targeted therapies are often administered orally. Pharmacoeconomic studies have shown that oral medications are superior to in-hospital intravenous treatment with respect to cost¹. Most patients prefer to take medications orally²; therefore, the use of oral anticancer agents is likely to continue to increase. Oral anticancer agents are expected to improve the patient's quality of life by decreasing treatment interference with work and social activities, eliminating travel time to clinics for infusion, and reducing the discomfort

and potential complications associated with placing an intravenous line for each administration.

Until recently, the problem of assessing adherence was not a subject of major interest in cancer care. As recent developments in oral therapies for oncology could mark a turning point in the perceived need for assessing adherence among cancer patients, adherence has become an important issue in modern oncology. Ruddy et al. reported 16%–100% adherence and persistence rates with oral anticancer agents³. Several studies have reported patient adherence rates for capecitabine within the range of 58%–100%, mainly depending on the measurement

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method⁴. The superiority of capecitabine plus oxaliplatin (XELOX) compared with 5-fluorouracil/leucovorin was maintained at 4 and 5 years, indicating that the benefits of XELOX are durable⁵. In particular, improving treatment adherence is critical to achieving optimal therapeutic efficacy in adjuvant therapy.

Adherence to treatment with oral anticancer agents (dasatinib, erlotinib, everolimus, etc.) and factors influencing adherence have been assessed⁶. Most such studies have included heterogeneous target tumor types, regimens, and therapy settings⁷. Our study focused on capecitabine during XELOX treatment as an adjuvant therapy for colorectal cancer. The main aim of this study was to evaluate real-life adherence to capecitabine on XELOX treatment and investigate candidate factors that might decrease adherence.

MATERIALS AND METHODS

Study Design and Treatment

We obtained data from 338 consecutive patients who received XELOX treatment as an adjuvant therapy for colorectal cancer between December 1, 2011, and April 30, 2015, at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. Our study assessed adherence with capecitabine using patient-reported treatment diaries and interviewed nonadherents regarding their reasons for not taking capecitabine at a pharmaceutical outpatient clinic every XELOX treatment cycle.

Adherence rate was defined as the number of times that a patient took capecitabine in a 14-day cycle divided by the prescribed 28 doses. Relative dose intensities⁸ and factors associated with deteriorating adherence to capecitabine were retrospectively surveyed from electronic patient records.

Patients were assigned to adjuvant treatment with the XELOX regimen. The XELOX regimen comprised a 2-h intravenous infusion of oxaliplatin 130 mg/m² on day 1, and oral capecitabine at 1,000 mg/m² twice daily was given for 14 days on a 3-week cycle, for a total of eight cycles (24 weeks). The first dose of capecitabine was given on the evening of day 1, and the last dose on the morning of day 15 for each cycle⁹.

Pharmaceutical Outpatient Clinic

In our hospital, proactive intervention by pharmacists to check adherence and side effects (which represent one cause of nonadherence) is considered necessary, and we hold a pharmaceutical outpatient clinic for patients receiving oral chemotherapy treatment¹⁰. The main tasks of XELOX performed in the pharmaceutical outpatient clinic are as follows: 1) use of the capecitabine treatment diary to check for capecitabine adherence and left-over medication; 2) provision of prescription support for

XELOX treatment; 3) assessment of side effects; and 4) suggestion of prescriptions for medication as supportive therapy. In practice, prescription support for XELOX treatment consists of a pharmacist recording the capecitabine and oxaliplatin doses and administration period required for the next cycle in the electronic medical record. This is then checked and authorized by a physician to enable the prescription to be issued. If capecitabine is left over from the previous cycle, the amount to be prescribed is adjusted accordingly.

Study Population

Patients in this study were receiving XELOX treatment as an adjuvant therapy for colorectal cancer. Patients were excluded on the basis of previous cytotoxic chemotherapy or immunotherapy for colorectal cancer. All participants in this study visited a pharmaceutical outpatient clinic and completed XELOX treatment at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. The study protocol was reviewed and approved by the Clinical Research Ethics Review Committee at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (Approval No. 2012-1035).

Statistical Analysis

This analysis was based on 282 patients evaluated for adherence to capecitabine. The outcome variable was adherence, dichotomized according to success defined as adherence rate $\geq 95\%$ in the first cycle. All independent variables were first tested in univariate analyses. Independent variables with a two-tailed $p < 0.05$ value in univariate analyses were included in multivariate logistic regression analysis, where forward selection was used to build the final model. Dichotomous independent variables included in the analyses were Eastern Cooperative Oncology Group (ECOG) performance status, age, gender, and living status (alone vs. with others). All other independent variables (clinical stage and primary tumor site) were included as continuous variables. Odds ratios and p values were computed for the variables in logistic regression models. All analyses were performed using SPSS version 11.5 (SPSS, Chicago, IL, USA).

RESULTS

Patients and Characteristics

A total of 338 patients were extracted from outpatient pharmacy information systems in the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. A flowchart shows patients and the reason for exclusion (Fig. 1). Reasons for nonparticipation included no data collected ($n=22$), XELOX+bevacizumab treatment ($n=20$), participation in another clinical trial ($n=8$), prior adjuvant treatment at another hospital ($n=4$), and change

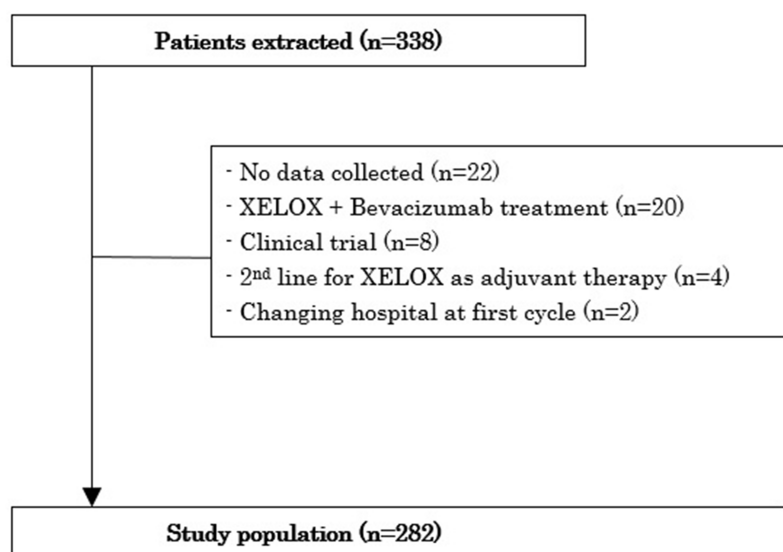


Figure 1. Flowchart of patients and reasons for exclusion.

in hospital after the first cycle ($n=2$). Clinical and socio-demographic characteristics data for the 282 patients analyzed are reported in Table 1. The study included 135 male and 147 female patients, and median age was 60 years (range: 26–81 years). In terms of living status, 254 patients (90.1%) were living with family, and 28 (9.9%) were living alone. Mean duration of XELOX treatment was 7.28 cycles (range: 1–8 cycles), and total number of XELOX treatments was 2,055 cycles.

Adherence Rate

The capecitabine adherence rate was determined by pharmacists from patient-reported treatment diaries during XELOX treatment as adjuvant therapy (Fig. 2). The ratio of patients who completed capecitabine treatment on XELOX treatment was 83.6%. Median adherence rate was 94.0% ($n=282$) in the first cycle of XELOX treatment, 95.5% ($n=271$) in the second cycle, and rising to 98.2% ($n=236$) in the eighth cycle. The median relative dose intensity of capecitabine was 77.8%.

Factors Reducing Capecitabine Adherence

In total, nonadherence was seen in 2,103 instances. The most common reasons for nonadherence were nausea/vomiting (21.5%, 435 instances), diarrhea (13.3%, 279 instances), missed dose (13.0%, 271 instances), and pain (11.7%, 246 instances) (Fig. 3).

Multivariate Model of Factors Associated With Adherence

Results of multivariate analysis are shown in Table 2. Clinical and sociodemographic factors were not significantly associated with capecitabine adherence on XELOX

Table 1. Clinical Characteristics and Sociodemographic of the Study Population

Characteristic	No. of Patients ($n=282$)
Gender	
Male	135 (47.9%)
Female	147 (52.1%)
Age at study entry (years)	
Median	60
Range	26–81
ECOG performance status	
0	273 (96.8%)
1	9 (3.2%)
Primary tumor site	
Colonic	147 (52.1%)
Rectal	109 (38.7%)
Others	26 (9.2%)
Clinical stage	
Stage II	31 (11.0%)
Stage IIIa	141 (50.0%)
Stage IIIb	81 (28.7%)
Stage IV	29 (10.3%)
Living status	
Living with family	254 (90.1%)
Living alone	28 (9.9%)
Duration of use (cycle)	
Mean (SD)	7.28 (1.84)
Range	1–8
Total treatment number	2,055

ECOG, Eastern Cooperative Oncology Group.

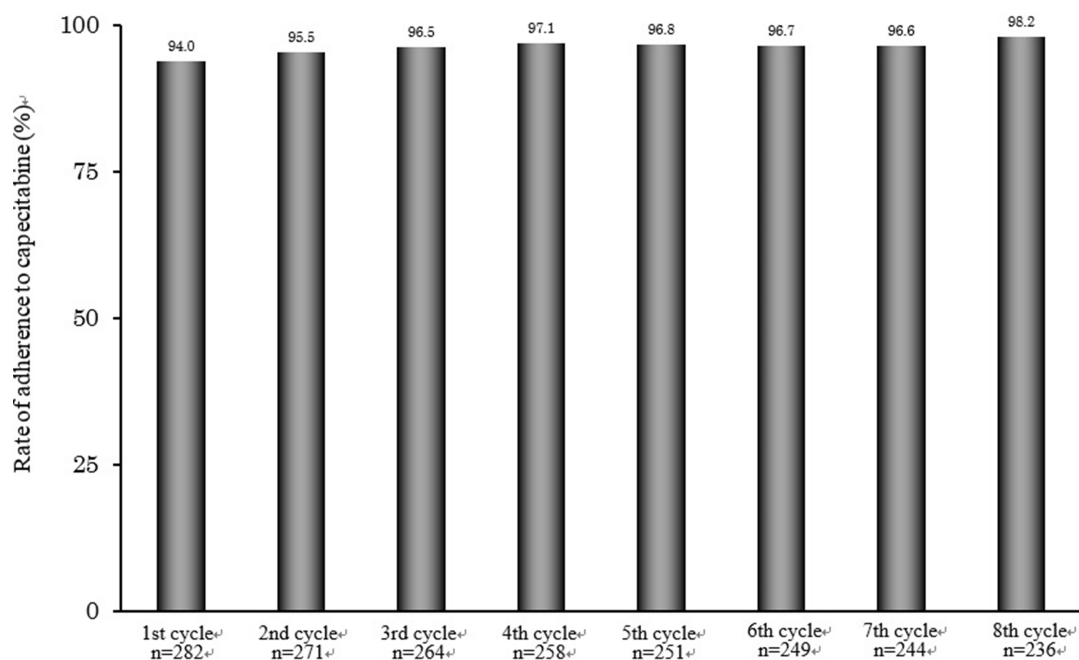


Figure 2. Capecitabine adherence rate on XELOX treatment as adjuvant therapy for colorectal cancer. Adherence rate with capecitabine during cycles 1–8. Adherence to capecitabine was checked by pharmacists via the self-reported treatment diaries at a pharmaceutical outpatient clinic.

in the first cycle. The presence of the following factors was not significantly associated with adherence: ECOG performance status ≥ 1 ($p=0.715$), clinical stage ($p=0.408$), primary tumor site ($p=0.576$), age ≥ 70 years at study entry ($p=0.757$), female sex ($p=0.504$), and not living alone ($p=0.579$).

DISCUSSION

The median capecitabine adherence rate on XELOX treatment in the first cycle as an adjuvant therapy for colorectal cancer as measured by patient self-report was 94.0%. The median relative dose intensity of capecitabine was comparable to a previous randomized phase III study of XELOX as adjuvant therapy for colorectal cancer (77.8% vs. 78.0%)¹¹. Although the adherence rate was high, a considerable number of patients (16.4%) showed non-adherence. In analysis of the total number of instances of nonadherence (2,103 instances), the main reasons for non-adherence were nausea or vomiting (21.5%, 435 instances), diarrhea (13.3%, 279 instances), and missed dose (13.0%, 271 instances). Clinical and sociodemographic factors were not significantly associated with capecitabine adherence on XELOX treatment in the first cycle.

Our study focused on adjuvant therapy for colorectal cancer and on XELOX treatment in clinical practice. Previous studies have reported on several oral anticancer agents, tumor types, and therapy settings^{6,12,13}. Our data

focused on a specific agent, tumor type, country, and treatment setting will be highly valuable in clinical practice.

Studies investigating patient adherence to capecitabine have found that median adherence across all cycles and studies was 78%¹⁴, and median adherence rate was 93.5% in the first cycle of XELOX treatment for unresectable metastatic disease¹⁵. An interesting finding is that adjuvant chemotherapy was associated with a higher probability of adherence among breast cancer patients on oral endocrine therapy. This is consistent with a previous cohort study, which also used persistence as an outcome variable in conjunction with a 4- to 5-year follow-up^{16,17}. Adherence rates in our study were higher than those reported previously^{14–16}. The high adherence results in this study might be explained by the fact that patient state (e.g., performance status, kidney function, hepatic function, motivation for treatment) was better under an adjuvant therapy setting than under an unresectable metastatic setting. The incentive for patients to maintain adherence to oral chemotherapy would thus seem higher in the adjuvant setting where there is true intent compared to patients with advanced, metastatic cancer, in which case treatment is being administered in the palliative setting. Nonadherent instances were seen throughout the first to eighth cycles. However, the ratio of patients who completed capecitabine treatment on XELOX treatment was 83.6%. As a result, the median capecitabine adherence rate was 94.0% in the first cycle.

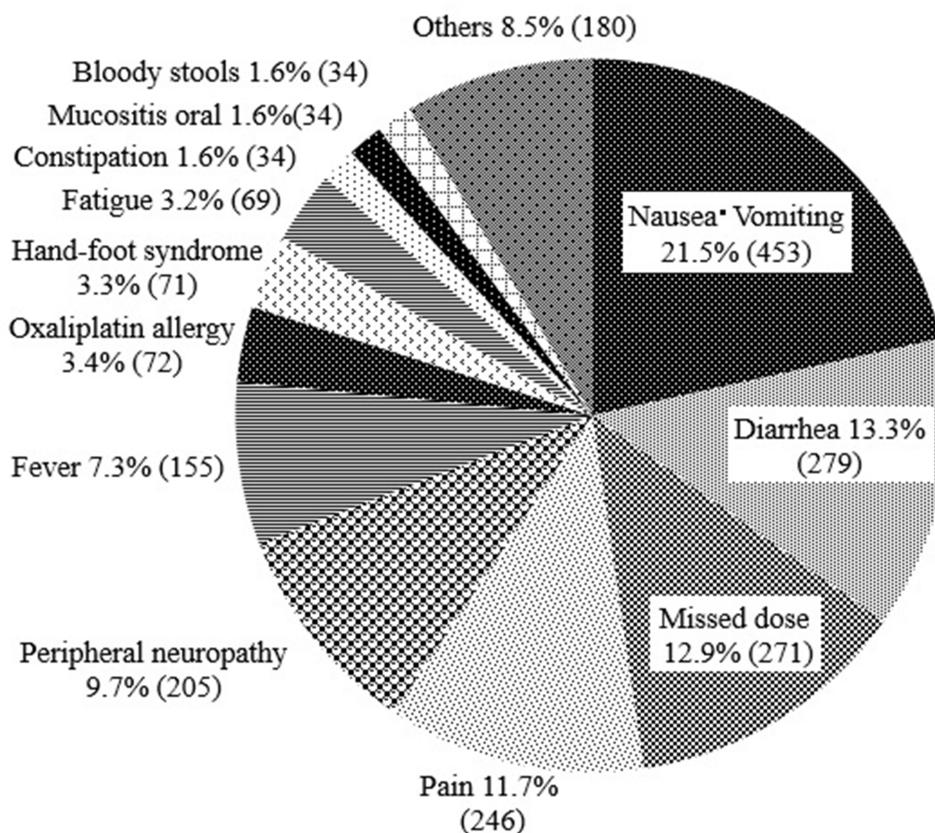


Figure 3. Factors reducing adherence to capecitabine on XELOX treatment as adjuvant therapy ($n=2,103$). Factors reducing adherence to capecitabine during cycles 1–8.

The high adherence rate in this study might have been associated with Japanese characteristics such as increased commitment to treatment, punctuality, earnestness, and listening more carefully to their physicians. Side effects of medications are known to represent major predictors of poor adherence¹⁸, and treatment-related side effects are the most frequently reported factor cited in previous studies of patients with nonadherence to oral anticancer

drug therapy^{12,19}. Diarrhea and hand-foot syndrome are consistent with adverse effects reported in previous studies in patients with nonadherence to capecitabine¹³. Our study indicated that nonadherence correlated with a higher number of adverse effects. We prescribed supportive therapy for all cases in this study beforehand, but appropriate antiemetic medication is necessary for patients with risk factors for chemotherapy-induced nausea and vomiting

Table 2. Logistic Regression Analysis of Optimal Adherence Behavior in Relation to Sociodemographic and Clinical Factors

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	<i>p</i> Value	OR (95% CI)	<i>p</i> Value
Sociodemographic factors				
Age at study entry (ref. <70 years)	1.16 (0.45–2.99)	0.757	NA	NA
Gender (ref. male)	1.28 (0.61–2.67)	0.504	NA	NA
Living status (ref. living alone)	0.89 (0.25–3.14)	0.579	NA	NA
Clinical factors				
ECOG performance status (ref. 0)	0.94 (0.11–7.77)	0.715	NA	NA
Clinical stage	0.82 (0.52–1.30)	0.408	NA	NA
Primary tumor site	0.85 (0.49–1.47)	0.576	NA	NA

OR, odds ratio; CI, confidence interval; NA, not applicable.

during highly emetogenic chemotherapy. We recommend prophylactic treatment with aprepitant for patients with high-risk factors of age <55 years, female sex, and non-habitual alcohol intake²⁰.

Factors influencing adherence among patients taking oral anticancer agents have recently been reviewed²¹. Low or very high age seems to be associated with lower adherence^{17,22–24}, and women seem to be less adherent than men²⁵. Cancer stage seems to have no influence on adherence¹⁷, but performance status is related to adherence^{24,26}, as is the living status of patients^{6,27}. The frequency of adverse events during adjuvant XELOX therapy in older patients was similar to that in younger patients, suggesting that age should not be a barrier to intensive adjuvant therapy⁵. Unfortunately, our study showed no significant predictors of adherence, although a large population was investigated.

For that reason, some limitations of this study should be taken into consideration. First, we might have missed relevant patient-related factors, such as education⁶ or out-of-pocket expenses^{7,23}, which might be related to adherence. In terms of the pharmacoeconomic aspects of adherence to oral chemotherapy, one of the challenges with oral chemotherapy in the US relates to the financial burden on the patient, as such treatment may not be covered by insurance to the same extent as intravenous chemotherapy. In Japan, where patients are covered by the national health insurance system, this is not as much of an issue. Whether out-of-pocket expenses affect adherence to oral chemotherapy in Japan thus merits investigation. Second, we relied on patient self-reports (via diary) in assessing the key primary outcome of adherence. The World Health Organization recommends using one objective measure with a self-reported measure for the assessment of adherence²⁸. Further research should consider using more objective methods such as pill count. Third, we used self-reported adherence based on patient-completed medication diaries, rather than a medication event monitoring system (MEMS) or the Morisky Medication Adherence Scale (MMAS). A MEMS is unsuitable for patients using oral cytotoxic agents, which require close monitoring of side effects and regular patient visits. Although various methods for measuring adherence are available, self-reporting is the most widely used²⁹. The MMAS has been validated with outstanding reliability in patients with other chronic diseases^{30,31}. In oncological settings, the MMAS allows for rapid assessment of adherence to oral adjuvant endocrine therapy^{32,33}. The MMAS eight-item questionnaire contains “Did you take your medication yesterday?”—which is unsuitable for measuring adherence to anticancer drugs within the rest period. Previous studies of oral cytotoxic chemotherapeutic drugs have mainly used self-reported questionnaires¹⁷, which tend to overestimate adherence because patients are inclined to overreport to please their doctors.

In conclusion, the median capecitabine adherence rate on XELOX treatment as adjuvant therapy was 94.0% in the first cycle. The main reasons for nonadherence were nausea and vomiting. We recommend prophylactic treatment with an aprepitant for patients with high-risk factors such as age <55 years, female sex, or nonhabitual alcohol intake. ECOG performance status ≥ 1 , clinical stage, primary tumor site, age ≥ 70 years, female sex, and living alone seem to be negatively associated with adherence. These findings may contribute to achieving higher adherence to capecitabine during XELOX treatment as adjuvant therapy for colorectal cancer.

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