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Adverse reactions and adherence to capecitabine: A prospective study in patients with gastrointestinal cancer

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Abstract

Introduction: Capecitabine is an oral anticancer drug which can cause some adverse reactions and the great challenge for its use is to ensure the medication adherence. The aim of this study was to analyze adverse reactions and adherence to capecitabine in patients with gastrointestinal cancer.

Methods: A prospective study was performed in a tertiary teaching hospital in Brazil. Outpatients undergoing capecitabine treatment for colorectal or gastric cancer were followed for three cycles of treatment. Patient demographic and clinical characteristics data were collected. Adverse reactions were analyzed using Common Terminology Criteria for Adverse Events (CTCAE) v.4. Adherence to capecitabine were evaluated using Morisky-Green and MedTake tests. Statistical analysis was conducted using Chi-square, Fisher's exact and McNemer tests.

Results: One hundred and four patients were enrolled in this study, with a mean age was 58.5 ± 10.9 years; 51.0% were men and 51.0% Caucasian. Nausea and diarrhea were the most frequently reported adverse reactions (82.7% and 62.5%, respectively), followed by vomiting (54.8%), fatigue (54.8%), and hand-foot syndrome (53.9%). Nausea and diarrhea were also the most severe adverse reactions. Most patients were adherent to capecitabine in all cycles of treatment using the Morisky-Green test. Adherence increased significantly between cycle 1 and cycle 2 by MedTake test ($p < 0.001$). Some demographic and clinical characteristics were associated with adverse reactions (e.g., age and nausea, gender and nausea and vomiting) and capecitabine adherence (e.g., marital status and educational level) as well as some adverse reactions were associated with capecitabine adherence (hand-foot syndrome and nausea).

Conclusions: Clinical oncology pharmacists must provide patient information on the correct use of capecitabine, manage adverse reactions, and monitor adherence to treatment. Strategies to prevent non-adherence to capecitabine must be adopted to ensure the success of pharmacotherapy.

Keywords

Capecitabine, antineoplastic agents, drug-related side effects and adverse reactions, medication adherence

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Introduction

Capecitabine is an antimetabolite drug mostly used in the treatment of breast and gastrointestinal cancers. This oral anticancer agent was developed as a prodrug of fluorouracil (5-FU) and has numerous advantages over intravenous 5-FU therapy, such as decreased health costs and increased patient comfort and acceptability.[1,2] On the other hand, the great challenge for the use of capecitabine is to ensure the adherence to treatment, making the patients active in their self-care.

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Medication adherence is "the extent to which patients take medications as prescribed by their health care providers".[3] There are several direct and indirect methods to evaluate medication adherence, such as measurement of the level of medicine in blood, patient questionnaires, pill counts, electronic medication monitors, and patient diaries[3]; however, all have limitations. Measuring adherence to drug treatment is important for both research and clinical practice.[4] Thus, healthcare workers must be aware of non-adherence to oral antineoplastic agents focusing on high-risk individuals to improve patient adherence.[5]

Although very effective, capecitabine may cause some adverse reactions such as hand-foot syndrome, gastrointestinal effects and fatigue.[6,7] Adverse drug reactions may lead to non-adherence to treatment and poor quality of life. Patient counseling and medication management for oncologic patients receiving oral anticancer treatment is necessary to increase adherence, identify and manage common adverse drug reactions, and improve the quality of life.[8]

As a result of the significant increase in the use of oral therapies in cancer management worldwide, the postmarketing surveillance is essential. Concerned about this issue, we recently have investigated toxicity, adherence and quality of life in hepatocellular carcinoma patients taking sorafenib, another oral anticancer drug.[9] In the present study, we aimed to analyze adverse reactions and medication adherence in Brazilian patients undergoing capecitabine treatment for colorectal and gastric cancers.

Material and methods

Study design and setting

A prospective and quasi-experimental study was conducted from April 2017 to September 2018 and performed at the adult oncology outpatient service of a tertiary teaching hospital located in the city of Campinas, Sao Paulo, Brazil. Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) was used to plan this research.[10]

Patient selection criteria and treatment regimens

Patients were selected by consecutive nonprobabilistic sampling. Patients were eligible for the study if they were taking capecitabine for colorectal or gastric cancer with at least one complete treatment cycle. Patients unable to provide informed consent, or under 18 years of age were excluded.

Patients were invited to participate for this study at the time of the first capecitabine dispensation provided by the clinical pharmacist. On this occasion, patients also received oral and written instructions on the correct ingestion, storage and disposal of the medicine, as well as about management of the most common adverse reactions to capecitabine. Patients were followed by the pharmacist for three cycles of treatment.

Gastric cancer patients were treated with capecitabine combined with other intravenous chemotherapy:

- XELOX: intravenous oxaliplatin 130 mg/m^2 on day 1 followed by oral capecitabine 1000 mg/m^2 twice a day for 14 consecutive days starting on day 1 (day 1, evening, to day 15, morning); cycle repeated every 21 days;
- EOX: intravenous epirubicin 50 mg/m^2 and oxaliplatin 130 mg/m^2 on day 1 followed by oral capecitabine 625 mg/m^2 twice a day for 14 consecutive days starting on day 1 (day 1, evening, to day 15, morning), cycle repeated every 21 days.

Colorectal cancer patients were treated with capecitabine combined with intravenous chemotherapy (XELOX regimen) or as monotherapy with oral capecitabine 1000 mg/m^2 twice a day for 14 consecutive days starting on day 1 (day 1, evening, to day 15, morning), cycle repeated every 21 days.

On each day of intravenous chemotherapy (XELOX and EOX regimens), the patients received vigorous hydration and prophylaxis of acute emesis (dexamethasone plus ondansetron, intravenously). Regarding delayed adverse reactions, patients were instructed to use metoclopramide and-or dimenhydrinate if nausea and vomiting, loperamide if diarrhea, and moisturizing cream and urea cream on the palms of the hands and soles of the feet to attenuate hand-foot syndrome. A decrease in capecitabine dose may occur during treatment if the patient experiences a severe adverse reaction and/or a significant decrease in functional status.

Demographic and clinical data

Data regarding baseline patient characteristics were obtained from medical records and interview with patients, including information concerning age, gender, race, marital status, education level, work situation, smoking and drinking habits, comorbidities, type of cancer, presence of metastasis, therapeutic regimen, prior chemotherapy, and prior tumor resection surgery.

Smoking category was classified based on the study by Jindal et al.[11] Non-smokers were patients that denied having ever smoked; light, moderate and heavy smokers were smokers and ex-smokers, and they were classified according to the smoking index (SI), which was the product of the average number of cigarettes smoked per day and the duration of smoking

in years; light (SI = 1 – 100), moderate (SI = 101 – 300) and heavy (SI ≥301) smokers.

Drinking category was classified based on the study by Whitcomb et al.[12] The average weekly alcohol intake during the maximum lifetime drinking period (drinks/week): abstainers, no alcohol use or <20 drinks in lifetime; light drinkers, ≤3 drinks/week; moderate drinkers, 4–7 drinks/week for females and 4–14 drinks/week for males; heavy drinkers, 8–34 drinks/week for females and 15–34 drinks/week for males; very heavy drinkers, ≥35 drinks/week.

Adverse reactions

Adverse drug reaction was considered as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product".[13] Common adverse reactions for capecitabine include hand-foot syndrome, diarrhea, nausea, vomiting, and fatigue. Diarrhea and vomiting were graded by severity using the Common Terminology Criteria for Adverse Events (CTCAE) v.4: grade 0 – absent or none, grade 1 – mild, grade 2 – moderate, grade 3 – severe, and grade 4 – life-threatening consequence. Hand-foot syndrome, nausea, and fatigue are ranked to grade 3 using the same criteria.[14] Adverse reactions were evaluated after each cycle of chemotherapy.

Medication adherence

Medication adherence has been previously defined by Osterberg and Blaschke.[3] Adherence to capecitabine was evaluated after each cycle of treatment using Morisky-Green[15] and MedTake[16] tests.

Morisky-Green test comprises four yes/no questions: (1) Have you ever forgotten to take your medicine? (2) Are you sometimes careless about the time you take your medicine? (3) Do you ever stop taking your medicine when you feel better? (4) Do you ever stop taking your medicine if you feel worse?[15] We considered as non-adherent all patients who answered "yes" to at least one of the four questions.

MedTake test consists of four test subcomponents (dosage, indication, food or water coingestion, and regimen). For each subcomponents, the test is scored as a percentage of correct actions, equally weighted, and compared with label directions or self-expressed physician changes. A MedTake test score (0-100%) summarized a subject's overall ability to take their drug safely.[16] A patient was considered to be non-adherent if he/she obtained a score lower than 100%.

Data analysis

All data obtained were entered into Excel® database. The results of the descriptive data were expressed as absolute frequencies and percentages for categorical variables and as the means with standard error and/or range for numerical variables.

Statistical analysis was conducted through the SPSS® program, version 23. Chi-square or Fisher's exact tests were used to compare categorical variables. McNemer were used to compare the same variable in two different times. The significance level for all analyses was 5% ($P < 0.05$).

Ethical considerations

The Research Ethics Committee of the institution approved this study. All participating subjects provided a written informed consent.

Results

One hundred and four patients were enrolled and completed at least one cycle of treatment. The mean age of the participants was 58 years old. The majority were men (51.0%), Caucasian (51.0%), married (64.4%), with 1 to 4 years of literacy (36.5%), not working (87.5%), smokers (52.9%), and drinkers (59.6%). Moreover, the most had at least one comorbidity (52.9%), had colorectal cancer (71.2%), had non-metastatic tumor (50.0%), were treated with XELOX regimen (95.2%), have not received prior chemotherapy (58.7%), and have undergone prior surgical resection of the tumor (68.3%). Table 1 presents complete demographic and clinical data for the studied subjects.

Of the 104 patients who underwent the cycle 1, only 95 were assessed for the cycle 2 and 83 were assessed for the cycle 3 (Figure 1). The mean daily capecitabine dose in the 1st cycle was 3052.0 ± 636.9 mg, 2942.1 ± 660.3 mg in the 2nd cycle, and 2901.4 ± 648.9 mg in the 3rd cycle. A decrease in the daily dose (mg) is noted since there was a reduction in body surface (m^2) during the study or also due to the fact that some patients had a dose reduction (mg/m^2) due to capecitabine adverse reactions.

Regarding the adverse reactions, 82.7%, 62.5%, 54.8%, 54.8% and 53.9% of patients had some degree of nausea, diarrhea, vomiting, fatigue and hand-foot syndrome, respectively, during the study. Besides being more frequent, nausea and diarrhea were the most serious and debilitating adverse reactions, since these were the symptoms with more patients presenting grade 3 and 4 of severity (Table 2). There was no significant difference regarding the presence or absence of each adverse reactions between the cycles (all p values > 0.05).

Table 1. Demographic and clinical characteristics of patients with gastrointestinal cancer treated with capecitabine (n = 104).

Characteristics	
Age, mean ± SD (range), years	58.5 ± 10.9 (33-82)
Gender, n (%)	
Men	53 (51.0)
Women	52 (49.0)
Race, n (%)	
Caucasian	53 (51.0)
Non-Caucasian	51 (49.0)
Marital status, n (%)	
Married	67 (64.4)
Single	13 (12.5)
Divorced	13 (12.5)
Widowed	8 (7.7)
Other	3 (2.9)
Education level, n (%)	
Illiterate	5 (4.8)
1–4 years	38 (36.5)
5–8 years	27 (26.0)
9–11 years	28 (26.9)
≥12 years	6 (5.8)
Work situation, n (%)	
Work	13 (12.5)
Not working	91 (87.5)
Smoking category, n (%)	
Non-smokers	49 (47.1)
Light smokers	13 (12.5)
Moderate smokers	11 (10.6)
Heavy smokers	31 (29.8)
Drinking category, n (%)	
Abstainers	42 (40.4)
Light drinkers	22 (21.1)
Moderate drinkers	20 (19.2)
Heavy drinkers	9 (8.7)
Very heavy drinkers	11 (10.6)
At least one comorbidity, n (%)	55 (52.9)
Type of cancer, n (%)	
Colorectal	74 (71.2)
Gastric	30 (28.8)
Presence of metastasis, n (%)	
Non-metastatic cancer	52 (50.0)
Metastatic cancer	50 (48.1)
Not assessed	2 (1.9)
Therapeutic regimen, n (%)	
XELOX	99 (95.2)
EOX	4 (3.8)
Capecitabine monotherapy	1 (1.0)
Prior chemotherapy, n (%)	43 (41.3)
Prior surgery, n (%)	71 (68.3)

EOX: epirubicin, oxaliplatin, capecitabine; n: absolute number of patients; SD: standard deviation; XELOX: oxaliplatin, capecitabine.

Most of patients taking capecitabine were adherent to treatment by Morisky-Green test (80.8%, 82.1% and 81.9% after cycles 1, 2 and 3, respectively). Regarding the MedTake test, the percentage of adherent patients increased over the course of the study (44.2%, 68.4% and 75.9% after cycles 1, 2 and 3, respectively), which shows that they were acquiring knowledge about the correct capecitabine dose, indication, ingestion, and regimen throughout the treatment (Table 3). By MedTake test, comparing the percentages of adherent and non-adherent patients between cycle 1 and 2, there was a statistically significant difference ($p < 0.001$) and the same result was found in the comparison between cycle 1 and 3 ($p < 0.001$); unlike the Morisky-Green test, which had no significant difference between the cycles. Moreover, the results obtained with the Morisky-Green test were compared with the results of MedTake test and no associations were observed (cycle 1: $p = 0.154$; cycle 2: $p = 0.251$; cycle 3: $p = 0.750$).

Table 4 presents statistically significant associations found between studied variables. In addition, see results of all variables tested in Appendices 1 to 7.

Discussion

The findings of this study showed that nausea and diarrhea were the most frequently reported adverse reactions, followed by vomiting, fatigue, and hand-foot syndrome. Nausea and diarrhea were also the most severe adverse reactions. Most patients were adherent to capecitabine in all cycles of treatment using the Morisky-Green test. Adherence increased significantly between cycle 1 and cycle 2 by MedTake test. Some demographic and clinical characteristics were associated with adverse reactions and capecitabine adherence as well as some adverse reactions were associated with capecitabine adherence. These associations can be used for patient prioritization for pharmaceutical care.

To be best of our knowledge, this is the first Brazilian study that evaluated adverse reactions and adherence to capecitabine in patients with gastrointestinal cancer. Figueiredo Junior and Forones[17] evaluated the adherence to capecitabine in Brazilian hospital; however, they correlated adherence with changes in quality of life of colorectal and breast cancer patients and did not assess adverse reactions to capecitabine. Therefore, further research is needed to provide more robust results.

A previous study showed a high frequency of adverse reactions in patients treated with capecitabine.[6] We found that more than half of patients had some degree of nausea, diarrhea, vomiting, fatigue, and hand-foot syndrome during the study, despite the pharmacist providing information on preventing and managing adverse reactions (e.g., use of moisturizing cream and urea cream on the palms of the hands and soles of the feet, correct use of antiemetics and antidiarrheals, and non-pharmacological measures). Otherwise, we

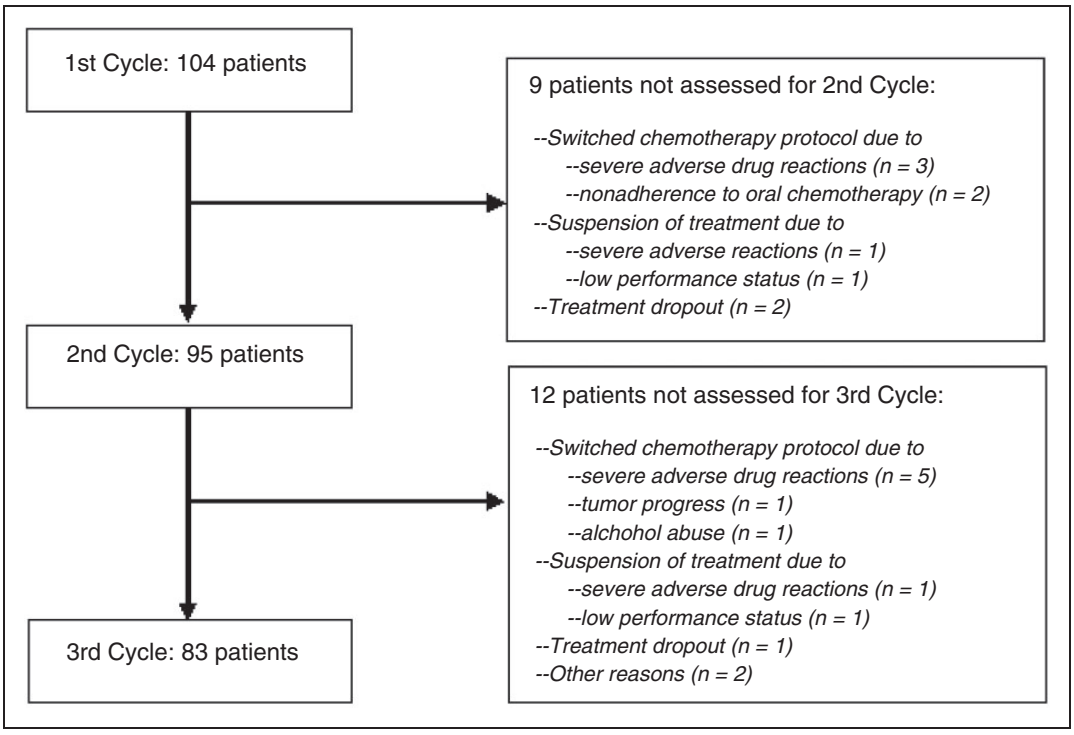

Figure 1. Flow diagram of the patients with gastrointestinal cancer treated with capecitabine included in the study.

Table 2. Adverse reactions and severities experienced by patients with gastrointestinal cancer after each chemotherapy cycle.

Adverse reaction/severity	1st Cycle (n = 104)	2nd Cycle (n = 95)	3rd Cycle (n = 83)
Hand-foot syndrome (n, %)			
Grade 0	71 (68.3)	58 (61.1)	52 (62.7)
Grade 1	29 (27.9)	28 (29.5)	23 (27.7)
Grade 2	3 (2.9)	6 (6.3)	8 (9.6)
Grade 3	1 (0.9)	3 (3.1)	0 (0.0)
Nausea (n, %)			
Grade 0	34 (32.7)	40 (42.1)	35 (42.2)
Grade 1	36 (34.6)	33 (34.7)	28 (33.7)
Grade 2	22 (21.2)	18 (19.0)	20 (24.1)
Grade 3	12 (11.5)	4 (4.2)	0 (0.0)
Vomiting (n, %)			
Grade 0	73 (70.2)	66 (69.5)	62 (74.7)
Grade 1	16 (15.4)	20 (21.1)	14 (16.9)
Grade 2	9 (8.6)	8 (8.4)	7 (8.4)
Grade 3	6 (5.8)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	1 (1.0)	0 (0.0)
Diarrhea (n, %)			
Grade 0	58 (55.8)	55 (57.9)	58 (69.9)
Grade 1	24 (23.1)	20 (21.1)	15 (18.1)
Grade 2	14 (13.4)	15 (15.8)	7 (8.4)
Grade 3	6 (5.8)	3 (3.1)	3 (3.6)
Grade 4	2 (1.9)	2 (2.1)	0 (0.0)
Fatigue (n, %)			
Grade 0	68 (65.4)	66 (69.5)	55 (66.3)
Grade 1	27 (26.0)	19 (20.0)	18 (21.7)
Grade 2	9 (8.6)	9 (9.5)	9 (10.8)
Grade 3	0 (0.0)	1 (1.0)	1 (1.2)

n: absolute number of patients.

Table 3. Adherence to capecitabine among patients with gastrointestinal cancer measured with Morisky-Green and MedTake tests after each chemotherapy cycle.

Adherence	1st Cycle (n = 104)	2nd Cycle (n = 95)	3rd Cycle (n = 83)
Morisky-Green test (n, %)			
Adherent patients	84 (80.8)	78 (82.1)	68 (81.9)
Non-adherent patients	20 (19.2)	17 (17.9)	15 (18.1)
MedTake test (n, %)			
Adherent patients	46 (44.2)	65 (68.4)	63 (75.9)
Non-adherent patients	58 (55.8)	30 (31.6)	20 (24.1)

n: absolute number of patients.

hypothesized that the frequency and severity of adverse reactions could be even higher.

Our findings showed that nausea was one of the most frequent and severe adverse reaction. Vomiting was not the two most frequent adverse reactions, but it occurred in $> 50\%$ of patients. Capecitabine has a low emetic risk by the American Society of Clinical Oncology (ASCO) guideline.[18] However, in the case of antineoplastic combination, the emetic risk of treatment is determined by the agent of greatest emetic risk.[18] Thus, patients treated with XELOX (most of the subjects in this study) and EOX had a moderate emetic risk. According to ASCO guideline,[18] for patients treated with moderate emetic risk therapy, in day 1 should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone, what happened in our study. In addition, patients treated with oxaliplatin (it is known to cause delayed nausea and vomiting) may be offered oral dexamethasone on days 2 to 3; however, patients of this study were not treated this way. In our institution, oral dexamethasone for delayed nausea and vomiting is prescribed more frequently for patients using highly emetogenic chemotherapy. In addition, many patients do not have access to oral ondansetron due to higher costs, and therefore use only metoclopramide and-or dimenhydrinate. Thus, only patient counselling is not enough to improve the management of nausea and vomiting. It is also necessary to expand access to antiemetics and to implement strategies to increasing adherence to the guideline's recommendations by the prescribers.[19]

This study also showed an association between nausea and vomiting with women as well as association between nausea and non-elderly patients. It is in agreement with a recent systematic review that reported that female sex and younger people are at higher risk for chemotherapy-induced nausea and vomiting.[20] This is possibly related to the pathophysiology of these groups, although it is not very clear in the literature. However, our study did not observe any association between low alcohol intake and nausea or vomiting, as shown by recent review.[20]

Diarrhea was the second most frequent and most severe adverse reaction in this study. Bhattacharya et al.[6] found a frequency of diarrhea of 53.5%, slightly different to our study. Our study also showed an association between diarrhea and tumor resection surgery. This result is expected since diarrhea is known to be one of the effects of the gastrectomy and colectomy surgery.[21,22] Diarrhea following surgery on the gastrointestinal tract occurs due to accelerated gastric emptying, increased secretion of bile salts, decreased gastric secretion leading to proliferation of intestinal bacteria, mucosal changes, and deficient lactase production.[21,22] Patients with diarrhea were treated with loperamide, but other drugs can also be used to manage diarrhea as octreotide, tincture of opium, atropine and budesonide.[23,24] Moreover, patients with severe adverse reactions to capecitabine, especially diarrhea, should be checked for genetic polymorphisms in the dihydropyrimidine dehydrogenase gene.[23,24]

Hand-foot syndrome is a common skin adverse reaction of capecitabine and usually starts or seems to be more severe within the first two cycles of treatment,[25] although there was no significant difference in the frequency of hand-foot syndrome between cycles in the present study. Among the patients included in our study, 53.9% had hand-foot syndrome and it is in accordance with the literature data.[26] Urea-based cream, vitamin E, clobetasol, topical retinoids, pyridoxine, dimethylsulfoxide, and inhibitors of cyclooxygenase 2 (COX-2) are most management strategies of hand-foot syndrome resulting from anticancer drugs.[26–28] Furthermore, preventive measures must also be taken, such as submerging hands and feet in cool water and using topical emollients, as well as to avoid exposure hands and feet to extreme changes in temperature, excessive exercise, skin friction and pressure.[27,29]

This study showed an association between age and hand-foot syndrome. Moderate hand-foot syndrome was more frequent in patients aged 18–39 years old. The only patient who had severe hand-foot syndrome aged $\geq$60 years old. Hand-foot syndrome induced by 5-FU seems to be more common in elderly and female

Table 4. Statistically significant associations found between studied variables (demographic/clinical data of patients, adverse reactions, and adherence to capecitabine).

Associations between:	Variable 1	Variable 2	Cycle	Frequencies	P value	Commentaries
Demographic/ clinical data and adverse reactions	Age	Hand Foot Syndrome	1	18–39 y (g0: 40.0%; g1: 20.0%; g2: 40.0%; g3: 0%) 40-59 y (g0: 74.4%; g1: 23.3%; g2: 2.3%; g3: 0%) ≥60 y (g0: 66.1%; g1: 32.1%; g2: 0%; g3: 1.8%)	0.017[a]	Moderate hand foot syndrome was more frequent in patients aged 18-39 years old. The only patient who had severe hand foot syndrome aged ≥60 years old.
		Nausea	3	18–39 y (g0: 33.3%; g1: 0%; g2: 66.7%; g3: 0%) 40–59 y (g0: 26.5%; g1: 50.0%; g2: 23.5%; g3: 0%) ≥60 y (g0: 54.4%; g1: 23.9%; g2: 21.7%; g3: 0%)	0.018[a]	Younger patients had more nausea than patients ≥60 years old.
	Gender	Nausea	1	Women (g0: 21.6%; g1: 39.2%; g2: 19.6%; g3: 19.6%) Men (g0: 43.4%; g1: 30.2%; g2: 22.6%; g3: 3.8%)	0.017[a]	Women had a higher frequency of nausea and more severe nausea than men.
			2	Women (g0: 45.7%; g1: 23.9%; g2: 28.3%; g3: 2.1%) Men (g0: 38.8%; g1: 44.9%; g2: 10.2%; g3: 6.1%)	0.034[a]	Women had more moderate nausea than men. Men had more mild nausea than women.
		Vomiting	1	Women (g0: 54.9%; g1: 19.6%; g2: 13.7%; g3: 11.8%; g4:0%) Men (g0: 84.9%; g1: 11.3%; g2: 3.8%; g3: 0%; g4:0%)	0.002[a]	Women had a higher frequency of vomiting and more severe vomiting than men.
	Prior surgery	Diarrhea	2	Prior surgery (g0: 50.0%; g1: 28.8%; g2: 15.2%; g3: 4.5%; g4: 1.5%) No prior surgery (g0: 75.8%; g1: 3.5%; g2: 17.2%; g3: 0%; g4: 3.5%)	0.015[a]	Patients undergoing prior tumor resection surgery had a higher frequency of diarrhea than patients without previous surgery.
Demographic/ clinical data and adherence	Age	Adherence (Morisky-Green test)	2	18–39 y (adherent: 50.0%; non-adherent: 50.0%) 40–59 y (adherent: 73.8%; non-adherent: 26.2%) ≥ 60 y (adherent: 91.8%; non-adherent: 8.2%)	0.013[a]	Patients ≥60 years old were more adherent to capecitabine than younger patients.
		Adherence (MedTake test)	2	18–39 y (adherent: 75.0%; non-adherent: 25.0%) 40–59 y (adherent: 83.3%; non-adherent: 16.7%) ≥ 60 y (adherent: 55.9%; non-adherent: 44.9%)	0.011[a]	Younger patients were more adherent to capecitabine than patients ≥60 years old.
			3	18–39 y (adherent: 100%; non-adherent: 0%) 40-59 y (adherent: 88.2%; non-adherent: 11.8%) ≥ 60 y (adherent: 65.2%; non-adherent: 34.8%)	0.042[a]	Younger patients were more adherent to capecitabine than patients ≥60 years old.
	Marital status	Adherence (Morisky-Green test)	1	Married (adherent: 91.0%; non-adherent: 9.0%) Not married (adherent: 62.2%; non-adherent: 37.8%)	0.000[b]	Married patients were more adherent to capecitabine than not married patients.
		Adherence (MedTake test)	1	Married (adherent: 53.7%; non-adherent: 46.3%) Not married (adherent: 27.0%; non-adherent: 73.0%)	0.009[b]	Married patients were more adherent to capecitabine than not married patients.

(continued)

Table 4. Continued.

Associations between:	Variable 1	Variable 2	Cycle	Frequencies	P value	Commentaries
	Educational level	Adherence (Morisky-Green test)	1	Illiterate (adherent: 60.0%; non-adherent: 40.0%) 1–4 years (adherent: 65.8%; non-adherent: 34.2%) 5–8 years (adherent: 81.5%; non-adherent: 18.5%) 9–11 years (adherent: 100%; non-adherent: 0%) ≥12 years (adherent: 100%; non-adherent: 0%)	0.001[a]	More educated patients were more adherent to capecitabine.
	Presence of metastasis	Adherence (Morisky-Green test)	3	Non-metastatic (adherent: 90.2%; non-adherent: 9.8%) Metastatic (adherent: 72.5%; non-adherent: 27.5%)	0.049[a]	Non-metastatic cancer patients were more adherent to capecitabine than metastatic cancer patients.
	Race	Adherence (MedTake test)	1	Caucasian (adherent: 54.7%; non-adherent: 45.3%) Non-Caucasian (adherent: 33.3%; non-adherent: 66.7%)	0.028[b]	Caucasian were more adherent to capecitabine than non-Caucasian patients.
	Prior chemotherapy	Adherence (MedTake test)	3	Prior chemotherapy (adherent: 62.5%; non-adherent: 37.5%) No prior chemotherapy (adherent: 84.3%; non-adherent: 15.7%)	0.024[b]	Patients undergoing no prior chemotherapy were more adherent to capecitabine than patients undergoing prior chemotherapy.
Adverse reactions and adherence	Hand foot syndrome	Adherence (Morisky-Green test)	1	Adherent (g0: 64.3%; g1: 32.1%; g2: 3.6%; g3: 0%) Non-adherent (g0: 85.0%; g1: 10.0%; g2: 0%; g3: 5.0%)	0.044[a]	Mild and moderate hand foot syndrome was more frequent in adherent patients. The only patient who had severe hand foot syndrome was non-adherent to capecitabine.
		Adherence (MedTake test)	2	Adherent (g0: 60.0%; g1: 30.8%; g2: 9.2%; g3: 0%) Non-adherent (g0: 63.3%; g1: 26.7%; g2: 0%; g3: 10.0%)	0.027[a]	Mild and moderate hand foot syndrome was more frequent in adherent patients. Severe hand foot syndrome was more frequent in non-adherent patients.
	Nausea	Adherence (MedTake test)	3	Adherent (g0: 39.7%; g1: 41.3%; g2: 19.0%; g3: 0%) Non-adherent (g0: 50.0%; g1: 10.0%; g2: 40.0%; g3: 0%)	0.017[a]	Mild nausea was more frequent in adherent patients. Moderate nausea was more frequent in non-adherent patients.

g: grade.
[a]Fisher's exact test.
[b]Chi-square test.

patients, although no mechanism has been proposed to explain this association.[27] However, studies with capecitabine showed no relationship between hand-foot syndrome and age or gender.[25,30]

It is common for cancer patients to experience fatigue. Several factors can be associated with fatigue such as the tumor and its complications, comorbidities conditions, anticancer treatments (e.g., chemotherapy) as well as other medications, and psychological factors.[31] In this study, fatigue was not one of the most frequent adverse reactions to capecitabine and almost no patient had severe fatigue. Moreover, no association was found with fatigue.

Morisky-Green and the MedTake tests are indirect methods of measuring adherence (patient questionnaires). They are simple and inexpensive methods and the most useful in the clinical setting; however, they are susceptible to error with increases in time between visits and the results are easily distorted by the patient.[3] Both assess adherence but with a different point of view: while Morisky-Green assesses whether or not the patient has taken his medication, the MedTake test assesses the knowledge related to drug treatment that directly interferes with adherence. This explains why they did not present a significant association in the present study. There are many other indirect methods that can be used to assess capecitabine adherence, such as patient diaries, electronic medication monitor, rates of prescription refills, pill counts, and other questionnaires. We tried to use the pill count in this study but were unsuccessful since the patients did not return the blister packs. Electronic medication monitors method is very precise; however, it is very expensive which limits its use in most hospitals and clinics in developing countries. On the other hand, a qualitative study suggested that self-report questionnaires to assess the adherence to oral chemotherapy is not a good measure and a direct patient observation would be the best way to assessment.[32]

In this study, we considered adherent patients as those who showed 100% adherence, as well as in two other previous studies.[6,33] Even so, adherence to capecitabine was high, as other studies have shown.[6,17,33–35] This can be explained due to the severity of cancer disease compared to other chronic diseases. On the other hand, the results obtained with the Morisky-Green test may be overestimated due to the ease in giving affirmative answers. In addition, patients may not respond negatively for fear of interfering with their medical treatment.

Our results showed that adherence by Morisky-Green test was associated with educational level, marital status and presence of metastasis that corroborate with the literature.[17,36–38] In addition, adherence measured by MedTake test was associated with race and marital status, results also expected.[4,37,39,40] However, an unexpected result was that patients treated with no prior chemotherapy were more adherent to capecitabine by MedTake than patients treated with prior chemotherapy. Moreover, elderly people were more attentive to take the medication because they showed greater adherence by Morisky-Green test, but had more difficulty in answering MedTake questions. Regarding the association between medication adherence and adverse reactions, our results did not clearly demonstrate that adverse reactions impact on adherence to capecitabine, unlike Zahrina et al.[34]

It is important to note that the significant associations found did not occur in all cycles of treatment. These findings are expected, since many factors may be related to adherence and adverse reactions to capecitabine and these factors are not always interfere significantly in all cycles of treatment. Moreover, this is a longitudinal study and most of studies that evaluated these associations are cross-sectional studies, making it difficult to compare this behavior.

Our results revealed a significant increase in adherent patients (using MedTake test) after cycle 1 of treatment. Our hypothesis is that patient counselling provided by the clinical pharmacist may have improved the knowledge of pharmacotherapy in patients previously classified as non-adherent. A review showed that pharmacist interventions are crucial to increase medication adherence in adult outpatients with cancer.[41]

This study has some limitations. First, the treatment was evaluated in a short time, though this evaluation in three times was able to detect adverse reactions and problems of adherence treatment. Second, the instruments used to assess adherence to capecitabine present some disadvantages, as previously discussed; therefore, we used two instruments complementary to minimize these disadvantages. Moreover, no regression analysis was used due the heterogeneity of sample. Finally, this study was conducted at a single center and the conclusions that may be drawn are limited.

Conclusion

The mean age of patients was 58 years and most of them were men, Caucasian, married, with 1 to 4 years of literacy, had non-metastatic tumor, and have undergone prior surgical resection of the tumor. Moreover, our findings showed that more than half of patients had some degree of nausea, diarrhea, vomiting, fatigue and hand-foot syndrome during the study. Nausea and diarrhea were the most serious adverse reactions. Nevertheless, most patients were adherent to capecitabine during practically the entire treatment. Some demographic and clinical characteristics were associated with adverse reactions and capecitabine adherence.

Hand-foot syndrome and nausea were associated with capecitabine adherence. Clinical oncology pharmacists must provide patient information on the correct use of capecitabine, manage adverse reactions, and monitor adherence to treatment. Strategies to prevent non-adherence to capecitabine must be adopted to ensure the success of pharmacotherapy.

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Supplemental material

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