Adherence to Capecitabine Among Patients With Gastrointestinal Cancer: A Prospective Cohort Study

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Abstract- Adherence to capecitabine, an effective oral chemotherapy agent, is essential in achieving treatment response in cancer. In this study, we aimed to investigate factors associated with non-adherence to capecitabine in a sample of patients with gastrointestinal cancer. We enrolled 98 patients with colon, rectal or gastric cancers who were undergoing treatment with capecitabine as part of their single or multi-agent chemotherapy regimen. The patients were followed during cohort time up to four consecutive cycles of their chemotherapy. For adherence measurement, the participants were asked to bring back the leftover medicines at the time of follow-up visits and were considered adherent if they had taken ≥95% of their prescribed dose. The mean adherence rate was 97.7%, and the patients were adherent to capecitabine in 93.1% of their cycles. The patients who underwent neoadjuvant chemotherapy were significantly less adherent to capecitabine (60%) as compared with adjuvant (95.2%) and palliative chemotherapy (94.6%) [*P*=0.004]. Multivariable logistic regression revealed that neoadjuvant chemotherapy and the presence of nausea and mucositis were inversely associated with adherence rate. We did not find any association between adherence and any of our laboratory findings. Our findings suggest a high adherence rate to capecitabine among patients with gastrointestinal cancers. Neoadjuvant chemotherapy and the presence of nausea and mucositis may play a significant role in non-adherence to capecitabine.

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Keywords: Capecitabine; Adherence; Gastrointestinal cancer; Oral chemotherapy; Side effects

Introduction

Nowadays, the number of oral chemotherapy agents is continuously growing. While these drugs have a different spectrum of adverse effects, they are better tolerated than intravenous medications in most cases. Studies have shown that patients prefer oral to intravenous agents as long as their effectiveness is adequate (1,2). Medication adherence can be defined as a ratio of the number of drug doses taken to the number of prescribed doses in a period of time. Adherence is a major issue of oral chemotherapy agents. Oral chemotherapy agents are normally self-administered by the patient; therefore, as opposed to parenteral drugs, adherence to oral agents can be unpredictable and varied among patients. Poor adherence to oral chemotherapy agents has been associated with poor outcomes, increased toxicity, and increased healthcare costs. Patient's poor adherence can be mistakenly interpreted as the ineffectiveness of treatment and may result in dissatisfaction on the part of both the patient and physician (3).

Capecitabine is an oral fluoropyrimidine that has replaced intravenous 5-fluorouracil (5-FU) in various chemotherapy regimens since it has been shown to have a similar therapeutic outcome with fewer adverse effects

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(4,5). Capecitabine should be used twice daily within 30 minutes after a meal at a 12-hour interval. In certain chemotherapy regimens, patients need to take several capsules/tablets (sometimes up to 4) at once, which can result in undesired side effects and poor adherence.

Reasons for non-adherence can be classified into the patient, healthcare provider, and treatment-related issues and include forgetting to take the medication on time, complex treatment regimen, patient dissatisfaction with care, lack of access to the medication, or inadequate social support (6). Patient-reported symptoms regarding the toxicity of drugs are also known as an important factor in their non-adherence (7,8). Previous studies have reported adherence rates to capecitabine to be between 73.7 to 99.3% (7,9-18). The present study aims to evaluate factors associated with adherence to capecitabine in patients with gastrointestinal cancer. Given that the role of laboratory abnormalities on adherence is not well understood yet, in this study, we aimed to assess the effect of laboratory abnormalities and also self-reported symptoms on patients' adherence.

Materials and Methods

This study was a prospective observational cohort study conducted between July 2020 and April 2021 in the Aram oncology clinic and outpatient clinic of Cancer Institute, Tehran, Iran. We recruited patients with colon, rectal or gastric cancer, with or without metastasis, who were undergoing neoadjuvant, adjuvant, or palliative chemotherapy with capecitabine as part of their single or multi-agent therapy regimen. In our sample, two-agent (capecitabine with oxaliplatin, irinotecan, bevacizumab, or cetuximab) or three-agent (capecitabine with oxaliplatin plus bevacizumab, oxaliplatin plus cetuximab, irinotecan plus bevacizumab, irinotecan plus cetuximab or oxaliplatin plus epirubicin) combination chemotherapies were prescribed as indicated. Individuals older than 18 years old who were being treated with capecitabine without concurrent radiotherapy were eligible to participate in this study. The study was approved by the Medical Ethics review board of Tehran University of medical sciences. Participation was voluntary, and written informed consent was obtained from all patients before taking part in the study.

Enrolled patients were followed during cohort time up to four cycles of chemotherapy. Due to the termination of chemotherapy, change of chemotherapy regimen, or loss of follow-up for some patients, available data was from less than four cycles. Details of the patients' follow-ups are presented in Figure 1.

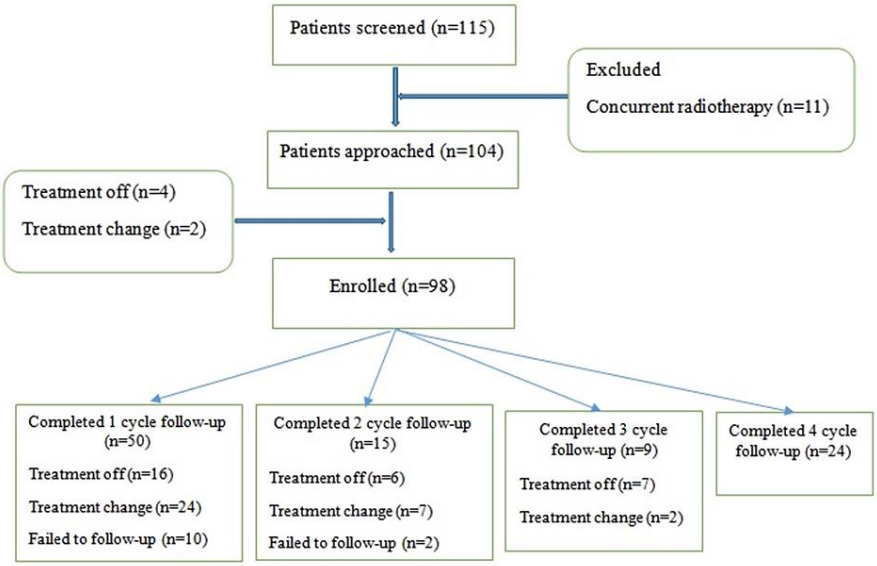

Figure 1. Patients' follow-up diagram

Demographics and characteristics of the patient's comorbidity, co-medications, performance status, indication for treatment, line, and the cycle of chemotherapy, the brand of capecitabine, the starting dose and dose adjustments as well as laboratory abnormalities were collected from clinical records of the patients. Throughout the cohort, the patients were asked to return any leftover medicines at their follow-up visits.

The returned medications were then counted to determine their adherence to the medication. Adherence percentage was calculated by dividing the amount of medication used by the patient by the total amount of medication prescribed by the physician in a given period of time. Patients' symptoms and the adverse effects of capecitabine, including diarrhea, hand-foot syndrome (HFS), nausea, constipation, chest pain, fatigue, mucositis, and loss of appetite, were documented at every follow-up visit. Diarrhea, HFS, and laboratory abnormalities (i.e., elevated liver enzyme, neutropenia, anemia, and thrombocytopenia) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5 (19).

Statistical analysis

The findings were presented as frequencies (percentages) and means (standard deviation) for categorical and continuous variables, respectively. Patients were considered adherent to capecitabine if the calculated adherence rates were ≥95%. We used $\chi 2$ and Fisher's exact test to compare the rates of adherence between categorical variables. We used logistic regression to investigate the associated factors of non-adherence to capecitabine. First, using univariate regression analysis, we calculated the OR and *P* of each variable, then any variable with a P value of less than 0.25 was considered valid to enter the multivariable logistic regression model. $P<0.05$ was considered statistically significant. We used PASW statistics 22 for statistical analysis.

Results

Baseline characteristics

Of the 98 enrolled patients (age range 28-84, mean=57.1 years), 44 (44.9%) had comorbid diseases, with hypertension being the most common comorbidity. Sixty-three (64.3%) patients had a diagnosis of colon cancer, 23 (23.4%) had rectal cancer, and 12 (12.2%) had gastric cancer. The baseline characteristics of the patients are listed in Table 1.

Table 1. Baseline characteristics of the patients.

Characteristic		No (%) of patients (n=98)
Sex	**Female**	34 (34.7%)
	Male	64 (65.3%)
Age	**<55**	35 (35.7%)
	55-64	29 (29.6%)
	65-74	26 (26.5%)
	≥75	8 (8.2%)
Education	**Low level (≤grade 12)**	55 (56.1%)
	Higher level (college degree)	43 (43.9%)
ECOG performance status	**0**	60 (61.2%)
	1	38 (38.8%)
Comorbidities	**No**	54 (55.1%)
	Yes	44 (44.9%)
	Hypertension	26 (26.5%)
	Ischemic heart disease	13 (13.2%)
	Diabetes	8 (8.1%)
	Other	8 (8.1%)
Co-medication	**No**	51 (52%)
	1-4	40 (40.8%)
	≥5	7 (7.1%)
Type of Disease	**Non-metastatic colon cancer**	21 (21.4%)
	Metastatic colon cancer	42 (42.9%)
	Non-metastatic rectal cancer	8 (8.1%)
	Metastatic rectal cancer	15 (15.3%)
	Non-metastatic gastric cancer	6 (6.1%)
	Metastatic gastric cancer	6 (6.1%)

ECOG Eastern Cooperative Oncology Group

Treatment regimens and adjustments

Data from 50, 15, 9, and 24 patients were collected in one, two, three, and four cycles of chemotherapy and entered into adherence analysis, respectively. A total number of 203 patient cycles were analyzed in the study. The mean dose of capecitabine was 1316.7 mg/m2/day (SD=404.4). Capecitabine dosing was decreased in 16 patients (16.3%), increased in 2 patients (2.1%), or

remained unadjusted in 80 (81.6%) throughout the cohort. While the majority of patients used medications that were manufactured by Iranian companies (i.e., Capecitabine acte 71 (72.4%), Oncocap 9 (9.2%) and Xetabin 10 (10.2%)) 8 (8.2%) patients used Xeloda. Details of chemotherapy regimens are presented in Table 2. Capecitabine was prescribed in 19 (9.4%) cycles as a single-agent chemotherapy, while two-drug and three-drug combination chemotherapy was arranged in 98 (48.2%) and 86 (42.3%) cycles, respectively.

Table 2. Treatment-related factors

Characteristic		No (%) of cycles (n=203)
Number of capecitabine tablets (n/day)	**1-4**	105 (51.7%)
	5-7	98 (48.3%)
Dose of capecitabine (mg/m^2/day)	**500-1000**	67 (33%)
	1001-1500	70 (34.5%)
	1501-2000	66 (32.5%)
Line of chemotherapy	1	119 (58.6%)
	≥2	84 (41.4%)
Cycle of chemotherapy	**1-4**	80 (39.4%)
	5-8	39 (19.2%)
	9-12	15 (7.4%)
	≥13	69 (34%)
Brand	**Xeloda**	20 (9.9%)
	Capecetabine acte	145 (71.4%)
	Oncocap	12 (5.9%)
	Xetabin	26 (12.8%)
Type of chemotherapy	**Adjuvant chemotherapy for colon cancer**	54 (26.6%)
	Palliative chemotherapy for colon cancer	86 (42.4%)
	Neoadjuvant chemotherapy for rectal cancer	4 (2%)
	Adjuvant chemotherapy for rectal cancer	6 (3%)
	Palliative chemotherapy for rectal cancer	29 (14.3%)
	Neoadjuvant chemotherapy for gastric cancer	6 (3%)
	Adjuvant chemotherapy for gastric cancer	3 (1.5%)
	Palliative chemotherapy for gastric cancer	15 (7.4%)
Chemotherapy regimen	**Single agent capecitabine**	19 (9.4%)
	Oxaliplatin	65 (32%)
	Irinotecan	2 (1%)
	Bevacizumab	15 (7.4%)
	Cetuximab	16 (7.9%)
Capecitabine with	**Oxaliplatin + Bevacizumab**	24 (11.8%)
	Oxaliplatin + Cetuximab	19 (9.4%)
	Oxaliplatin + Epirubicin	23 (11.3%)
	Irinotecan + Bevacizumab	11 (5.4%)
	Irinotecan + Cetuximab	9 (4.4%)

Adherence

The mean adherence rate was 97.7% (SD=10.55, range 7.1-100). Overall, patients had an adherence rate of ≥95% in 189 (93.1%) cycles and were considered adherent. Non-adherence (adherence rate of <100%) was found in 24 (11.8%) cycles. In five cycles (2.5%), the adherence rate was below 80%. One participant with an adherence rate of 7.1% had a history of coronary artery bypass grafting, mitral valve replacement, and taking warfarin. This patient discontinued capecitabine after 2 doses without consulting with his physician due to their concerns about the interaction of this medication with warfarin. Another participant missed one dose of capecitabine as their medication dropped on the floor. Adverse effects and forgetting to take a dose were the cause of non-adherence in 16 (7.8%) and 6 (2.9%) cycles, respectively. The rate of adherence was not significantly different among participants taking various capecitabine brands (i.e., Xeloda 100%, Capecitabine acte 93.1%, Oncocap 83.3%, Xetabin 92.3%) [*P*=0.34].

The percentage of adherence according to the patient characteristics and treatment-related factors are available upon request from the corresponding author. Only the type of chemotherapy was associated with adherence. Patients who underwent neoadjuvant chemotherapy (adherence rate=60%) were significantly less adherent to

capecitabine as compared with adjuvant (adherence rate=95.2%) and palliative chemotherapy (adherence rate=94.6%) [*P*=0.004].

Adverse effects

Results of the studied patients were available on an unequal number of cycles; therefore, we showed the percentage of patients-reported symptoms and laboratory abnormalities both per patient and per cycle in Table 3. HFS was the most frequently reported side effect in patients, as 50% of patients suffered from various degrees of HFS. Anemia was the most common laboratory abnormality and was detected in 28 (28.5%) patients.

Table 3. Patients-reported symptoms and laboratory abnormalities

Complaint		No (%) of cycles (n=203)	No (%) of patients (n=98)
Diarrhea	**No**	155 (76.4%)	73 (74.5%)
	Grade 1	30 (14.8%)	15 (15.3%)
	Grade 2	16 (7.9%)	8 (8.2%)
	Grade 3	2 (1%)	2 (2%)
HFS	**No**	97 (47.8%)	49 (50%)
	Grade 1	92 (45.3%0	40 (40.8%)
	Grade 2	13 (6.4%)	8 (8.2%)
	Grade 3	1 (0.5%)	1 (1%)
	Grade 4	0	0
Nausea	**No**	153 (75.4%)	70 (71.4%)
	Yes	50 (24.6%)	28 (28.6%)
Constipation	**No**	180 (88.7%)	84 (85.7%)
	Yes	23 (11.3%)	14 (14.3%)
Chest pain	**No**	191 (94.1%)	93 (94.9%)
	Yes	12 (5.9%)	5 (5.1%)
Fatigue	**No**	153 (75.4%)	68 (69.4%)
	Yes	50 (24.6%)	30 (30.6%)
Mucositis	**No**	178 (87.7%)	81 (82.7%)
	Yes	25 (12.3%)	17 (17.3%)
Loss of appetite	**No**	146 (71.9%)	62 (63.3%)
	Yes	57 (28.1%)	36 (36.7%)
Elevated liver enzyme	**No**	196 (96.6%)	92 (93.3%)
	Grade 1	6 (3%)	5 (5.1%)
	Grade 2	1 (0.5%)	1 (1%)
	Grade 3	0	0
	Grade 4	0	0
Neutropenia	**No**	197 (97%)	93 (94.9%)
	Grade 1	6 (3%)	5 (5.1%)
	Grade 2	0	0
	Grade 3	0	0
	Grade 4	0	0
Anemia	**No**	157 (77.3%)	70 (71.4%)
	Grade 1	38 (18.7%)	20 (20.4%)
	Grade 2	8 (3.9%)	8 (8.2%)
	Grade 3	0	0
Thrombocytopenia	**No**	198 (97.5%)	93 (94.9%)
	Grade 1	4 (2%)	4 (4.1%)
	Grade 2	2 (0.5%)	1 (1%)
	Grade 3	0	0
	Grade 4	0	0

HFS hand-foot syndrome

The presence of diarrhea, nausea, constipation, chest pain, fatigue, and mucositis were associated with a lower rate of adherence. HFS, loss of appetite, elevated liver enzymes, neutropenia, anemia, and thrombocytopenia were not associated with adherence. Details of the association between adherence and the patients-reported symptoms and laboratory abnormalities are available upon request from the corresponding author.

Multivariate logistic regression analysis of related factors to adherence

Sex, age, type of chemotherapy, chemotherapy regimen, and presence of diarrhea, nausea, constipation, chest pain, fatigue, mucositis, and loss of appetite had *P*<0.25 and were entered into our multivariable analysis

(Table 4). Logistic regression analysis showed that neoadjuvant therapy, nausea, and mucositis significantly predicted non-adherence to capecitabine. Neoadjuvant chemotherapy was significantly associated with a lower rate of adherence compared to palliative chemotherapy (OR=0.01, 95% CI: 0.001-0.38, *P*=0.01). The odds of adherence in patients without nausea were significantly (9.6 times) higher than in those with nausea (*P*=0.006). Patients without any mucositis were 13.7 times more adherent than patients who suffered from any kind of mucositis (*P*=0.004).

Table 4. Multivariate regression analysis of associated factors with adherence

Complaint		Adjusted OR (95%CI)	*P*
Sex	**Female**	1	0.31
	Male	2.82 (0.38-20.48)	
Age	**≤54**	1	
	55-64	1.46 (0.18-11.75)	0.72
	65-74	15.57 (0.84-77.19)	0.06
	≥75	0.15 (0.006-3.78)	0.25
Type of chemotherapy	**Palliative**	1	
	Adjuvant	7.2 (0.62-83.09)	0.11
	Neoadjuvant	0.01 (0.001-0.38)	0.01
Chemotherapy regimen	**Single agent capecitabine**	1	
	Two-drug combination	7.6 (0.97-54.30)	0.056
	Three-drug combination	5.1 (0.89-30.12)	0.06
Diarrhea	**Yes**	1	
	No	3.94 (0.53-28.87)	0.17
Nausea	**Yes**	1	
	No	9.6 (1.95-38.9)	0.006
Constipation	**Yes**	1	
	No	2.63 (0.25-27.03)	0.41
Chest pain	**Yes**	1	
	No	7.9 (0.66-31.97)	0.12
Fatigue	**Yes**	1	
	No	5.8 (0.95-35.37)	0.56
Mucositis	**Yes**	1	
	No	13.76 (2.58-51.23)	0.004
Loss of appetite	**Yes**	1	
	No	1.28 (0.45-6.76)	0.58

Discussion

In the present study, we investigated potential determinants of non-adherence to capecitabine among patients with colorectal and gastric cancers.

Adequate or satisfactory adherence was defined using cut-off points ranging between 80 and 95%, depending on the type of diseases and medications in the literature. Generally, when the self-report questionnaire is used for measuring adherence, higher values as high as 100% are considered the cut-off point for adherence (16). Despite this, some studies (10,15) considered 80% as their cut-off point for adherence to capecitabine, while a number of others set higher cut-off points with a hypothesis that even a small deviation from the optimal dosage may negatively affect the efficacy of chemotherapy. In this study, the adherence cut-off point was set at 95%.

Cancer patients are mostly expected to be highly adherent as they are suffering from a life-threatening disease. Our findings support this assumption by demonstrating a high adherence of 97.7% with capecitabine therapy measured with a pill count method. In our study, we found that patients were completely adherent to capecitabine in 93.1% of cycles. High rates of adherence to capecitabine have been reported in other relevant studies. In a study evaluating 30 patients, adherence to capecitabine was 88.3% for metastatic colon cancer, 90.4% for non-metastatic colon cancer, 94.3% for rectal cancer, and 96.2% for metastatic breast cancer (3). Timmers *et al*., (7) studied 92 patients who were being treated with capecitabine and reported a mean adherence rate of 99.3%. In their study, 91% of patients had an adherence rate of ≥95%. A group of studies investigated adherence by means of a self-reported questionnaire or electronic monitoring. Font *et*

al., (15), in an analysis of 119 participants who were undergoing preoperative oral capecitabine plus radiotherapy, showed a self-reported adherence rate of 83.2%. Using a cut-point of ≥80% for adherence and according to their pill count, they reported that 67.9% of patients were adherent to capecitabine. Bhattachayn *et al*., (1) reported an adherence rate of 72.7% in 43 patients with breast or colorectal cancers using the self-report method. Zahrina *et al*., (16) reported a mean adherence rate of 96.1% in a study of 113 patients on single regime capecitabine using a self-reported questionnaire. Partridge *et al*., (10) studied adherence to capecitabine with electronic monitoring in 161 patients with early-stage breast cancer and reported a mean adherence rate of 78%. In their study, 75% of patients had an adherence rate of ≥80%. Krolop *et al*., (18) assessed adherence using electronic monitoring in 73 patients in a prospective cohort study and demonstrated that 79.5% had an adherence rate of ≥90% and were adherent to capecitabine in the initial pre-intervention time.

Patients under treatment with capecitabine report a variety of adverse effects and symptoms during the course of chemotherapy. In our cohort, HFS was the most common side effect and was reported by 50% of our patients. Nonetheless, HFS was not associated with adherence to capecitabine. In our study, the occurrence of nausea and mucositis was significantly correlated with non-adherence to capecitabine. Most studies provide only limited information regarding the influence of adverse effects on adherence to capecitabine, with results in line with or contrary to our findings. In Timmers *et al*., (7) study, HFS was the most frequent side effect during treatment and was reported by 94.5% of patients after 5 cycles of chemotherapy. In this study, no factor was significantly associated with non-adherence, as only 6 patients (9%) were found to be non-adherent. Zahrina *et al*., (16) reported HFS in 65.5% of studied patients. In their study, grades 1, 2, and 3 of HFS were present in 48.7%, 13.3%, and 2.7% of patients, respectively. They found that the presence of nausea and vomiting, contrary to HFS, stomatitis, and diarrhea, was significantly associated with non-adherence. It is noteworthy that adverse effects were not related to adherence in a number of studies. Hefner *et al*., (11) found no association between the presence of adverse effects, including HFS, diarrhea, nausea, fatigue, mucositis, and fever, and being adherent to capecitabine. While we reported an association between non-adherence with the presence of nausea and mucositis, Font *et al*., (15) found no significant difference between non-adherent and adherent patients with respect to their reported side effects (e.g., fatigue, nausea, vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, and diarrhea). From a clinical perspective, we should note that effective strategies for reducing capecitabine side effects could be applied to increase patients' quality of life and their satisfaction with treatment and adherence.

In our sample, the group of patients who underwent neoadjuvant chemotherapy had the least adherence to capecitabine. Patients with rectal or gastric cancers who underwent neoadjuvant therapy were adherent to capecitabine in 60% of cycles, which is significantly lower than the patients who were under treatment with adjuvant or palliative chemotherapy. The possible reason for this finding could be that patients who received neoadjuvant therapy did not believe that they suffered from a serious life-threatening disease, maybe because they did not undergo a major surgery or their disease was optimistically described to them as a treatable disease. Through remarking on this group, more attention during the routine practice would become valuable to find early detection of non-adherent participants and facilitating discussion and elimination of potential reasons for non-adherence or change to intravenous drugs.

Some studies have suggested strategies to improve adherence through pharmaceutical care, focusing on treatment-related side effects, while others explore patients' attitudes toward medication therapy and their satisfaction with the information provided to them (11). These strategies, combined with more detailed discussions with patients about treatment side effects and potential risks of non-adherence, may be useful in reducing non-adherence to capecitabine. Educational tools, e.g., pamphlets that address the importance of adherence for achieving a good treatment response and methods to alleviate possible adverse effects, can be used to improve adherence to capecitabine.

The results of this study should be interpreted considering the following limitations. First, our sample size was relatively small, and we did not have access to data from all the cycles. Second, the diversity of variables and confounders and the small number of patients in certain subgroups affected our statistical power. Future investigations with more specific hypotheses can further expand our understanding of reasons for non-adherence in a patient undergoing chemotherapy. Further interventional studies focusing on the side effects of capecitabine and their preventive methods with a larger sample size, including all types of

chemotherapy (neoadjuvant/adjuvant/palliative), need to be done to investigate the role of side effects in non-adherence to capecitabine.

The results of our study demonstrate a high adherence to capecitabine among patients with gastrointestinal cancers, although the patients with gastric and rectal cancer who underwent neoadjuvant chemotherapy were at higher risk of poor adherence. The presence of nausea and mucositis were associated with poor adherence to capecitabine.

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