ORIGINAL

Toxicity of capecitabine compared with 5-fluorouracil in elderly patients with breast or gastrointestinal tract cancer

Gilberto L. Brandolt[1], Luísa S. Ely[2], Paula Engroff[2], Tatiana W. Almeid[3], Alan A. Azambuja[4], Irênio Gomes[5], Geraldo A. de Carli[6], Fernanda B. Morrone[7]

Abstract

Objectives: The aim of this study was to evaluate the toxicity of capecitabine compared with 5-fluorouracil in elderly patients with breast or gastrointestinal tract cancer. **Material and Methods:** A cohort study was used to evaluate toxicity parameters in elderly patients undergoing chemotherapy treatment. This study was conducted between 2006 and 2008 and was composed of 76 patients from the Oncology Ambulatory of Hospital São Lucas, PUCRS. Eligible patients included elderly individuals (aged 60 years or above) of both sexes who suffered from breast or gastrointestinal tract cancer and who used daily oral capecitabine or intravenous 5-fluorouracil. General side effects were evaluated and graded on a four-point scale. The study also analyzed the values of blood markers such as alanine aminotransferase and aspartate aminotransferase for hepatic toxicity, and troponine I and electrocardiogram for cardiotoxicity. **Results:** The data showed a higher frequency of general adverse effects in the patients who used 5-fluorouracil in relation of capecitabine. However, only the patients that used capecitabine suffered from hand-and-foot syndrome. Conversely, the levels of ALT in the elderly men who used capecitabine were significantly higher (p = 0.027) than those who used 5-fluorouracil. With regard to cardiac function, a significant difference (p = 0.023) in the median QT interval between the groups was found, while all the other exams presented normal results. **Conclusion:** The use of capecitabine should be frequently monitored in order to minimize or avoid the toxic effects of the chemotherapy in elderly patients. Other parameters should be subsequently analyzed to confirm this conclusion.

Keywords: breast neoplasms, capecitabine, fluorouracil, gastrointestinal neoplasms, toxicity.

INTRODUCTION

The elderly population is the fastest growing population in the world[1,2]. Patients are aging and some errors can occur in their cell repair mechanisms that may lead to a microscopic cancer that could become clinically significant[3,4]. Many therapeutic options exist for the treatment of cancer, including cytotoxic chemotherapy used alone or in association with other agents[3].

[1] Pharmacist, MS; Instituto de Geriatria e Gerontologia da Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS).
[2] Pharmacist; Instituto de Geriatria e Gerontologia da Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS).
[3] Pharmacist; Hospital São Lucas da PUCRS.
[4] MD, Oncologist; Hospital São Lucas da PUCRS.
[5] Statistics Professor, PhD; Instituto de Geriatria e Gerontologia da Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS).
[6] Professor of Medical Parasitology, PhD;Instituto de Geriatria e Gerontologia da Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS).
[7] Professor of Pharmacology, PhD; Hospital São Lucas da PUCRS. Faculdade de Farmácia da PUCRS.

Send correspondence to:
Dr. Fernanda Bueno Morrone.
Faculdade de Farmácia, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS).
Av. Ipiranga, nº 6681, prédio 12, Bloco A. CEP: 90619-900. PO Box: 1429.
E-mail: fernanda.morrone@pucrs.br

Submitted: 10/05/2010.
Aproved: 12/06/2012.

The work was developed in the Instituto de Geriatria e Gerontologia da PUCRS.

Since aging is associated with the decreased functional reserve of multiple organ systems with changes in the pharmacokinetics and pharmacodynamics of drugs, the risks of adverse reactions increase with age, especially in the elderly above 70 years of age[5-7]. It is known that the use of cytotoxic chemotherapy increases the survival of cancer patients, but it can also damage normal body tissues, resulting in adverse effects in different parts of the body[8]. The most common side effects observed are leucopenia, diarrhea, nausea, stomatitis, vomiting and alopecia. Some studies showed that chemotherapy could also present cardiotoxic effects[9].

Studies of new chemotherapy drugs are important for the evolution of cancer treatment, especially if the drug has a specific action on tumor cells, decreases side effects and offers a better quality of life for the patient[10].

Many drugs, including capecitabine and 5-fluorouracil, have mainly been used to treat breast and gastrointestinal tract cancer. 5-fluorouracil is a commonly used chemotherapeutic agent with activity in a variety of solid tumors, including those of the head and neck, breast, prostate, pancreas, liver, and genitourinary and gastrointestinal tracts[11]. It must be administered intravenously because of its variable gastrointestinal absorption and rapid degradation[12-15]. 5-fluorouracil acts on RNA and

DNA metabolism[16,17]. Cardiotoxicity and neurotoxicity are rare but serious adverse effects of 5-fluorouracil treatment that have been reported in some studies[16-19].

Capecitabine (N4-pentiloxicarbonil-5'-desoxi-5--fluorcitidine) is an orally administered prodrug of 5-fluorouracil that was designed to overcome the problems seen with intravenous (i.v.) therapies. In addition to the side effects of i.v. therapies, medical complications and inconvenience are also associated with (central) venous access[20,21]. Capecitabine has demonstrated efficacy in metastatic breast cancer, pancreatic cancer, gastric cancer, and colorectal cancer[22,23].

Thymidine phosphorylase, the final enzyme responsible for conversion of capecitabine to the active drug, is present at higher levels in tumor cells compared with healthy tissue. This theoretically allows for the selective activation of the drug and less systemic toxicity[13,15]. The most common adverse effects seen in patients receiving capecitabine monotherapy are leucopenia, anemia, diarrhea, hand-and-foot syndrome, nausea, fatigue, hyperbilirubinaemia, dermatitis, and vomiting[22-24].

Since the manifestation of the adverse affects in the elderly is variable and difficult to determine, the aim of this study was to evaluate the toxicity of capecitabine compared with 5-fluorouracil in elderly patients with breast or gastrointestinal tract cancer.

METHODS

Study design and patient selection

A cohort study was used to evaluate toxicity parameters in elderly patients receiving chemotherapy treatment. Part of the data collection was performed retrospectively through medical chart analysis and by the prospective mode through interviewing the patients. This research was completed between 2007 and 2008.

Eligible patients included elderly individuals (aged 60 years or above) from both sexes who were suffering from breast or gastrointestinal tract cancer. Histological or cytologic confirmation of colorectal adenocarcinoma and breast cancer was required to confirm the diagnosis. Patients who had a previous history of cardiovascular and hepatic disease or who used medications that modify cardiac and hepatic function, along with those who had severe renal impairment or central nervous system disorders were excluded from the study. Also excluded from the study were patients who had hypersensitivity to 5-fluorouracil or capecitabine, metastasis, had received other chemotherapy treatment or radiotherapy within 12 weeks before enrollment and those who had not fully recovered from recent major surgery.

Patients were enrolled aleatorially in two different groups: 1) daily 2000 mg/m^2 oral capecitabine for 14 days, followed by a 7-day rest period; 2) i.v. bolus 5-fluorouracil at 500-2000 mg/m^2, on days 1-5, every 21 days and with leucovorin. 5-fluorouracil was used as a comparative drug because it is a metabolite of capecitabine. Assessments included medical history, a general physical examination, vital signs, physical measurements and laboratory tests.

The sample of this study was initially composed of 86 patients from the Oncology Ambulatory of Hospital São Lucas, PUCRS. From these, the treatments of six patients were suspended and four patients died before the completion of 12-week treatment (Figure 1).

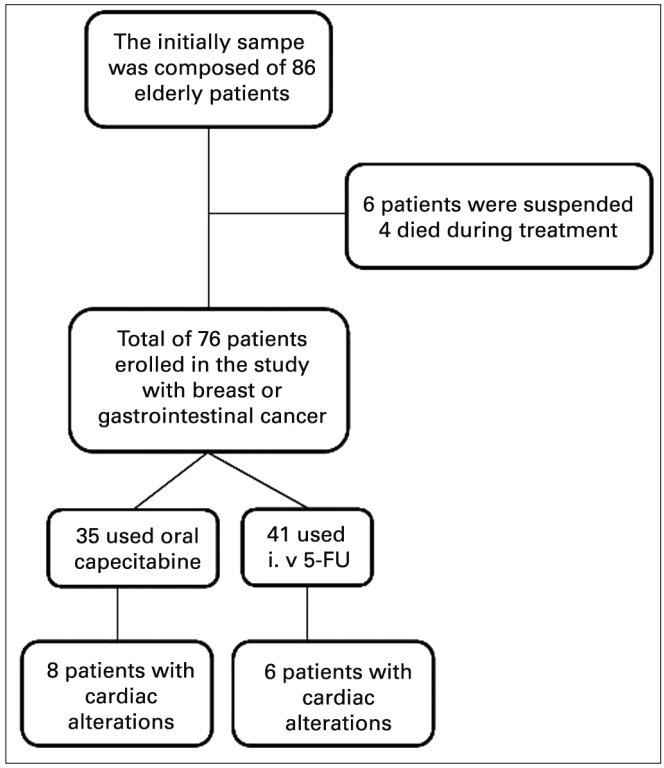

Figure 1. Flow of patients through the study.

This study was approved by the Institutional Ethics Committee of PUCRS (CEP 07/033603).

Data and blood sample collection

A previously validated pharmacotherapeutic questionnaire was used for data collection which contained the patients' identification, tumor type, drugs used, and the laboratory results. In addition to the interview, the side effects were analyzed by searching the patients' medical charts[25]. All information was transferred to a computer data file.

The blood samples were collected during the chemotherapy treatment (12 weeks after the beginning of the treatment). The blood samples (4 mL) were sent to the Clinical Pathology Laboratory at Hospital São Lucas, PUCRS, to perform the biochemistry exams.

Parameters Analyzed

General side effects (main adverse events) were evaluated and graded on a four-point scale as mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening (grade 4), as classified by the World Health Organization (WHO)[26].

The study also analyzed the values of blood markers such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) for hepatic toxicity, and tropinine I and the electrocardiogram (ECG) for cardiotoxicity.

For alanine aminotransferase (ALT) and aspartate aminotransferase (AST) measurements, the dry chemistry methodology was performed with *Fusion* equipment. The reference values for AST were men (17-59 U/L); women (14-36 U/L). The reference values for ALT were men (21-72 U/L); women (9-52 U/L). The Rits quotient was used to verify the occurrence of hepatic injury. The AST value was divided by the ALT value, and a result above 1 indicated hepatic injury.

Troponine I is a cardiac muscle-specific protein that is used to verify possible cardiac alterations. Troponine I was measured using the *ADVIA Centaur* system (Bayer Diagnostics, Tarrytown, NY, USA), and the *chemiluminescence* methodology was used. Values above 1 ng/mL were considered to be indicative of cardiac problems.

The ECG was the other parameter used to evaluate the changes in cardiac function. The ECG was only analyzed in the patients who had, according to the doctors, symptoms of possible cardiac alterations, since this test was not requested in the ambulatory routine. The QT intervals and corrected QT intervals are considered elongated when they are over 440 ms. Fourteen patients from both sexes were evaluated[7,8,22,23]. To evaluate the eletrocardiogram (ECG), an HP PageWriter 200i Interpretive ECG (Palo Alto, CA, USA) was used at a standard of 1.0 and a speed of 25 mm/s. This test was requested by the doctor only for those patients who had possible cardiac alterations. Fourteen patients from both sexes underwent the ECG in the Pneumology Ambulatory of Hospital São Lucas, PUCRS. The QT interval and corrected QT intervals were analyzed. Values above 440 ms for the QT intervals and corrected QT interval were considered abnormal.

Statistical Analysis

The data were first tabulated and analyzed using the SPSS program, version 11.0. The results are expressed as the mean ± (SD). To analyze the frequency of the side effects in the groups, the chi-square test was used. To compare the medium of two groups, the *Student's t* test was used. $p < 0.05$ was considered significant.

RESULTS

Comparative general side effects of capecitabine and 5-fluorouracil

A total of 76 elderly patients from both sexes were enrolled in this study. These patients suffered from breast or gastrointestinal tract cancer and used oral capecitabine or i.v. 5-fluorouracil. Of the patients, 52.63% were women and 47.37% were men with a mean age of 63 ± 9.4 years for the combined groups. The data showed that 46.05% patients were treated with capecitabine and 53.95% with 5-fluorouracil (Table 1).

Table 1. Characteristics of the elderly population studied (n = 76).

Characteristic	Capecitabine n (%)	5-fluorouracil n (%)
Gender		
Male	13 (37.14)	23 (56.10)
Female	22 (62.86)	18 (43.90)
Mean age	63.68 ± 8.02	63 ± 10.53
Cancer		
GI Tract Cancer	22 (28.94)	37 (48.70)
Breast cancer	13 (17.10)	4 (5.26)
Total	35 (46.05)	41 (53.95)

Table 2 shows the general side effects observed in the elderly population caused by the use of oral capecitabine and i.v. 5-fluorouracil after 12 weeks of cancer treatment. Analyzing the main general side effects frequency, we observed that all patients (100%) presented at least one of these effects. A significant difference in the frequency of vomiting ($p < 0.001$), nausea ($p = 0.001$), and inappetence ($p = 0.017$) was found when the patients using 5-fluorouracil were compared with those who used capecitabine. Conversely, the adverse effect of hand-and-foot syndrome was significantly more frequent ($p = 0.007$) in the group using capecitabine than the 5-fluorouracil group.

Furthermore, the other side effects, such as diarrhea, abdominal pain, weakness, and dyspnea, did not show significant differences between the groups. In this study, toxic effects like insomnia, mucositis, neutropenia, myelodysplasia, dormancy, tinnitus, alopecia, stomatitis, and dysphagia were rarely found.

Most of the toxic effects were classified as grade 1/2 (WHO) - those that did not cause the risk of permanent injury or death. Only one patient using 5-fluorouracil presented with lymphopenia and one patient using oral capecitabine presented with stomatitis; both events were classified as grade 3/4 (Table 2).

Evaluation of the hepatic function by the ALT and AST markers

To evaluate hepatotoxicity, we analyzed the ALT and AST levels. Since the reference values are different for men and women, we performed a further analysis by gender. The data showed that all patients from both sexes had higher levels of ALT and AST when using capecitabine compared to those using 5-fluorouracil.

Regarding the AST levels, the women who used oral capecitabine had a greater level (36.0 ± 34.72 U/L) of this marker when compared with those women who used

Table 2. General side effects observed in the patients using capecitabine and 5-fluorouracil (n = 76).

Side Effect	WHO Grade	Capecitabine (n = 35)	5-fluorouracil (n = 41)	*p*
Abdominal Pain	1/2	1 (2.9%)	6 (14.6%)	0.116
Alopecia	1/2	0 (0%)	1 (2.4%)	1.000
Diarrhea	1/2	5 (14.3%)	8 (19.5%)	0.546
Dormancy	1/2	1 (2.9%)	0 (0%)	0.461
Dysphagia	1/2	0 (0%)	1 (2.4%)	1.000
Dyspnea	1/2	4 (11.4%)	1 (2.4%)	0.74
Fatigue	1/2	4 (22.4%)	4 (9.8%)	1.000
Hand-and-foot syndrome	1/2	6 (17.1%)	0 (0%)	0.007*
Inappetence	1/2	1 (2.9%)	9 (22.0%)	0.017*
Insomnia	1/2	1 (2.9%)	0 (0%)	0.461
Lymphopenia	3/4	0 (0%)	1 (2.4%)	1.000
Mucosite	1/2	0 (0%)	2 (4.9%)	0.496
Myelodisplasia	1/2	0 (0%)	1 (2.4%)	1.000
Nausea	1/2	5 (14.3%)	22 (53.7%)	0.001*
Stomatitis	3/4	1 (2.9%)	0 (0%)	0.461
Tinnitus	1/2	0 (0%)	1 (2.4%)	1.000
Vomiting	1/2	3 (8.6%)	22 (53.7%)	0.000*

* $p < 0.05$ - Chi - Square Test.

i.v. 5-fluorouracil (24.50 ± 8.57 U/L), but the difference between the groups was not significant ($p = 0.306$). The elderly men who used capecitabine had a median AST level of 29.75 ± 11.616 U/L, and those that used 5-fluorouracil had a median AST level of 22.81 ± 10.43 U/L ($p = 0.109$) (Figure 2A).

The ALT results for the female patients who used oral capecitabine was 27.18 ± 14.07 U/L, whereas those who used i.v. 5-fluorouracil had a median level of 21.07 ± 10.55 U/L ($p = 0.227$). Interestingly, when comparing the ALT levels of the elderly men using capecitabine (33.58 ± 19.31 U/L) with those who used 5-fluorouracil (19.06 ± 6.33 U/L), we observed a significant difference ($p = 0.027$) in this parameter (Figure 2B).

By utilizing the De Ritis quotient to verify the occurrence of hepatic injury[27,28], the AST/ALT ratio was above 1 (SD = 1.26) in most of the elderly men who used oral capecitabine. This data confirms the hepatotoxicity caused by the drug in this group.

Cardiotoxicity evaluation of capecitabine and 5-fluorouracil

Exams such as measuring troponine I and performing ECG were used to evaluate possible alterations in the cardiac function of the elderly in this study. The study did not show a comparison with creatinokinase (CK) levels because this exam is not routinely requested by the doctors. Thus, it was not possible to study this parameter.

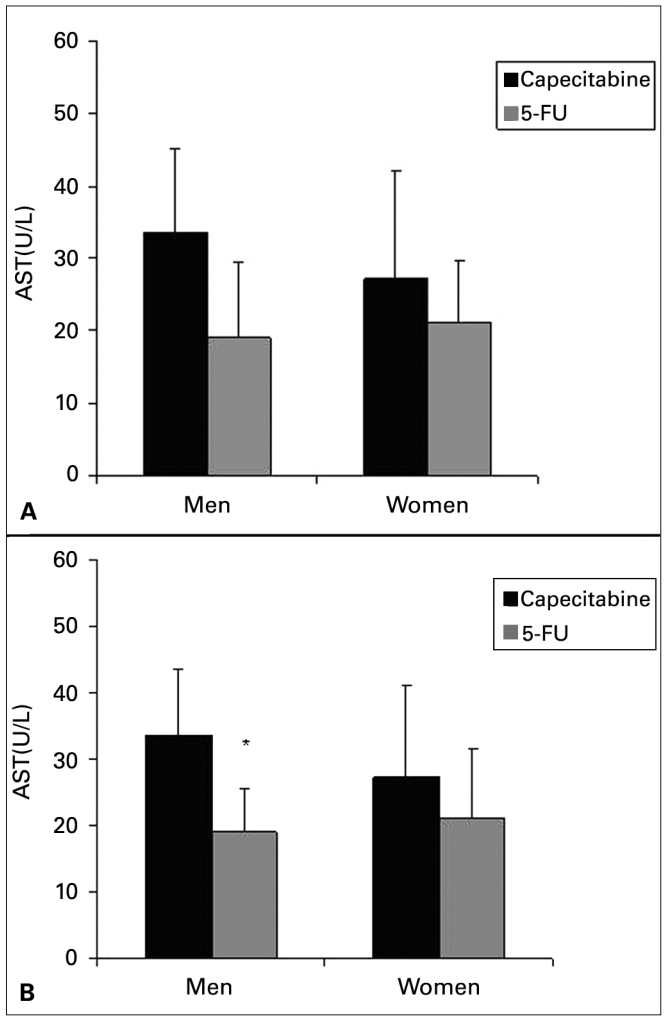

Figure 2. A: Levels of AST (U/L) in the elderly (men and women) treated with oral capecitabine and i.v. 5-fluorouracil (n = 76); B: Levels of ALT (U/L) in elderly (men and women) treated with oral capecitabine and i.v. 5-fluorouracil (n = 76). The *Student's t* test was used to compare the medians of the two groups; * $p < 0.05$.

According to Table 3, all patients from this study (n = 76) had troponine I levels lower than 0.5 ng/mL. None of the patients studied presented significant alterations in the levels of this protein.

Table 3. Levels of troponine I in the elderly patients (n = 76).

Drug	Patients n (%)	(%) Lower than 0.5 ng/mL
5-fluorouracil	41 (53.95)	100
Capecitabine	35 (46.05)	100

As shown in Figure 3, the median of the QT intervals of the patients who used oral capecitabine and i.v. 5-fluorouracil were different. The median result in the capecitabine group was 364.44 ± 36.470 ms, and the median result in the 5-fluorouracil group was 427.00 ± 46.27 ms. The results showed a significant difference when the QT interval was compared between the groups ($p = 0.023$).

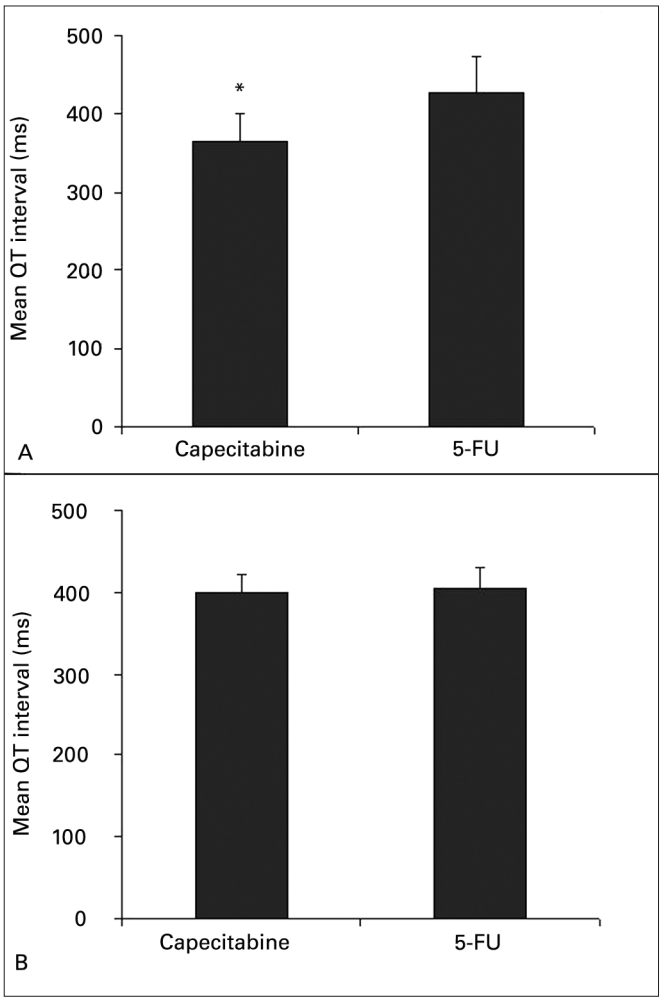

Figure 3. A: QT intervals found in elderly patients who used oral capecitabine and i.v. 5-fluorouracil (n = 14); B: Mean of the corrected QT interval found during the examinations of patients who used 5-fluorouracil and capecitabine (n = 14). Statistics were performed as in Figure 2. Student's t test: * $p < 0.05$.

The median value of the corrected QT interval in patients who used oral capecitabine was 400.00 ± 21.97 ms, and was 404.50 ± 26.44 ms ($p = 0.754$) for the patients who used i.v. 5-fluorouracil.

DISCUSSION

In this study, the adverse effects of treatment with oral capecitabine and i.v. 5-fluorouracil were evaluated in elderly patients. The advantage of oral chemotherapy administration is important, especially for elderly patients; however, the adverse effects of oral chemotherapy should be carefully studied in this population.

Our data showed that some general adverse effects in the gastrointestinal tract such as nausea, vomiting, and diarrhea were frequent during treatment with 5-fluorouracil or capecitabine. Other studies have already demonstrated a similar pattern in different populations. The studies demonstrated that, although both capecitabine and 5-fluorouracil induce toxicities characteristic of fluoropyrimidines[22], the onset of typical grade 3 and 4 fluoropyrimidine-related adverse reactions was significantly delayed and less frequent with capecitabine[24].

In accordance to other studies, our results showed that capecitabine offers an improved convenience and safety profile compared with i.v. 5-fluorouracil/LV, along with significantly lower incidences of nausea, vomiting and inappetence[20,29-31]. In addition, capecitabine is associated with a significantly lower incidence of grade 3/4 stomatitis and grade 3/4 neutropenia, leading to significantly less grade 3/4 neutropenic fever/sepsis and fewer associated hospitalizations. In our study, only two events (stomatitis and lymphopenia) were considered WHO grade 3/4 (Table 1).

Here, elderly patients using capecitabine presented a higher incidence of hand-and-foot syndrome, as in a similar study where capecitabine was associated with higher rates of hand-and-foot syndrome[32,33].

Another group of adverse effects are those related to hepatotoxicity in patients treated with the chemotherapy drugs. The enzymes AST and ALT are considered markers for the evaluation of hepatic function and the measurement of cellular injury[34]. This study showed interesting results regarding hepatic function in elderly cancer patients using oral capecitabine compared to those using i.v. 5-fluorouracil. Our data showed that patients of both sexes using capecitabine had higher ALT and AST levels than those patients who used 5-fluorouracil.

In fact, men using 5-fluorouracil had lower levels of ALT when compared with oral capecitabine users (Figure 2B). In the majority of the elderly men who used oral capecitabine, the De Ritis quotient was above 1 (SD = 1.26), confirming the hepatotoxicity caused by the capecitabine. This result could be related to capecitabine metabolism, since it is first metabolized in the liver by hepatic carboxylesterase and subsequently converted to 5'-deoxy-5-fluorouridine by cytidine deaminase, which is mainly located in the liver and in tumor tissues[24]. It is important to note that capecitabine treatment should be used with caution and with a laboratorial follow-up during the therapy.

Regarding cardiac toxicity, the results presented here showed that all elderly patients studied had normal levels of troponine I. However, it should be noted that this exam was performed after the first three months chemotherapy treatment, so enough time for symptoms to manifest in the cardiac muscle may not have passed.

Some abnormalities found in the ECG can represent changes in ventricular repolarization, such as the QT interval dispersion, which is a marker for mortality risk[35]. The QT interval is measured from the beginning of wave Q to the end of wave T and represents the ventricular

depolarization and repolarization. The data in this study only showed a significant difference in the values of the QT interval in the elderly patients that used 5-fluorouracil compared to those patients who used capecitabine. The patients who used oral capecitabine had corrected QT interval values similar to the patients that used i.v. 5-fluorouracil. The difference between groups was not significant.

Although current studies show that capecitabine and 5-fluorouracil are cardiotoxic in adults, our data revealed that the drugs studied here did not cause significant cardiotoxicity in the elderly, since troponine and ECG exams presented normal results. Interestingly, the elderly patients who used oral capecitabine had a median QT interval that was smaller than those who used i.v. 5-fluorouracil; however, the median corrected QT interval did not show a significant difference between the groups.

This study evaluated the toxicity of the oral cabecitabine compared with i.v. 5-fluorouracil in elderly patients with breast or gastrointestinal tract cancer. The data showed a higher frequency of general adverse effects in the patients who used 5-fluorouracil compared to those who used capecitabine. However, only the patients who used capecitabine developed hand-and-foot syndrome. Conversely, the levels of ALT in the elderly men who used capecitabine were significantly higher than those who used 5-fluorouracil. With regard to cardiac function, a significant difference was only observed in the QT interval between the groups, all the other exams presented normal results.

Capecitabine use should be frequently accompanied and monitored in the elderly in order to minimize or avoid the toxic effects of the chemotherapy. The action of a multidisciplinary group should bring benefits to geriatric patients, helping to avoid possible complications caused during the treatment. Other parameters could be analyzed subsequently to confirm this idea.

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