



Capecitabine toxicity in colorectal cancer: a cross-over study

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Abstract

Colorectal cancer is a major public health issue in Algeria, due to its constantly rising incidence. Oral chemotherapy in oncology is booming, with several molecules available on the market, including capecitabine. Our study focused on the evaluation of capecitabine toxicity in colorectal cancer. A descriptive, cross-sectional and multicentre study was carried out in the cancer centre of University Hospital Centre of Constantine (CHU) and Batna Cancer Centre (CAC) with group of 40 patients, over a 3-months period. For this purpose, an information sheet was drawn up, including questions on age, sex, medical history, methods of diagnosis and protocol used in the management of colorectal cancer. Statistical analysis was performed using SPSS and Excel. Our results showed a predominance of males (70%), with an average age of 65.5 years, and a history of cardiovascular disease (43%). Rectal location of the tumour was more frequent in our patients (53%), with a predominance of advanced stages (stages 3 and 4) in 52.5% of cases. The most widely prescribed therapeutic protocol was the combination of capecitabine with oxaliplatin; capecitabine was used at a dose of 3,000 to 3,500 mg per day. With this protocol and capecitabine dosage, haematological, digestive and cutaneous toxicities were most frequently reported. Most of these adverse effects appeared one month after the start of treatment in patients of both sexes. It is therefore essential to evaluate the various chemo-induced toxicities in order to improve their management, and to adapt the dosage according to the patient's tolerance and general condition.

Keywords:

Colorectal cancer, Capecitabine, Protocol, Dosage, Toxicity.

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1. Introduction

Colorectal cancer (CRC) represents a major public health problem in terms of frequency and severity.

Worldwide, CRC ranks 3rd among the most frequently diagnosed cancers, with 1.93million cases, after lung and breast cancer in women (2.21million), in men, CRC ranks 2nd in mortality, with 916 000 deaths, after lung cancer (1.8 million deaths) [1].

In Algeria, nearly 6 500 new cases of CRC are recorded every year, including 3 500 in men and 3 000 in women, according to the cancer registers of the national institute of public health [2].

CRC is rare before the age of 45, its incidence increases with age, with an average age at diagnosis of 69.5 for men and 72.8 for women. Incidence is identical for both sexes up to the age of 60, after which CRC becomes predominantly male [3].

5-fluorouracil (5-FU) is the oldest molecule used in the treatment of CRC, its administration by prolonged infusion requires the use of an implantable chamber, exposing the patient to infectious or thrombotic complications.

The possibility of outpatient treatment in certain situations makes oral precursors a better alternative to 5-FU, including capecitabine, a powerful antimetabolite agent of the fluoropyrimidine carbamate class, it can be used alone or in combination.

Like all drugs, capecitabine has side effects that can alter the patient's general condition and quality of life.

Aim of study

Study of the frequency of the main toxicities associated with the use of capecitabine in colorectal cancer.

2. Material and methods

The study carried out is a descriptive, cross-sectional, multicentre study; in the centre anti-cancer of University Hospital Center of Constantine (CHU) and Batna Cancer Centre (CAC). It was carried out over a three-months period (from April 2023 to June 2023).

During our study, we were able to collect 40 patients with colon and/or rectal cancer who had received oral capecitabine-based chemotherapy in the oncology departments already mentioned.

Selection criteria

- Inclusion criteria
 - Patients with colorectal cancer.
 - Patients having taken capecitabine (whatever the generic).
- Non-inclusion criteria
 - Patients with colorectal cancer not receiving capecitabine.
 - All patients with follow-up irregularities preventing data collection.
- Exclusion criteria
 - Data sheets with incomplete or incorrect information.

Data collection and analysis

In order to collect as much specific data as possible and provide relevant information to reinforce our study we used an information sheet adapted to our study.

Statistical study

The statistical study was carried out using SPSS software. Chi-square and Fisher's exact tests have been performed by SPSS, with alpha risk set at 5%.

3. Results

Characteristics of the study population

- Age

The following histogram (figure 1) shows the distribution of patients by age, with an average age of 65.5years.

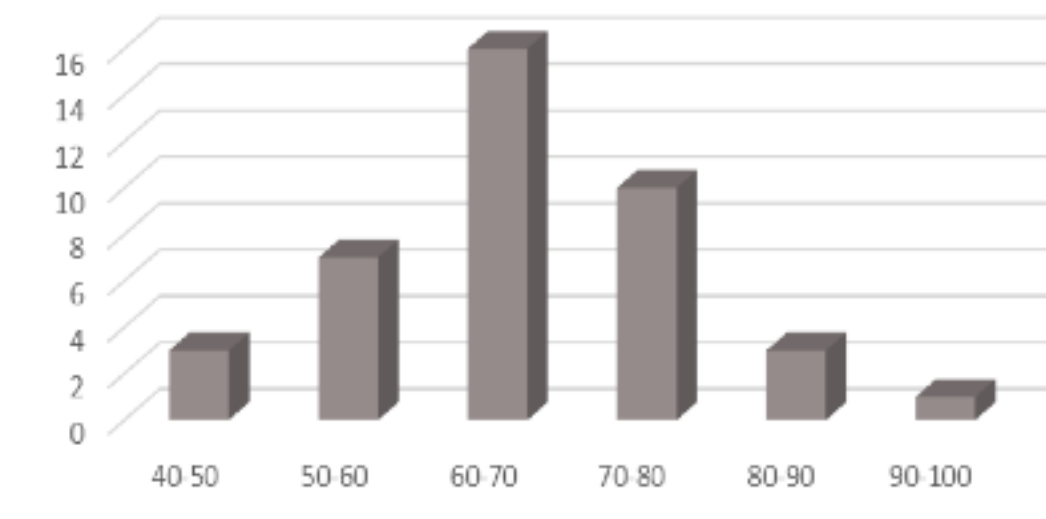


Fig. 1. Patients age histogram.

- Gender

The majority are male (70%), while female sex represents 30% of the studied population.

- Residence

The majority of patients are from the wilaya of Constantine (57%), followed by patients from the wilaya of Batna (32%).

- Medical history

The most common disease among patients is cardiovascular disease (43%), followed by endocrine disease (26%). We note that 26% of the population have no medical history.

- Cancer location

53% have a rectal cancer while 47% have a colon cancer.

- Cancer stage

The following histogram shows the distribution of patients by cancer stage. The majority of the studied population suffers from stage 4 cancer, followed by those with stage 3 cancer.

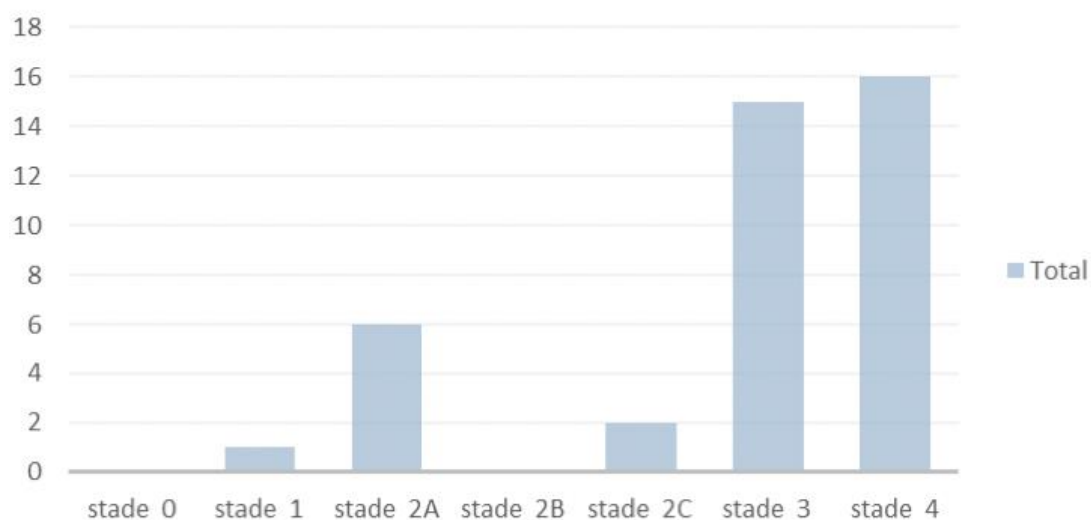


Fig. 2. Different stages of cancer.

- Performance status

Figure 3 shows that 24 patients were in good general condition (grade 0).

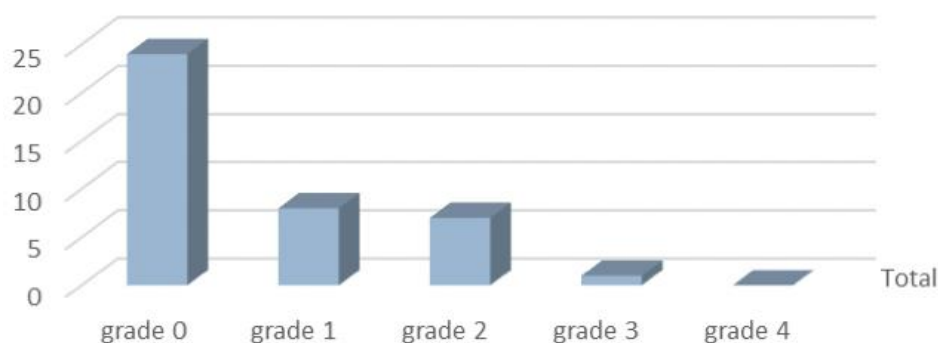


Fig. 3. Breakdown by performance statuses.

Diagnostic methods

- Clinical diagnosis

The majority of patients were diagnosed after presenting with digestive disorders.

- Radiological diagnosis

11 of the 40 patients were found to have colorectal cancer after a radiological examination including colonoscopy, MRI and CT scan.

- Biological diagnosis

100% of the study population performed a biological analysis by FNS, 60% of whom combined their FNS examinations with an assay of tumour markers (ACE and CA 19-9).

Protocol and dosage

- Prescribed medication

48% took a treatment consisting of the capecitabine-oxaliplatin combination. Whereas 32% took capecitabine alone.

- Dosage of capecitabine

The most commonly used dosage of capecitabine ranges from 3000 mg to 3500 mg.

Observed toxicities

- Hematotoxicity

The majority of patients (58%) developed hematotoxicity. Table 1 shows that 13 patients in the study population developed grade 2 hematotoxicity, while 17 patients developed no toxicity.

Table 1. Breakdown by grade of haematological toxicity.

Hematotoxicity	Number
Grade 1	5
Grade 2	13
Grade 3	4
Grade 4	1
Grade 5	0
No toxicity	17
Total	40

- Digestive toxicity

48% of the patients presented adverse effects of a digestive nature.

According to the table below, the majority of patients who experienced digestive toxicity developed grade 1 toxicity.

Table 2. Distribution according to grade of digestive toxicity.

Digestive toxicity	Number
Grade 1	9
Grade 2	7
Grade 3	5
Grade 4	0
Grade 5	0
No toxicity	19
Total	40

- Skin toxicity

33% of the studied population developed skin toxicity.

The table below shows that the grade of cutaneous toxicity most frequently reported by patients was is grade 1.

Table 3. Breakdown by grade of cutaneous toxicity.

Cutaneous toxicity	Number
Grade 1	8
Grade 2	4
Grade 3	1
Grade 4	0
Grade 5	0
No toxicity	27
Total	40

- Cardio-toxicity

87% of patients showed no signs of cardiac toxicity.

Table 4 shows that two patients developed grade 1 cardiac toxicity, three patients with grade 2 toxicity.

Table 4. Breakdown by grade of cardiac toxicity.

Cardio-toxicity	Number
Grade 1	2
Grade 2	3
Grade 3	0
Grade 4	0
Grade 5	0
No toxicity	35
Total	40

- Neurological toxicity

One third of the patients included in the study experienced adverse events of a neurological nature.

From Table 5, it can be seen that the grade of neurological toxicity most frequently expressed by patients is grade 1.

Table 5. Breakdown by grade of neurological toxicity.

Neurological toxicity	Number
Grade 1	11
Grade 2	2
Grade 3	0
Grade 4	0
Grade 5	0
No toxicity	27
Total	40

- Osteomuscular toxicity

18% of patients suffered from osteomuscular toxicity.

Time of adverse event onset

92% presented the adverse reactions one month after the start of treatment, 5% after 2 weeks and 3% after 1 or 2 days.

Response to treatment

Only 45% of patients responded to treatment.

4. Discussion

The mean age of patients in our study was 65.5 years, with extremes of 42 and 91 years. This age is higher than that reported in the study presented by D. Mallem, who found an average age of 57.5 years [4].

We note a predominance of patients in the 60 to 70 years (40%) of patients. These results are similar to those of H. Housse and his team in subjects with CRC, where the age group most affected is 61-70 years [5].

Our study showed a predominance of men (70%), a study carried out by Saïd Belhamid in 2018 on 36 cases of CRC, showed a predominance of men (61%) [6].

In our study, cancer of the rectum accounts for the majority of CRCs, representing 53% of cases, whereas cancer of the colon, which is less frequent, represents 47%. Contrary to the literature, colon cancers represent 2/3 overall and rectal cancer 1/3 [4].

We found that the distribution of colon cancers is equal to that of the rectum in men, whereas in women we note the predominance of rectal cancer, this result can be explained by the fact that rectal location is the most frequent in our series whatever the sex. The p value is 0.4 (> 0.05) difference is not statistically significant. Contrary to the study conducted by D. Maalem who found a high frequency of colon cancers compared with rectal cancers in men [4].

The majority of CRC cases were diagnosed at a late stage, stage III and stage IV (82.5%); this same finding was noted in the study carried out by D. Mallem in 2010, which found that around 94% of patients had stage III and stage VI CRC at the time of diagnosis [4].

A high frequency of stage 3 and 4 CRC was found in both sexes. There was no statistically significant association between sex and cancer stage (p value = 1).

The majority of patients included in our study had a PS less than or equal to 2.

60% (24 cases) of patients had a PS 0, followed by those with a PS1 (20% or 8 cases), while PS2 was found in 17.5% of our patients.

The clinical diagnosis of CRC was made in 100% of cases in the presence of symptoms including digestive disorders whether or not associated with rectal discharge, asthenia, etc. This percentage is identical to the result of Sedkaoui study. According to Sedkaoui, the lack of diagnosis in the asymptomatic phase may be explained by the absence of a national colorectal cancer screening policy, on the one hand, and by a certain negligence on the part of patients and certain practitioners when faced with relatively non-alarming symptoms, on the other [7].

In almost 100% of cases in our study population, radiological diagnosis included colonoscopy, whether or not combined with MRI, CT and CAT scans. This percentage is higher than that found by D. Mallem, with 51.2% who underwent colonoscopy [4].

Most diagnoses are based on the tumour markers ACE and CA19-9; in our population all patients underwent the FNS test, 24 patients (60%) of whom had the tumour markers ACE and CA19-9 measured initially with the FNS test. In the literature, it is mentioned that the presence of high levels of tumour markers is most often associated with the development of cancer [8].

A protocol based on the combination of capecitabine and oxaliplatin was used in 48% of cases. The common use of this combination may be explained by the high clinical activity of this combination as oxaliplatin up-regulates thymidine phosphorylase, the key enzyme involved in tumour-specific 5-FU production [9].

In our study, chemo-induced haematological toxicity was expressed as a percentage of 58%, the majority developed grade II adverse reactions, the study of B. Touzoula in 2022 showed that almost all patients experienced haematological toxicity from the initiation of chemotherapy [10]. The occurrence of haematological adverse reactions is most often marked in patients aged between 60 and 70 years. Our result is identical to that found by N.H. Khzam where all patients with a mean age of 62.66 years developed haematological toxicity related to chemotherapy [11].

48% developed digestive toxicity. In a study conducted by A. Carrato, diarrhoea was one of the main toxicities of this oral chemotherapy after the second cycle of treatment, due to a cumulative component of these toxic adverse effects [12].

33% of cases developed cutaneous toxicity, Takashi Yamaguchi found 92% of occurrence of cutaneous side effects [13]. A predominance of cutaneous adverse reactions was found in patients aged between 60 and 70 years, whereas a high frequency of neurological toxicity was observed in patients aged between 70 and 80 years. According to Fisher's test, these two results are not statistically significant.

A male predominance of haematological, digestive and neurological toxicities was observed in our study. but these results are not statistically significant. Annamaria Ruzzo found in her study a higher frequency of chemo-induced toxicity in males. This may be explained by genetic variations between the two sexes [14]. In the study by M. Launay et al, the female sex was considered to be a risk factor for the occurrence of adverse effects due to reduced elimination clearance and/or a greater incidence of DPD (Dihydropyrimidine dehydrogenase) deficiency [15].

Patients with stage 3 or 4 CRC were the most affected by haematological toxicity; this result may be justified by the fact that the majority of cases in our study had these two stages.

There was no statistically significant association between stage and haematological toxicity (p value= 0.2).

There was a statistically highly significant association (p value = 0.01) between stage and digestive toxicity.

The occurrence of haematological, cutaneous and digestive toxicity was most frequently associated with capecitabine in combination with oxaliplatin. This result was not statistically significant. The study by T. Wadelle and colleagues supports our results [16].

Our results show a relationship between the occurrence of adverse effects and the dosage of capecitabine. There is a statistically significant association between the occurrence of haematological toxicity and the dosage ranging from 3000 - 3500 mg of capecitabine (P value = 0.005) and There was a statistically significant association between the occurrence of cutaneous toxicity in patients taking capecitabine 3000 - 3500 mg (p value = 0.007).

These results are comparable to those found by M. Launay et al who stated that a dosage of capecitabine of 3000 - 3500 mg was most often associated with toxicities of all types [15].

In our study, the majority of toxic effects appeared one month after the start of treatment regardless of the therapeutic protocol used, but there is no statistically significant association between the protocol and the time of onset of adverse effects (p = 0.2).

5. Conclusion

Assessment of the various chemo-induced toxicities enables their management to be improved, and dosage to be adapted according to the patient's tolerance and general condition. A management policy to prevent side-effects must be adopted, therapeutic education sessions should be organised to help patients better understand, accept and adapt to their condition. In order to prevent colorectal cancer, patients should be advised to adopt a healthy lifestyle, eat a healthy diet, avoid a sedentary lifestyle, exercise and consult their doctor in the event of abdominal discomfort or the presence of blood in the stools.

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