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Safety and Quality of Life in the Treatment of Non-Metastasic Colorectal Cancer patients: 5-Fluorouracil versus Capecitabine

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Abstract

Colorectal cancer (CRC) is the most frequent neoplasm of the digestive system and the third most frequent tumour worldwide. In stages I and II the treatment is only surgical and, in high-risk stages II and stages III surgery is complemented with adjuvant chemotherapy. Traditional adjuvant therapy consists of 5-fluorouracil, in combination with leucovorin, and oxaliplatin (FOLFOX regimen, all for iv administration). Alternatively 5-fluorouracil can be substituted by capecitabine, precursor of 5-fluorouracil, which has the advantage that it is administered orally (XELOX regimen). Both regimes are considered interchangeable.

The aim of this study is to compare these regimens (FOLFOX and XELOX) in terms of safety and quality of life (QoL) in patients diagnosed with stage II and III non-metastatic CRC.

For this purpose, a descriptive prospective study with patients diagnosed with stage II and III non-metastatic CRC in adjuvant treatment with FOLFOX and XELOX schemes was carried out. The appearance of symptomatic, haematological and hepatic adverse events (AE) during the treatment was established by evaluating their clinical and pharmacotherapeutic history. The severity of the AE was established following the Common Terminology Criteria for Adverse Events (CTCAE v.4.03). To evaluate the QoL, the QoL EORTC QLQ-C30 version 3.0 questionnaire was given to patients at the beginning and the middle of the adjuvant treatment. The statistical analysis of the data was carried out with the SPSS®15.0 program.

33 patients were finally included in the study. All the patients treated with FOLFOX and with XELOX presented some of the AE studied. The most frequent AE for both groups were neurotoxicity, diarrhoea, constipation and thrombocytopenia, but only statistically significant difference was found in case of palmar-plantar erythrodysesthesia síndrome (PPE), and more frequent in patients treated with XELOX.

According to QoL, patients with FOLFOX presented a worsening in terms of daily activities, constipation and insomnia while in those treated with XELOX a worsening in daily activities, constipation, fatigue, nausea, vomiting, anorexia and diarrhoea was observed. Only statistically significant difference was found in the emotional role item at the middle of the treatment, at which point, patients treated with FOLFOX were better emotionally than those treated with XELOX.

As conclusion, both schemes seem to be safe, although differences in PPE (more frequent with XELOX) and emotional role (better with FOLFOX) were found. However, it should be taken into account that patients treated with FOLFOX presented higher frequency of haematological AE, which are difficult to perceive. In contrast, patients treated with XELOX had higher frequency of symptomatic AE, which probably leads to this slightly worse QoL.

Keywords:

Colorectal Cancer,

Safety,

Quality Of Life,

5-Fluorouracil,

Capecitabine.

1. Introduction

Colorectal cancer (CRC) is the most frequent neoplasm of the digestive system and the third most frequent tumor worldwide, with approximately one million people diagnosed annually [1]. It is also the fourth cause of death, after lung cancer, liver cancer and stomach cancer [2]. The incidence of CRC shows a marked geographical variation, being Central Africa the region with the lowest incidence rate (2.3 patients per 100,000 population) and Japan the region with the highest rate (49.3 patients per 100,000 population). This demographic variation is conditioned by the economic development of the country, with two-thirds of all CRCs diagnosed in developed countries [3].

More than 90-95% of these neoplasms seem to be sporadic [3] and only 5-10% seems to have a hereditary component. After CRC diagnosis, the best possible treatment is stablished acoording to the disease stage. The most used staging system is the TNM system of the American Joint Committee [4]. In stage 0 or carcinoma in situ, the tumor cells are located in the most superficial part of the mucosa, without grown beyond the mucosa. In stage I, the tumor affects the wall of the colon or rectum without passing through the muscle layer. In stage II, the tumor has infiltrated all the layers of the wall of the colon or rectum, being able to invade the surrounding organs. In stage III the tumor has invaded the nearest organs and affects the lymph nodes and in stage IV the tumor has spread to affect organs distant from the colon or rectum such as liver, lung, ovary or non-regional ganglion.

In stages I and II the treatment is only surgical and, in high-risk stages II and stages III surgery is complemented with adjuvant chemotherapy. Traditional adjuvant chemotherapy in these stages is based on the administration of 5-fluorouracil (5-FU) intravenously in monotherapy or in combination with another chemotherapeutic, also intravenously, such as oxaliplatin (FOLFOX regimen). The development of capecitabine, 5-FU precursor of oral administration [5], extended the therapeutic possibilities, since it is used orally as monotherapy or in combination with intravenous administration of oxaliplatin (XELOX regimen).

In the case of metastatic CRC (mCRC), the general therapeutic strategy depends on whether the metastatic disease is resectable or is only susceptible to palliative treatment. If the first case, the priority of the first-line treatment is the immediate control of the disease before the surgery, in order to reduce the related symptoms, to stabilize quickly the progression of the disease and to reduce the metastases. Currently, the regimens used as first-line treatment are FOLFOX, XELOX or FOLFIRI (combination of 5-FU with irinotecan) plus bevacizumab (recombinant humanized monoclonal antibody that binds and neutralizes vascular endothelial growth factor [VEGF]), without having found differences in long-term survival (LTS) or OS among the different combinations [6,7].

Several clinical trials have analized the safety and efficacy of these adjuvant therapies. In the case of capecitabine and 5-FU as monotherapy, numerous studies have shown that capecitabine is an alternative at least as effective and well tolerated as 5-FU in patients with stage III CRC [7,8], so that intravenous 5-FU can be replaced by capecitabine with the advantage of its oral administration.

When monotherapy was compared to combination therapy, an improvement in efficacy was observed, in general, when 5-FU or capecitabine were combined with oxaliplatin (FOLFOX and XELOX regimens respectively) [9]. For example, the MOSAIC study [10,11], which compares adjuvant treatment with 5-FU monotherapy and the treatment of 5-FU in combination with oxaliplatin, showed an increase in the 5-year LTS rate (from 67.4% to 73.3%) and the 6-year OS rate (from 76.0% to 78.5%) in the patients treated with FOLFOX regimen.

In the same way, the association of capecitabine and oxaliplatin (XELOX regimen) also improved survival when compared to the administration of 5-FU/leucovorin (5-FU/LV) monotherapy (leucovorin increases the effect of 5-fluorouracil by inhibiting thymidylate synthase) , data that are concluded from the XELOXA study [12,13], where the 3-year LTS rate was 70.9% for patients treated with the XELOX regimen and 66.5% for those treated with 5-FU/LV, and the 5-year OS rate was 77.6% for the XELOX group vs 74.2% for the 5-FU/LV group.

The duration of adjuvant chemotherapy should be 6 months, although the important cumulative neurotoxicity of oxaliplatin sometimes requires not to complete the treatment. In general, the benefits of the addition of oxaliplatin are less clear when the risk of recurrence is low or in case of high risk patients (associated comorbidities, elderly). In these patients the alternative treatment could be 5-FU or capecitabine in monotherapy [5].

FOLFOX and XELOX regimens are comparables in terms of efficacy. Regarding the toxicity profile of both regimens, it is worth mentioning the study carried out by Schmoll et al [14,15] in which the FOLFOX regimen is compared with XELOX regimen in patients with mCRC and CRC in state III. It was observed that, as in efficacy, both regimens haved a similar safety profile, although there were differences in terms of rates and severity of adverse reactions (AR). On the one hand, patients treated with the FOLFOX regimen showed, in general, more grade 3-4 AR (45% versus 36%) and more grade 3-4 AR associated with oxaliplatin, such as neurotoxicity (8% versus 6%), neutropenia (24% versus 5%) and febrile neutropenia (2% versus <1%). Similar results were already perceived in

previous studies where patients diagnosed with mCRC were analyzed [16]. On the other hand, patients treated with the XELOX regimen presented a higher frequency of grade 3-4 gastrointestinal disorders, such as diarrhea (15% versus 12%), vomiting or nausea (7% versus 5%) and palmar-plantar erythrodysesthesia (PPE) (12% versus <1%) [16].

Currently, in most of the countries FOLFOX and XELOX therapeutic schemes are considered, in general, interchangeable [17,18]. However, it is important when choosing a chemotherapeutic scheme over another, to take into account not only the efficacy and the adverse reactions associated with each scheme but also the quality of life (QoL) of the patients.

The measurement of the QoL is not easy, because it is conditioned, to a certain extent, by the subjectivity in the "perception of the disease" that each patient has. For this reason, questionnaires and scales are used trying to reflect as accurately as possible the impact of the disease and its treatment on this QoL and so standardize its evaluation. There are few clinical studies that include the evaluation of the QoL of patients with CRC. Commella P et al. [19] compared the QoL of patients diagnosed with mCRC in treatment with FOLFOX and XELOX regimens, by using of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC30 version 3.0) at the beginning of the treatment and after 8 week, and differences in QoL between both groups were not found. Seymour MT et al. [20] also evaluated with the EORTC QLQ-C30 questionnaire the QoL of patients with mCRC in treatment with capecitabine or 5-FU with or without oxaliplatin. The questionnaire was completed at the beginning of treatment and at week 12, concluding that there were no differences in terms of QoL between both groups. Conroy T et al [21] obtained the same result.

Most of the comparative studies evaluating the safety and quality of life of chemotherapy schemes have focused on patients with mCRC, while there are almost no studies with patients diagnosed with stage II and stage III CRC.

The objective of this study is to evaluate whether the substitution of 5-FU, of intravenous administration, by capecitabine, of oral administration, in combination chemotherapy with oxaliplatin (FOLFOX and XELOX schemes) modifies the safety profile of the treatment and the quality of life (QoL) of patients diagnosed with stage II and III non-metastatic CRC.

2. Methods

2.1 Patients

A prospective descriptive study of patients diagnosed with stage II and III non-metastatic CRC, under adjuvant treatment with the FOLFOX-6 and XELOX regimens, was carried out. The study was conducted in the Hospital Virgen de la Luz (Cuenca, Spain) for 24 months (October 2015-October 2017) and included patients who during this period began and ended the adjuvant treatment, that is, they completed the 24 weeks of adjuvant treatment. The study was authorized by the Ethics Committee for Clinical Research of the region (Ref. 2015/PI1115).

All patients signed their consent to participate in the study after being informed of the objectives of the study.

2.2 Treatments

The patients were divided into two groups according to the chemotherapeutic regimen they followed [22,23]:

- FOLFOX: treated wih the FOLFOX-6 regimen, which consists of an initial intravenous administration of oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2) and 5-FU (400 mg/m^2) on the first day of the cycle, following of a continuous infusion for two days of 5-FU (1200 mg/m^2/day). All this repeated every two weeks until completing a total of 24 weeks (12 total cycles).

- XELOX: treated with the XELOX regimen, which consists of a dose of intravenous oxaliplatin (130 mg/m^2) on the first day of the cycle, and capecitabine orally administered twice a day (2,000 mg/m^2 daily) for 14 days since the first day of the cycle. All this repeated every three weeks for a total of 24 weeks (8 total cycles).

2.3 Control variables

Demographic data (age and gender), data related to the disease (location, stage and ECOG (scale developed by the Eastern Cooperative Oncology Group with the objective of measuring the functional repercussion of the oncology disease in the patient as a criterion for progression)) and data related to the treatment (existence or not of previous chemoradiation, number of cycles received, time from diagnosis to start of treatment, starting dose, reduction or not of

the dose during the treatment and reason for dose reduction or suspension, if any), were collected in all the patients finally included in the study.

2.4 Response variables

- Safety: The ARs were divided into:

  - Symptomatic ARs: diarrhea and/or constipation, nausea and/or vomiting, mucositis, PPE and neurotoxicity;
  - Haematological alterations: anemia, thrombocytopenia, lymphopenia, neutropenia;
  - Liver disorders: increase in total bilirubin and hypertransaminemia (increases in glutamic-oxalacetic transaminase (GOT) or aspartate aminotransferase, increases in glutamic-pyrubic transaminase (GPT) or alanine aminotransferase and increases in gamma glutamyl transpeptidase (GGT)).

  The severity of the ARs was established following the Common Terminology Criteria for Adverse Events (CTCAE v.4.03), except for liver disorders. These do not come stamped in this document and only the presence or absence of these alterations was analyzed, establishing the limit values according to those indicated by the Clinical Analysis Laboratory of the Hospital in which the study was conducted.

- Quality of life: it was evaluated from the EORTC QLQ-C30 questionnaire that consists of 30 questions divided into 3 scales:

  - Functional scale: physical function (questions 1 to 5), daily activities (questions 6 and 7), emotional role (questions 21 to 24), cognitive function (questions 20 and 25) and social function (questions 26 and 27).
  - Symptomatic scale: fatigue (questions 10, 12 and 18), pain (questions 9 and 19), nausea/vomiting (questions 14 and 15), dyspnea (question 8), insomnia (question 11), anorexia (question 13), constipation (question 16); diarrhea (question 17) and economic impact (question 28).
  - Global health status scale (questions 29 and 30).

2.5 Data collection

- Safety: The appearance of AR during the treatment was established through the review, for each patient, of the computerized clinical history (Mambrino XXI®), the pharmacotherapeutic history of the Farmatools-Dominion® External Patients module and the pharmacotherapeutic history of the Farhos Oncología®v.5.0 computer program. The data collection was carried out in an Excel database and another Access database. The management and maintenance of all the information guaranteed the rights of privacy and protection of personal data in accordance with current legislation on Protection of Personal Data [24].

- Quality of life: Patients completed the QoL questionnaire EORTC QLQ-C30 version 3.0 [25,26] at the beginning and half of the adjuvant treatment (in cycle 7 for patients treated with the FOLFOX regimen and in cycle 5 for those treated with XELOX).

2.6 Data Analysis

The statistical analysis of the data was carried out with the SPSS®15.0 program. (Windows® version). A descriptive analysis of the continuous or numerical variables was performed using measures of central tendency (mean and median) and dispersion (range), and absolute or relative frequencies were used for the categorical or qualitative variables. In the bivariate analysis, the relationship between the independent categorical variable (chemotherapeutic regimen administered) and the dependent variable was studied using the chi-square test (FISHER) in the case of the appearance or absence of any of the ARs studied. A level of significance of 0.05 was established.

For the analysis of the EORTC QLQ-C30 questionnaire, values of 1 and 2 (1: no, 2: yes) were assigned for questions 1 through 7; values between 1 and 4 for questions from 8 to 28 (1: nothing, 2: a little, 3: quite a bit, 4: a lot); and only in items 29 and 30 were evaluated with scores of 1 to 7 (1: extremely bad, 2: very bad, 3: bad, 4: fair, 5: good, 6: very good, 7: extremely good). The raw scores were obtained as the average of the items that contribute to the scale. The raw scores were standardized according equations 1, 2 and 3 obtaining a score between 0 and 100 (figure 1); so that higher values in the scale of global health status and functional scale indicated a better QoL and higher values in the symptomatic scale indicated a worse QoL [27].

Intra-group (at the beginning and half of the treatment) and inter-group (each therapeutic scheme) analysis of the scores were done. Changes on a scale from 5 to 10 points at the beginning and half of the adjuvant treatment were considered "small change", from 10 to 20 points were "moderate change" and greater than 20 points were "hight change". Only chages greater than 10 points were considered clinically relevant [28]. The comparison of means of a quantitative variable with a qualitative dichotomous one was carried out with the T test for independent samples. P <0.05 was considered statistically significant.

Equation 1	Functional scale	$S = \{1 - \frac{(RS-1)}{Range}\} * 100$
Equation 2	Symptomatic scale	$S = \{\frac{(RS-1)}{Range}\} * 100$
Equation 3	Global health status scale	$S = \{\frac{(RS-1)}{Range}\} * 100$

where RS is the raw score for each scale and Range is the difference between the maximum possible value of RS and the minimum possible.

Figure 1. Equations used for the standardization of the raw scores.

3. Results

3.1 Control variables

A total of 33 patients were finally included in the study, with an average age of 61 years (range: 21-76) and male predominance (24 patients, 73%). Regarding the data related to the disease, 17 (52%) patients presented colonic localization compared to 16 (48%) that presented rectal localization, and with respect to the stage of the disease, the majority of patients were classified as stage 3 (76%) and all patients (100%) had ECOG less than or equal to 2. The characteristics of the patients according to their demographic data and related to the disease are listed in Table 1. There were no statistically significant differences in the distribution of the patients between the two regimes when these variables were compared.

Table 1. Demographic data and disease data of the patients included in the study.

	FOLFOX regimen (n=12) N (%)	**XELOX regimen (n=21) N (%)**	**p value**
Age (years)			
Average (range)	61 (38-70)	62 (21-76)	p = 0.600
Gender			
Man	10 (83%)	14 (67%)	p = 0.289
Woman	2 (17%)	7 (33%)	
Desease location			
Rectal	7 (58%)	9 (43%)	p = 0.392
Colonic	5 (42%)	12 (27%)	
Desease stage			
II	3 (25%)	5 (24%)	p = 0.939
III	9 (75%)	16 (76%)	

Regarding the data related with the treatment, 21 patients (64%) received the XELOX regimen while 12 patients (36%) were treated with FOLFOX regimen. 12 patients, all of them diagnosed with rectal carcinoma, received previous chemoradiation (36%; 5 treated with FOLFOX and 7 treated with XELOX), and 6 of them received a lower number of cycles than the rest (1 patient received 10 cycles of FOLFOX and 5 patients received 6 cycles of XELOX). The average time period from diagnosis to the start of adjuvant treatment was 3 months (range: 1-7). The starting doses were all in agreement with that indicated in the data sheet with the exception of 4 patients (12%) who started the adjuvant treatment with reduced doses due to their bad general state. Regarding dose reduction or treatment suspension in the first half of adjuvant therapy (between cycles 1 and 7 for patients treated with FOLFOX and between cycles 1 and 5 for those treated with XELOX), 13 (39%) patients reduced the dose and 3 (9%) patients discontinued the oxaliplatin treatment, whereas that 11 (33%) patients reduced the dose of fluoropyrimidines, all due to AR. At the end of the adjuvant treatment (after 24 weeks of treatment), 15 (45%) patients had reduced the dose and 13 (39%) patients had discontinued the treatment with oxaliplatin, while 15 (45%) patients had reduced the dose and 7 patients (21%) had discontinued treatment of fluoropyrimidines. The data related to the treatment are shown in Table 2 and only statistically significant differences between chemotherapeutic regimes were found in the dose of oxaliplatin at the end of the treatment.

Table 2. Control variables related to treatment according to the received chemotherapeutic regimen. *statistically significant differences p<0.05.

	FOLFOX regimen (n=12) N (%)	XELOX regimen (n=21) N (%)	p value
Previous chemo-radiotherapy			
Yes	5 (42%)	7 (33%)	p = 0.633
Not	7 (58%)	14 (67%)	
Number of cycles received			
Average (range)	12 (10-12)	8 (6-8)	p = 0.105
Time from diagnosis to start of treatment (months)			
Average (range)	3 (1-7)	3 (1-6)	p = 0.431
Starting dose			
Complete	11 (92%)	18 (86%)	p = 0.605
Reduced	1 (8%)	3 (14%)	
Oxaliplatin dose in the middle of the treatment			
Complete	5 (42%)	12 (57%)	p=0.094
Reduced	7 (58%)	6 (29%)	
Suspended	-	3 (14%)	
Fluoropyrimidine dose in the middle of the treatment			
Complete	7 (58%)	15 (71%)	P = 0.446
Reduced	5 (42%)	6 (29%)	
Suspended	-	-	
Oxaliplatin dose at the end of treatment			
Complete	-	5 (24%)	p = 0.039*
Reduced	8 (67%)	7 (33%)	
Suspended	4 (33%)	9 (43%)	
Fluoropyrimidine dose at the end of treatment			
Complete	3 (25%)	8 (38%)	p = 0.734
Reduced	6 (50%)	9 (43%)	
Suspended	3 (25%)	4 (19%)	

3.2 Safety

When analyzing the appearance of AR according to the chemotherapeutic scheme administered, it was observed that 100% of the patients treated with FOLFOX regimen or with XELOX regimen presented some of the AR studied. The number of patients with grade 1-2 toxicity was 58% for the FOLFOX group and 81% for the XELOX group; and 42% and 19% patients with grade 3-4, respectively.

- Symptomatic ARs: The most frequent symptomatic ARs for both groups, FOLFOX or XELOX regimens, were neurotoxicity and diarrhea and/or constipation. In the group treated with the FOLFOX regimen, 100% of patients presented neurotoxicity, 83% of patients had diarrhea and/or constipation, 42% of patients had nausea and/or vomiting, 16% of patients mucositis and 8% of patient PPE. Regarding the group treated with the XELOX regimen, 90% of patients presented neurotoxicity, 67% of patients had diarrhea and/or constipation, 57% of patients nausea and/or vomiting, 38% of patients had PPE, and 28% of patients mucositis. The incidence of the symptomatic AR according to the chemotherapeutic regimen administered is shown in Figure 2a, finding statistically significant differences exclusively in the appearance of PPE, with a higher incidence in the group treated with the XELOX regimen. As can be seen in Figure 2g in the FOLFOX group all symptomatic ARs were grade 1-2 except for 8% of patient who presented mucositis grade 3 and other 8% that presented neurotoxicity also grade 3. For patients treated with the XELOX regimen, all these ARs were grade 1-2.

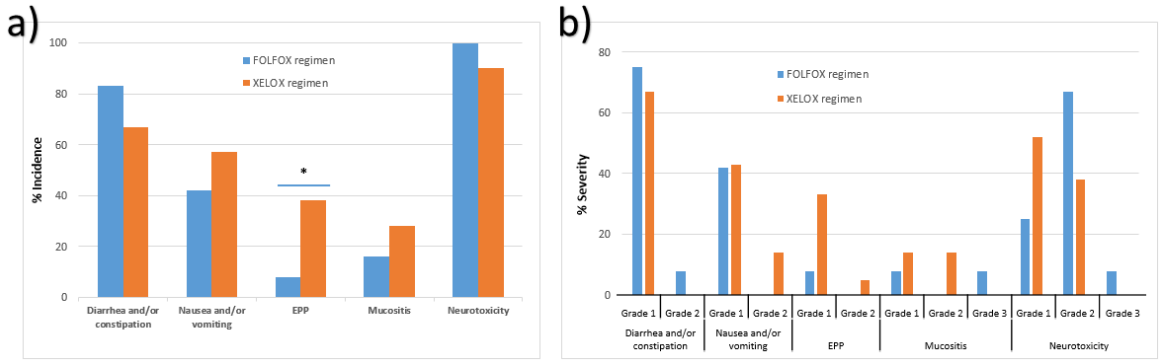

Figure 2. Frequency (2a) and severity (2b) of symptomatic AR according to the type of chemotherapeutic regimen administered. *statistically significant differences p<0.05.

- Haematological ARs: The most frequent hematologic AR for patients with both treatments was thrombocytopenia, and the less frequent was anemia for the group treated with FOLFOX and neutropenia for the group treated with XELOX. Specifically, in the group of patients treated with FOLFOX, 92% of patients had thrombocytopenia, 66% of patients had lymphopenia, 50% of patients had neutropenia and 33% of patients shown anemia. Regarding the group of patients treated with XELOX, 71% of patients had thrombocytopenia, 43% of patients anemia, 43% of patients lymphopenia and 38% of patients neutropenia. In addition, all anemia and thrombocytopenia were grade 1-2 for both treatments, and only lymphopenia and neutropenia (in the XELOX group) appeared in grade 3. The incidence and severity of the hematological AR depending on the drug administered are shown in Figure 3a and 3b. These differences between treatments were not statistically significant.

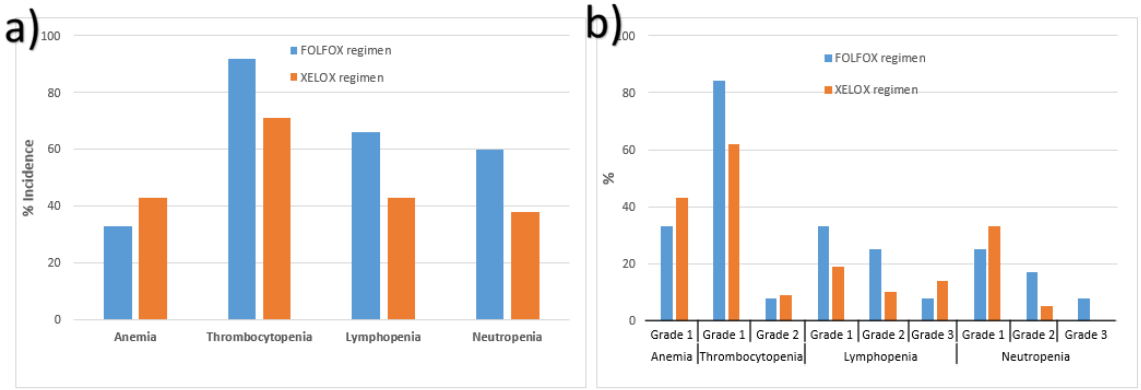

Figure 3. Frequency (3a) and severity (3b) of haematological AR according to the type of chemotherapeutic régimen administered.

- Hepatic ARs: The most frequent hepatic AR for the group treated with FOLFOX was the increase in GPT and for the group treated with XELOX the increase in GOT. Upon further analysis of hepatic ARs, within the group of patients treated with the FOLFOX regimen, in 75% of patients had increased GPT, in 50% of patients increased GOT and in 17% of patients increased GGT. Regarding the group of patients treated with the XELOX regimen, in 62% of patients had increased GOT, in 48% of patients increased GPT and in 14% of patients increased GGT. The incidence of hepatic ARs depending on the drug administered is shown in Figure 4, without finding statistically significant differences in any of the variables analyzed.

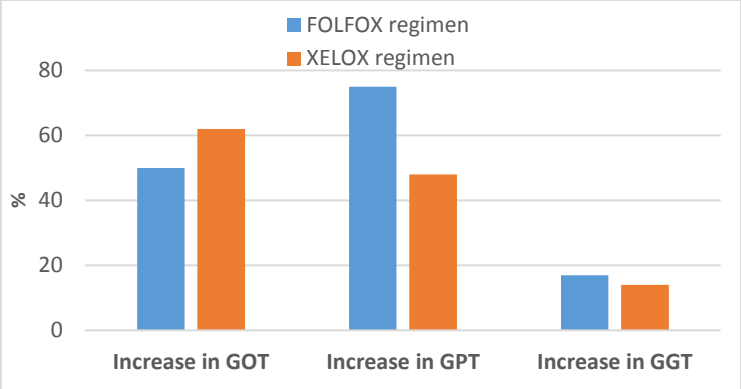

Figure 4. Frequency of hepatic ARs according to the chemotherapeutic regimen administered.

3.3 Quality of life

The results of the analysis of the different items of the questionnaire EORTC QLQ-C30 are shown in table 3. When comparing the scores obtained according to the treatment received, only statistically significant differences were found in the emotional role item (functional scale) at the middle of the treatment: patients treated with FOLFOX regimen exhibited better emotional state than those treated with XELOX.

When the scores obtained at the beginning and at the middle of the treatment are compared, moderate and hight clinically relevant changes are detected in several items. Regarding the daily activities, the patients of both groups presented a clinically relevant worsening, considered in both cases as "moderate".

The symptomatic scale worsened in both groups. Patients treated with FOLFOX presented a clinically relevant worsening in terms of constipation and insomnia throughout the treatment. The worsening of the first symotom was considered as moderate but in case of insomnia was a hight change. When analyzing patients treated with XELOX, a clinically relevant worsening was observed in constipation, fatigue, nausea, vomiting, anorexia and diarrhea throughout the treatment, considering this worsening for all items as "moderate".

Finally, when analyzing the global health scale, no variations were observed during the adjuvant treatment for any of the groups.

Table 3. Scores of the different items of the EORTC QLQ-C30 questionnaire at the beginning and half of the treatment. *statistically significant differences p<0.05.

	FOLFOX regimen		**XELOX regimen**		**p value**
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**	
Physical function					
Start	93	13.5	89	18.1	p = 0.609
Half of treatment	89	13.7	87	19.1	p = 0.777
Daily activities					
Start	95	15.1	92	18.7	p = 0.618
Half of treatment	82	33.7	79	30.3	p = 0.812
Emotional role					
Start	86	13.4	84	12.5	p = 0.705
Half of treatment	92	10.1	82	14.2	p = 0.036*
Cognitive function					
Start	94	11.2	96	11.9	p=0.569
Half of treatment	92	11.3	93	13.9	p=0.916
Social function					
Start	86	19.5	88	19.2	p=0.855
Half of treatment	85	21.7	85	18.3	p=0.976
Global functional scale					
Start	93	5.9	92	7.3	p=0.732
Half of treatment	93	7.3	90	7.9	p=0.283
Fatigue					
Start	15	17.4	18	20.3	p=0.686
Half of treatment	21	18.2	28	19.1	p=0.345
Pain					
Start	6	8.3	10	17.8	p=0.438
Half of treatment	9	17.2	10	14.8	p=0.819

Nausea/vomiting					
Start	0	0	3	8.8	p=0.104
Half of treatment	5	10.8	13	15.2	p=0.086
Dyspnoea					
Start	0	0	2	7.6	p=0.456
Half of treatment	9	15.4	5	16.7	p=0.550
Insomnia					
Start	2	39	24	34.9	p=0.839
Half of treatment	24	39.7	24	31.2	p=0.979
Anorexia					
Start	12	30.8	10	19.4	p=0.861
Half of treatment	15	31.1	30	24.7	p=0.165
Constipation					
Start	9	15.4	3	10.4	p=0.307
Half of treatment	21	22.4	14	23.1	p=0.420
Diarrhea					
Start	12	27.1	9	18.7	p=0.684
Half of treatment	21	34.2	24	21.8	p=0.753
Economic impact					
Start	18	34.6	14	32	p=0.740
Half of treatment	15	27.4	9	24.4	p=0.511
Global symptomatic scale					
Start	10	9.4	11	10.1	p=0.841
Half of treatment	15	13.6	18	17.1	p=0.468
Global health status					
Start	65	16.2	68	14	p=0.682
Half of treatment	69	15.3	66	16.7	p=0.663

4. Discussion

An study on safety and quality of life is presented, in which two therapeutc schemes, FOLFOX and XELOX, used as adjuvant chemotherapy in patients with CRC in stage II and III, are compared. All medication of FOLFOX scheme is administered intravenously: oxaliplatin and 5-FU+LV on the first day of the cicle, and 5-FU in continuous infusion the next two days, all repeated every two weeks until completing a total of 24 weeks (12 cycles). In XELOX scheme, 5-FU is substituted by capecitabine orally administered twice a day for 14 days, all repeated every three weeks until completing a total of 24 weeks (8 cycles). As previously commented, different clinical trials have evaluated the efficacy, safety and even the QoL of both schemes, but most of them in patients with mCRC. In these studies FOLFOX and XELOX showed an efficacy comparable, and although differences in terms of rates and severity of adverse reactions were detected, neither difference in QoL of the patients was demonstrated. However, there are very few studies performed on patients with stage III CRC and none with patients with stage II CRC. The lower overall deterioration of these patients could reveal differences between both schemes, especially in terms of QoL, due to the substitution of a continuous infusion administration for 2 days every two weeks (5-FU in FOLFOX scheme) by taking two tablets a day for 14 days every 3 weeks (capecitabine in XELOX scheme). The design of our study allows, in addition, to contrast the subjective results obtained with the QoL questionnaire with the objective results of adverse reactions reported in the same group of patients.

Several studies carried out in patients diagnosed with mCRC concluded that this type of patients preferred, in general, oral administration to intravenous administration [29,30], since oral treatment offers greater independence and control over therapy, it is easy to manage, avoid the problems associated with the insertion of venous access, such as infections and extravasations, and all with the same effectiveness. However, other studies showed that the safety profile of chemotherapeutic schemes plays an important role in the patient's preference for one route of administration or another, having little relevance the comfort that the route of administration may involve [31-34].

In our study of safety with stage II and III CRC patientes only statistical significant difference in the frecuency of appearance of PPE was detected, with a greater indicence in patients treated with XELOX. This coincides with other studies, which associate the highest incidence of PPE directly with the use of capecitabine [14,16].

Regarding QoL, it seems that it was better in patients treated with FOLFOX, although the scales of overall functionality and overall health status did not improve or worsen for both groups throughout the treatment and the overall symptomatic scale worsened only slightly for both groups. Lin JK et al. [8] studied the QoL in stage III CRC patients treated either with capecitabine or with 5-FU/LV, in monotherapy or associated with oxaliplatin, concluding that the

treatment with capecitabine did not offer a quality of life lower than the treatment with 5 –FU. In this study the EORTC QLQ-C30 questionnaire was completed at the beginning and end of the treatment.

In general, haematological ARs (thrombocytopenia, lymphopenia and neutropenia) were more frequent in patients who received FOLFOX, while patients treated with XELOX had a higher incidence of symptomatic ARs, such as PPE, nausea and vomiting and anemia. The study of Schmoll HJ. et al [14] also shows this higher incidence of nausea and vomiting in patients treated with XELOX. The fact that hematologic ARs, with the exception of anemia, are non-symptomatic ARs and that, therefore, the patient can not perceive them, may be the reason why patients treated with the FOLFOX scheme presented, in general, better results in the questionnaire QoL than patients treated with XELOX. Indeed, patients treated with XELOX showed a worsening during the treatment of fatigue (could be related to anemia), nausea/vomiting, anorexia and diarrhea, which did not manifest patients treated with FOLFOX. Patients treated with FOLFOX only showed a worsening of insomnia. This worsening in the symptomatology detected by patients treated with XELOX would be the cause of the statistically significant difference found when evaluating the emotional role in the middle of treatment in patients receiving FOLFOX and those receiving XELOX. The hematologic ARs such as neutropenia, lymphopenia and thrombocytopenia were not perceived by the patients because they did not limit their daily activities, but instead, the symptomatic ARs and anemia did condition and limit them in daily activities.

The clinically relevant worsening of insomnia detected in our study only in patients treated with FOLFOX, is not reported in other studies on QoL. On the contrary, the study by Cornmella et al [19] in patients diagnosed with mCRC showed that, with treatment, insomnia improved in patients who received FOLFOX and worsened in patients who received XELOX. The high standard deviation of the scores corresponding to this item in our study, could explain in part the different results.

The same occurs with the clinically relevant worsening in the perception of anorexia during XELOX treatment. In the study carried out by Conroy et al [21] no worsening of this item was detected with any of the treatments, probably because they performed the study with patients diagnosed with mCRC, who presented a significantly higher baseline incidence of anorexia than patients of our study. On the contrary, in the study carried out by Chen HH et al. in patients with stage III CRC, the questionnaire was completed at the beginning and after 12 and 28 weeks of treatment a lower loss of appetite in patients treated with capecitabine was detected [22].

In addition, in our study both groups of patients perceived constipation as a limiting symptom in their QoL, since this item presented a clinically relevant worsening throughout the adjuvant treatment for both the group treated with the FOLFOX scheme and the group treated with the XELOX scheme. In contrast, only patients treated with XELOX perceived diarrhea as a limiting and clinically relevant symptom. These data do not agree with the frequency of occurrence of these adverse reactions, greater in patients treated with FOLFOX (although the differences are not statistically significant). This disagreement is probably due to the difficulty in collecting this AR, as they were colostomized patients. In fact, the higher incidence of diarrhea/constipation associated with FOLFOX treatment is not reflected in other studies [14-16], and with respect to XELOX, in the study of Comella P. et al [19], with stage III CRC patients, there was even an improvement in the perception of constipation as the treatment progressed.

Although the differences were not statistically significant, grade 3-4 ARs were more frequent in patients treated with the FOLFOX scheme (42%), than in patients treated with XELOX (19%), especially due to the greater severity of the cases of mucositis, neurotoxicity and neutropenia. These results are consistent with those of other studies, such as that of Dureux M. et al, which reflects 45% of grade 3-4 ARs in patients treated with FOLFOX and 36% in patients treated with XELOX [16]. These differences are due, in part, to the higher incidence of neutropenia: it appeared in 24% of patients treated with FOLFOX compared to 5% in those treated with XELOX. This higher percentage of grade 3-4 ARs in patients treated with FOLFOX was probably the cause of greater number of dose reductions and discontinuations of treatment in these patients, specifically in the case of oxaliplatin due to the neurotoxicity associated with the use of this drug.

Probably the worsening in the performance of daily activities as treatment progressed, detected in all patients regardless of the therapeutic scheme, could be related to the neurotoxicity associated with oxaliplatin and also with the worsening of fatigue, dyspnoea, insomnia and nausea/vomiting.

5. Conclussions

The substitution of the continuous infusion of 5-FU for 3 days every two weeks (FOLFOX scheme) by the take of two tablets of capecitabine a day for 14 days every 3 weeks (XELOX scheme) slightly modifies the safety profile of the treatment and the quality of life of patients diagnosed with stage II and III CRC. Although statistically significant differences between both schemes were only found in the incidence of palmar-plantar erythrodysesthesia

(more frequent with XELOX), a higher incidence of non symptomatic hematologic adverse reactions was reported with FOLFOX while a higher incidence of symptomatic adverse reactions was related with XELOX, which led to a slightly worse assessment of the quality of life of these patients.

Patients relate their quality of life preferably to their perception of adverse reactions associated with the medication, and not to the route of administration used, so that the substitution of the intravenous route by the oral route is not perceived by the patient as a benefit.

Since the severity of an adverse reaction is independent of its perception by the patient, one scheme can not be generally selected over another, and an individual assessment of each patient is necessary in terms of general condition, comorbidity, lifestyle, age and even educational level.

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