

Patients' Adherence to Capecitabine Treatment Is Affected by The Drug-Related Adverse Effects Rather Than by Their Sociodemographic Characteristics

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ABSTRACT

Background: Colorectal cancer is the third most prevalent cancer worldwide as 1.80 million new cases of the cancer were diagnosed, and 862,000 patients died in 2018. Depending on the stage, upfront surgery is the main form of treatment, followed by adjuvant chemotherapy. Despite the importance of patients' adherence while they are on anti-cancer treatment, there was no published data in the literature evaluating this vital parameter concerning Iraqi patients receiving anti-cancer drugs, in general, or those on Capecitabine, in particular.

Methods: A cross-sectional, open-label prospective study was conducted at Al-Amal and Oncology Teaching Hospitals, Baghdad during the period from November 2021 to June 2022. A convenient sampling method was adopted to enrol patients in the current study. Assessment of adherence to capecitabine treatment was done using Morisky Medication-Taking Adherence Scale (MMAS). **Results:** Generalized fatigue was the most common adverse event as it presented in 63.7% of participants. Also, only 6.9% of participants had abnormal renal function tests. In addition, most of participants showed low-moderate adherence to capecitabine treatment.

Conclusion: The extent of adherence to capecitabine treatment by colorectal cancer seems to be more sensitive to capecitabine-related adverse effects rather than to patients' sociodemographic characteristics.

Keywords: Adherence, Adverse effects, Capecitabine, Colorectal cancer, Sociodemographic.

INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent cancer worldwide¹.

The causes of CRC play an important and effective role in genetic and environmental factors^{2,3}. Depending on the stage, upfront surgery is the main form of treatment, followed by adjuvant chemotherapy⁴.

Capecitabine, an oral prodrug, is a chemotherapy agent that was approved in 2001 and has been shown to be effective in the treatment of CRC, gastric cancer, and breast cancer⁵⁻⁷. The mechanism of action of the drug is presented in Figure (1).

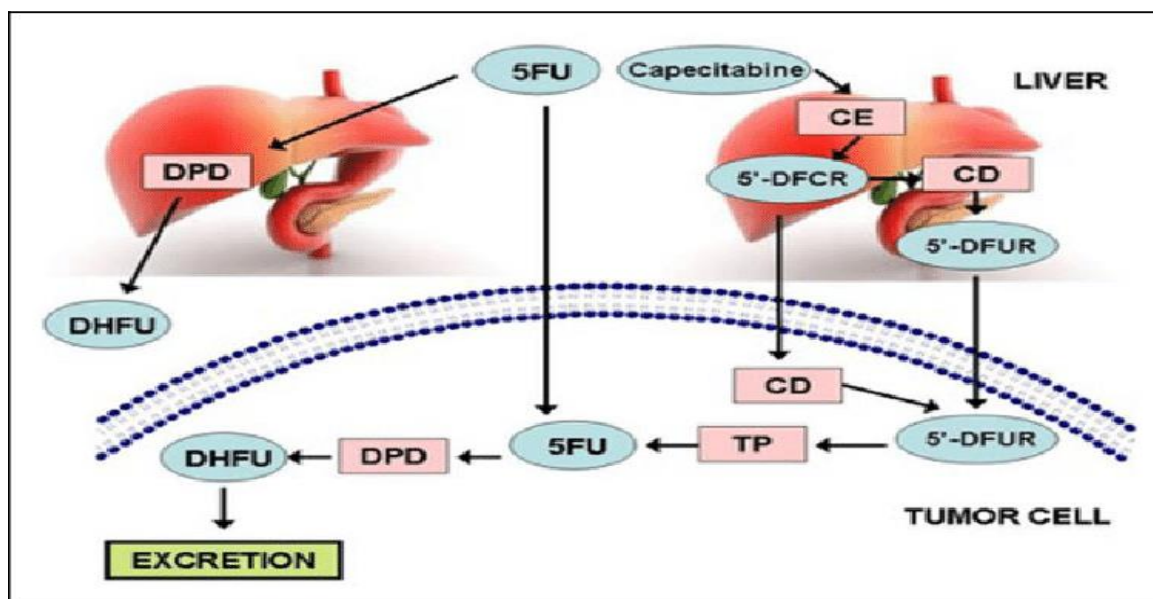


Figure (1): Mechanism of action of Capecitabine³⁵.

CE, carboxyl esterase; CD, cytidine deaminase; TP, thymidine phosphorylase; 5'-DFCR, 5'-deoxy-5-fluorocytidine; 5'-DFUR, 5'-deoxy-5-fluorouridine; DHFU, dihydro-5-fluorouracil; 5FU, fluorouracil; DPD, dihydropyrimidine dehydrogenase.

Adherence: It is the “extent to which a person’s behaviour (in terms of taking medications, following diets, or executing other lifestyle changes) coincides with the clinical prescription”^{8, 9}. Adherence to oral anti-cancer treatment was reported to be ranging from 16 to 100% with different anti-cancer therapies and various methods of measurement^{10, 11}. Moreover, adherence to medications is influenced by a range of variables including patient's personal traits, his/her family and cultural background, interactions with healthcare professionals, and the healthcare system as a whole. In addition, poor medication adherence is regarded as a potential contributor to disparities in health outcomes seen for various conditions across racial and ethnic groups due to its association with worse outcomes. As a consequence, ensuring adherence to chemotherapy is important to prevent disease progression, prolong survival and sustain a good quality of life (QoL)⁹.

Capecitabine is a complex chemotherapeutic agent with many side effects that might affect patient's adherence to treatment^{12, 13}. Also, patient's adherence is significantly increased as a result of the pharmaceutical care intervention. Additionally, patients who received more intensive medical care were kept on their capecitabine regimen for longer periods of time and displayed better regularity with regard to drug intake intervals. To fully utilize the potential of orally administered chemotherapies, an infrastructure for monitoring and improving adherence must be developed¹⁴.

The proposed methods of measuring non-adherence fall into two different groups¹⁵:

1. Direct measures of adherence include observed therapy and measurement of drug/metabolite levels.
2. Indirect measures include patient surveys, rate of prescription refills, electronic medication monitoring, and medical record documentation.

Despite the importance of patients' adherence while they are on anti-cancer treatment, there was no published data in the literature evaluating this vital parameter concerning Iraqi patients receiving anti-cancer drugs, in general, or those on Capecitabine, in particular. Therefore, the aim of current study was to assess adherence to treatment among Iraqi patients with CRC that were treated by Capecitabine.

METHODS

The current study was a cross-sectional, open-label prospective study that was conducted at Al-Amal and Oncology Teaching Hospitals in Baghdad during the period from November 2021 to June 2022. Patients were asked to participate voluntarily after an adequate explanation about the aim and method of the study.

A convenient sampling method was adopted to enroll the participants in current study. It was planned to recruit 50-100 patients.

Inclusion criteria: Patients who were diagnosed with colorectal cancer (CRC) and they were on capecitabine treatment for one month or more. Age should be ≥ 18 years and able to provide an informed consent.

Exclusion criteria:

Those who had another type of cancer, those with chronic respiratory, renal and/or hepatic diseases as well as those with diabetes mellitus, hypertension, cerebrovascular and/or cardiovascular disease. Moreover, pregnant and/or nursing mothers and patients with CRC but treated with radiotherapy.

The data necessary for the study, were collected using validated questionnaires through interviews performed by the researchers with candidate patients, and included sociodemographic characteristics (gender, age, education, residency, and employment), adverse events associated with capecitabine treatment (liver function test, renal function test, and white blood cell count) and assessment of treatment adherence based on Morisky Medication-Taking Adherence Scale (MMAS)^{16, 17}.

Ethical Approval:

Ethical Approval was obtained from the Scientific Research Ethics Committees at Department of Pharmacology/ College of Medicine, University of Baghdad and Baghdad Teaching Hospital for Oncology/ Ministry of Health, Iraq.

Statistical analysis

Microsoft Excel 2019 and the Statistical Package for the Social Sciences (SPSS, version 25) were used for data entry and analysis. The descriptive analysis focused on frequencies and percentages. Continuous variables were presented as mean \pm SD. Categorical data were presented as proportions and the Chi-squared test was used for the difference between two proportions. The level of significance was considered at $P \leq 0.05$.

RESULTS

Demographic data of participants

A total of 102 patients were enrolled in current study (52% were males and 48% were females). The patients who were 51-60 years old constituted the largest group (30.4%). In addition, 88.2% of the patients were living in urban areas, 5.5% of them were unemployed and 37.3% had college or higher education (Table 1).

Table (1): Demographic characteristics of participants

| Demographic characteristic | | No. | % |
|----------------------------|-------------------|-----|------|
| Gender | Male | 53 | 52.0 |
| | Female | 49 | 48.0 |
| Age group (year) | <40 | 9 | 8.8 |
| | 41-50 | 18 | 17.6 |
| | 51-60 | 31 | 30.4 |
| | 61-70 | 25 | 24.5 |
| | >70 | 19 | 18.6 |
| Education | Primary school | 31 | 30.4 |
| | Secondary school | 33 | 32.4 |
| | College or higher | 38 | 37.3 |
| Residency | Urban | 90 | 88.2 |
| | Rural | 12 | 11.8 |
| Employment | Unemployed | 77 | 75.5 |
| | Employed | 25 | 24.5 |

Adverse effects of Capecitabine experienced by participants

Generalized fatigue was the most common adverse event as it was experienced by 63.7% of participants, followed by nausea, diarrhea, and anaemia (52%, 38%, and 32%, respectively), while only 6.9% of the participants had abnormal renal function tests (Table 2).

Table (2): Frequency of adverse effects of Capecitabine experienced by participants

| Adverse effect | No. | % |
|-----------------------------|-----|------|
| Generalized fatigue | 65 | 63.7 |
| Nausea | 53 | 52.0 |
| Diarrhea | 39 | 38.2 |
| Anaemia | 33 | 32.4 |
| Hand foot | 24 | 23.5 |
| Low white blood cells count | 22 | 21.6 |
| Vomiting | 18 | 17.6 |
| Abnormal liver function | 8 | 7.8 |
| Abnormal renal function | 7 | 6.9 |

Participants' adherence to treatment

Regarding adherence to treatment, 39.2% of the patients had low adherence and 44.1% had moderate adherence, while only 16.7% of them had high adherence (Figure 3.1)

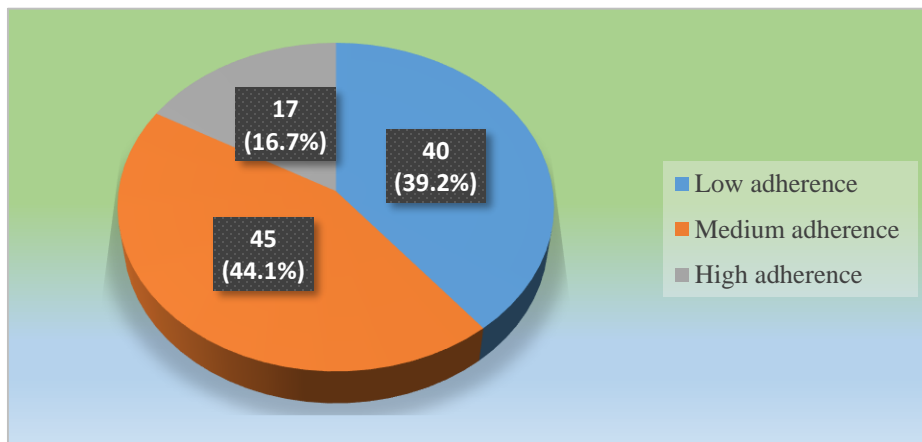


Figure (1): Participants' adherence according to Morisky Medication-Taking Adherence Scale

Association between Participants' adherence to treatment and their demographic characteristics

There was no significant association between participants' adherence to capecitabine treatment and their demographic characteristics (Table 3).

Table (3): Association between Participants' adherence to capecitabine and their demographic characteristics

| Demographic characteristic | | Level of adherence | | | P-value |
|----------------------------|-------------------|--------------------|-------------------|-----------------|---------|
| | | Low No. (%) | Medium No. (%) | High No. (%) | |
| Gender | Male | 20 (37.3) | 22 (41.5) | 11 (20.8) | 0.212 |
| | Female | 20 (40.8) | 23 (46.9) | 6 (12.2) | |
| Age group (year) | ≤40 | 3 (33.3) | 4 (44.4) | 2 (22.2) | 0.526 |
| | 41-50 | 5 (27.8) | 10 (55.6) | 3 (16.7) | |
| | 51-60 | 13 (41.9) | 16 (51.6) | 2 (6.5) | |
| | 61-70 | 10 (40.0) | 8 (32.0) | 7 (28.0) | |
| | >70 | 9 (47.4) | 7 (36.8) | 3 (15.8) | |
| Residency | Urban | 33 (36.7) | 40 (44.4) | 17 (18.9) | 0.169 |
| | Rural | 7 (58.3) | 5 (41.7) | 0 (0.0) | |
| Education | Primary school | 15 (48.4) | 12 (38.7) | 4 (12.9) | 0.572 |
| | Secondary school | 13 (39.4) | 13 (39.4) | 7 (21.2) | |
| | College or higher | 12 (31.6) | 20 (52.6) | 6 (15.8) | |
| Occupation | Unemployed | 34 (44.2) | 30 (39.0) | 13 (16.9) | 0.145 |
| | Employed | 6 (24.0) | 15 (60.0) | 4 (16.0) | |

Chi-Squared test.

Association between participants' adherence to capecitabine treatment and their experienced adverse effects

Vomiting, anaemia, abnormal liver function test, abnormal renal function test, and low white blood cell count did significantly impact participants' adherence to capecitabine treatment (Table 4).

Table (4): Association between participants' adherence to capecitabine treatment and their experienced adverse effects

| Variable | | Levels of adherence | | | P-value |
|----------------------------|----------|---------------------|-------------------|-----------------|---------------|
| | | Low No. (%) | Medium No. (%) | High No. (%) | |
| Hand foot | Yes | 13 (54.2) | 8 (33.3) | 3 (12.5) | 0.230 |
| | No | 27 (34.6) | 37 (47.4) | 14 (17.5) | |
| Nausea | Yes | 26 (49.1) | 19 (35.8) | 8 (15.1) | 0.100 |
| | No | 14 (28.6) | 26 (53.1) | 9 (18.4) | |
| Vomiting | Yes | 12 (66.7) | 5 (27.8) | 1 (5.6) | 0.028* |
| | No | 28 (33.3) | 40 (47.6) | 16 (19.0) | |
| Diarrhea | Yes | 12 (30.8) | 21 (53.8) | 6 (15.4) | 0.227 |
| | No | 28 (44.4) | 24 (38.1) | 11 (17.5) | |
| Weakness | Yes | 29 (44.6) | 25 (38.5) | 11 (16.9) | 0.267 |
| | No | 11 (29.7) | 20 (54.1) | 6 (16.2) | |
| Anaemia | Yes | 20 (60.6) | 12 (36.4) | 1 (3.0) | 0.003* |
| | No | 20 (29.0) | 33 (47.8) | 16 (23.2) | |
| Liver function | Abnormal | 7 (87.5) | 1 (46.8) | 0 (0.0) | 0.014* |
| | Normal | 33 (35.1) | 44 (46.8) | 17 (18.1) | |
| Renal function | Abnormal | 6 (85.7) | 1 (14.3) | 0 (0.0) | 0.032* |
| | Normal | 34 (35.8) | 44 (46.3) | 17 (17.9) | |
| White blood cells count | Low | 15 (68.2) | 7 (31.8) | 0 (0.0) | 0.003* |
| | Normal | 25 (31.3) | 38 (47.5) | 17 (21.3) | |

Chi-Squared test. *: Statistically significant at P<0.05.

DISCUSSION

Demographic data of participants

Results of current study revealed that 102 patients with colorectal cancer (CRC) on capecitabine treatment were enrolled in current study and 52% of them were males. The age of participants was more than 50 years. Similar results are obtained by another study which concluded that the overall incidence of CRC is higher in men mainly among those aged >70 years¹⁹. Also, **Siegel et al.**³⁷ obtained similar data in their study as most of the participants were males with ages > 50 years. Moreover, the finding of the current study agrees with another study that revealed that 89% of participants with CRC were diagnosed at an age of \geq 50 years, and 11% were diagnosed at an age < 50 years²⁰. The suggested protective effects of estrogens and progestins, the exposure to risk factors in diet and lifestyle, such as alcohol and smoking, as well as the observation that men over the age of 50 are less likely to seek medical advice or to participate in screening programs, all these reasons might explain the higher prevalence of CRC among males aged more than 50 years than their age-matched females^{21, 22}.

Adverse effects of Capecitabine experienced by participants

Regarding the adverse events, fatigue was the most common adverse event, followed by nausea, diarrhea, anaemia, and hand-foot syndrome. Another study¹³ concluded that 46.5% of participants experienced hand-foot syndrome while 44.2% of patients experienced diarrhea, nausea, vomiting or abdominal pain during treatment. Also, **Visacri et al.**²⁴ reported that nausea, diarrhea, vomiting and hand-foot syndrome were the most prevalent adverse reactions (82.7%, 62.5%, 54.8% and 53.9%, respectively) experienced by participants. The variations in the frequency of adverse events might be related to patients' demographic and clinical characteristics like age, gender, presence of other diseases, and interaction with other treatments^{25, 26}.

Participants' adherence to treatment

In current study, the highest percentage of patients had moderate adherence, followed by low adherence, while high adherence was achieved by the lowest percentage of participants. A previous study was conducted in Spain reported that adherence to capecitabine in clinical practice was high as 93% of the patients were considered to be adherent²⁷. However, another study, which also was conducted in Spain showed that 78.4% of participant had good adherence at the initiation of capecitabine treatment, however, only 17% of the patients were still on treatment at the 4th cycle²⁸. In Netherlands the adherence to capecitabine treatment was generally high²⁹ and in Brazil most patients were adherent to capecitabine during practically the entire treatment²⁴.

However, in the UK 23.3% of the patients were non-adherent³⁰. The level of adherence seems to be affected by the duration of treatment, adverse events, and clinical evolution in addition to the awareness about the disease and its management.

Association between participants' adherence to capecitabine treatment and their demographic characteristics

Current study revealed an insignificant association between the adherence level and the sociodemographic characteristics of the patients. Similar results are obtained by other studies which did not obtain significant association between daily adherence and the sociodemographic profile of the patients^{31, 32}. However, a previous study revealed that some demographic and clinical characteristics were associated with adherence to capecitabine such as marital status and educational level²⁴.

Association between participants' adherence to capecitabine treatment and their experience of drug-related adverse effects

In the current study, nausea, anaemia, abnormal liver function test, abnormal kidney function test, and low white blood cell counts were significantly associated with low adherence. These data are in agreement with another study, which revealed that nausea, vomiting, and diarrhea were the most affecting factors that reduced the adherence to Capecitabine³³. In Brazil, a study revealed that dyspnea at the beginning of capecitabine treatment had been correlated with low adherence to the treatment³⁴. Moreover, in the Netherlands²⁹ and France¹⁰, it was concluded that management of adverse events is important to support adherence to capecitabine treatment. The negative association between low adherence to, and some of the adverse events caused by, capecitabine might be related to the degree of impacting the life and health status of the patients.

CONCLUSION

The extent of adherence to capecitabine treatment by colorectal cancer seems to be more sensitive to capecitabine-related adverse effects rather than to patients' sociodemographic characteristics.

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Author contribution: Authors contributed equally in the study.

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