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Sánchez-Gundín, Julia; Fernández-Carballido, Ana María; Torres-Suárez, Ana Isabel; Barreda-Hernández, Dolores

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BRIEF ORIGINAL

Quality of life in non-metastasic colorectal cancer patients in FOLFOX or XELOX therapy

Calidad de vida en pacientes con carcinoma colorrectal no metastásico tratados con esquema FOLFOX o XELOX

Julia Sánchez-Gundín [12*] julia.sanchez.gundin@gmail.com
Hospital Virgen de la Luz, Spain
Ana María Fernández-Carballido [23]
Universidad Complutense de Madrid, Spain
Ana Isabel Torres-Suárez [23]
Universidad Complutense de Madrid, Spain
Dolores Barreda-Hernández [1]
Hospital Virgen de la Luz, Spain

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Abstract

Objective: To evaluate and to compare quality of life of patients with non-metastasic colorectal cancer treated either with FOLFOX or with XELOX scheme.

Method: Descriptive prospective study during 24 months (October 2015-October 2017) for patients with non-metastasic colorectal cancer in chemotherapy adyuvant treatment. EORTC QLQ-C30 questionnaire was filled by patients at the beginning and at week 12 of adjuvant treatment. Variables collected: exposure (chemotherapeutic scheme administered), control (demographic data, disease data, treatment data) and response (scores obtained from the questionnaire). The data statistical analysis was carried out with the SPSS® 15.0 programme.

Results: 30 patients were included. Statistically significant differences were found in emotional role item at the middle of the treatment (FOLFOX 92 points vs. XELOX 82 points; p = 0,036). Patients with FOLFOX presented a clinically relevant worsening in terms of daily activities, constipation and insomnia. Patients treated with XELOX a clinically relevant worsening in daily activities, constipation, fatigue, nausea, vomiting, anorexia and diarrhoea were observed.

Conclusions: Patients with XELOX scheme referred to have worse emotionally status in the middle of the adjuvant treatment than patients treated with FOLFOX scheme and presented a worsening in items fatigue, nausea, vomiting, anorexia and diarrhoea.

KEYWORDS: Adyuvant treatment++ Colorectal cancer++ FOLFOX++ Quality of life++ Safety++ XELOX.

Resumen

Objetivo: Evaluar y comparar la calidad de vida de pacientes con cáncer colorrectal no metastásico tratados con el esquema FOLFOX o XELOX.

Método: Estudio descriptivo prospectivo de 24 meses de duración (octubre 2015-octubre 2017) en pacientes con cáncer colorrectal no metastásico en tratamiento quimioterápico adyuvante. Se pasó a los pacientes el cuestionario de calidad de vida EORTC QLQ-C30 al inicio del tratamiento y a las 12 semanas. Variables recogidas: exposición (esquema quimioterápico), control (datos demográficos, de la enfermedad y del tratamiento) y respuesta (puntuaciones del cuestionario). El análisis estadístico se efectuó con el programa SPSS® 15.0.

Resultados: Se incluyeron 30 pacientes, encontrándose diferencias estadísticamente significativas en el ítem rol emocional a las 12 semanas de tratamiento (FOLFOX 92 puntos versus XELOX 82 puntos; p = 0,036). Además, los pacientes tratados con FOLFOX presentaron un empeoramiento clínicamente relevante en actividades cotidianas, estreñimiento e insomnio; mientras que los tratados con XELOX mostraron un empeoramiento clínicamente relevante en actividades cotidianas, estreñimiento, fatiga, náuseas, vómitos, anorexia y diarrea.
Conclusiones: Los pacientes tratados con el esquema XELOX se encontraron peor emocionalmente a las 12 semanas del tratamiento adyuvante que los tratados con FOLFOX y presentaron empeoramiento en fatiga, náuseas, vómitos, anorexia y diarrea.
PALABRAS CLAVE: Calidad de vida, Cáncer colorrectal, FOLFOX, Seguridad, Tratamiento adyuvante, XELOX.

Introduction

Colorectal cancer (CRC) is the most frequent neoplasia in the digestive system, and its control is currently one of the priorities within public health, given the mortality and morbidity caused. There has been a great evolution in pharmacological treatment during recent years, and 5-fluorouracil (5-FU) has become the basic treatment for patients with non-metastatic CRC (nmCRC). 5-FU has been used in combination with other agents in order to increase survival, specifically with folinic acid or leucovorin (LV)[1] , and subsequently with oxaliplatin[2].

Another drug used for these patients is capecitabine, a precursor of 5- FU[3]. Several studies have demonstrated that the use of capecitabine in patients with nmCRC is an alternative option as effective and well tolerated as 5-FU/LV[4]; therefore, intravenous 5-FU can be replaced by oral capecitabine. The combination of capecitabine and oxaliplatin (XELOX regimen) has also demonstrated an improvement in survival, and has been compared with 5-FU/LV[5]. When comparing the FOLFOX and XELOX regimens, the study by Schmoll HJ et al. demonstrated that adjuvant treatment with 5-FU/LV or capecitabine with or without oxaliplatin provided optimal results; the conclusion was that both regimens presented equivalent efficacy[6].

However, it is also important to analyze the quality of life (QoL) of patients in order to understand the experience of the patient with their disease and its treatment, and to be able to choose a chemotherapy regimen over another[7]. Therefore, the objective of the study is to evaluate and compare the QoL of patients diagnosed with nmCRC treated with the FOLFOX or XELOX regimen, based on the EORTC QLQ-C30 questionnaire, version 3.0.

Methods

A descriptive prospective study on patients diagnosed with nmCRC receiving adjuvant chemotherapy treatment with the FOLFOX and XELOX regimens. The FOLFOX adjuvant regimen (intravenous oxaliplatin + intravenous 5-FU/LV) consists of 12 14-day cycles during

24 weeks, and the XELOX adjuvant regimen (intravenous oxaliplatin + oral capecitabine) consists of 8 21-day cycles during 24 weeks[8]. A lower number of cycles could be administered to patients with rectal cancer, if they had received chemoradiotherapy before surgery[8].

The study was conducted in a second level hospital during 24 months (October, 2015 to October, 2017), after being authorized by the Ethics Committee for Clinical Research. All patients who initiated and completed the adjuvant chemotherapy treatment and signed the informed consent for participation were included in the study. The patients excluded were those with cognitive impairment that prevented them for understanding and answering questionnaires, patients unable to understand Spanish, and those who did not agree to participate.

Patients were selected at the time of pharmacy validation of their chemotherapy treatments; after signing the Informed Consent, they were given the EORTC QLQ-C30 questionnaire, version 3.0, at that time and at week 12 of initiating adjuvant treatment. This is a questionnaire validated and developed by the European Organisation for Research and Treatment of Cancer Quality of Life, in order to measure the QoL of oncology patients; it consists of 30 questions split into three scales: functional, symptomatic, and overall health status[9,10]. Afterwards, there was a review of the computerized clinical record (Mambrino XXI®) and pharmacotherapeutic records (Farmatools-Dominion® and Farhos-Oncología® v.5.0).

Exposure variables were collected (chemotherapy regimen administered), as well as control variables (age, gender, location and stage of the disease, ECOG, existence or not of previous chemoradiation, number of cycles received, months since diagnosis until initiation of adjuvant treatment, initiation dose, dose reductions and reasons, and treatment interruptions and reasons), and response variables (questionnaire scores). Regarding the questionnaires, scores were standardized: high values in the functional scale and the overall health status scale pointed at a better QoL, and high values in the symptom scales pointed at a worse QoL[11]. Any changes in the items and/or scales superior by 10 points to the basal scores were considered clinically relevant. Alterations from 5 to 10 points entailed a "small" change, alterations from 10 to 20 points reported "moderate" changes, and a difference > 20 points involved "high" change[12]; therefore, only "moderate" and "high" changes involved clinical relevance.

Statistical analysis of data was conducted with the SPSS® 15.0 program (version for Windows®). A descriptive analysis of continuous or numerical variables was conducted by using central tendency and dispersion measures, while absolute and relative frequencies were used for categorical or qualitative variables.

Regarding QoL assessment, the mean value of each of the questionnaire items was obtained from the mean of the questions included. The comparison between mean values in a quantitative variable by another

dichotomous qualitative was conducted with the T test for independent samples. A $p < 0.05$ value was considered statistically significant.

Results

Thirty-six (36) patients were selected; one of them was excluded from the study because he was unable to understand Spanish. Of those 35 patients initially included in the study, five withdrew from the study once adjuvant treatment was initiated: one patient interrupted treatment after the first cycle due to cardiotoxicity, two patients due to disease progression, and another two patients because they did not complete the adjuvant treatment with the same chemotherapy regimen, alternating the FOLFOX and XELOX regimens.

Therefore, 30 patients were included in the analysis; their characteristics, according to the chemotherapy regimen received, appear in Table 1, and no statistically significant differences were found between the different variables.

Table 1.
Characteristics of patients according to the chemotherapy regimen received

	FOLFOX regimen (*n* = 11) N (%)	XELOX regimen (*n* = 19) N (%)	*p*-value
Age (years)			
Mean (range)	59 (38-70)	62 (21-76)	$p = 0.589$
Gender			
Male	9 (82%)	13 (68%)	$p = 0.415$
Female	2 (18%)	6 (32%)	
Location			
Rectal	7 (64%)	10 (53%)	$p = 0.389$
Colon	4 (36%)	9 (47%)	
Stage			
2	3 (27%)	5 (26%)	$p = 0.954$
3	8 (73%)	14 (74%)	
Previous chemo-radiotherapy			
Yes	5 (45%)	7 (37%)	$p = 0.643$
No	6 (55%)	12 (63%)	
Time from diagnosis until treatment initiation (months)			
Median (range)	2 (1-4)	2 (1-3)	$p = 0.436$
Initial dose			
Complete	10 (91%)	16 (84%)	$p = 0.594$
Reduced	1 (9%)	3 (16%)	

Regarding dose reductions or interruptions at the end of adjuvant treatment: 22 (73%) patients had reduced their dose and five (17%) patients had interrupted treatment. The main reason was the development of adverse reactions, mostly neurotoxicity (11 patients; 37%), thrombopenia (9 patients; 30%), neutropenia (9 patients; 30%) and mucositis (3 patients; 10%).

The results of the analysis of the different items in the EORTC QLQ - C30 QoL questionnaire appear in Table 2; no statistically significant differences were found in the majority of items. There were statistically significant differences in the emotional role item at 12 weeks of treatment; at this point, patients treated with FOLFOX were better emotionally than those treated with XELOX (FOLFOX 92 points vs. XELOX 82 points; p=0.036).

Table 2.
Analysis of the different items in the EORTC QLQ-C30 quality of life questionnaire

	FOLFOX regimen		XELOX regimen		p-value
	Mean	Standard deviation	Mean	Standard deviation	
Physical function					
Initiation	93	13.5	89	18.1	p=0.609
Mid-treatment	89	13.7	87	19.1	p=0.777
Daily activities					
Initiation	95	15.1	92	18.7	p=0.618
Mid-treatment	82	33.7	79	30.3	p=0.812
Emotional role					
Initiation	86	13.4	84	12.5	p=0.705
Mid-treatment	92	10.1	82	14.2	p=0.036*
Cognitive function					
Initiation	94	11.2	96	11.9	p=0.569
Mid-treatment	92	11.3	93	13.9	p=0.916
Social function					
Initiation	86	19.5	88	19.2	p=0.855
Mid-treatment	85	21.7	85	18.3	p=0.976
Overall functional scale					
Initiation	93	5.9	92	7.3	p=0.732
Mid-treatment	93	7.3	90	7.9	p=0.283
Fatigue					
Initiation	15	17.4	18	20.3	p=0.686
Mid-treatment	21	18.2	28	19.1	p=0.345
Pain					
Initiation	6	8.3	10	17.8	p=0.438
Mid-treatment	9	17.2	10	14.8	p=0.819
Nausea / Vomiting					
Initiation	0	0.0	3	8.8	p=0.104
Mid-treatment	5	10.8	13	15.2	p=0.086
Dyspnea					
Initiation	0	0.0	2	7.6	p=0.456
Mid-treatment	9	15.4	5	16.7	p=0.550
Insomnia					
Initiation	2	39.0	24	34.9	p=0.839
Mid-treatment	24	39.7	24	31.2	p=0.979
Anorexia					
Initiation	12	30.8	10	19.4	p=0.861
Mid-treatment	15	31.1	30	24.7	p=0.165
Constipation					
Initiation	9	15.4	3	10.4	p=0.307
Mid-treatment	21	22.4	14	23.1	p=0.420
Diarrhea					
Initiation	12	27.1	9	18.7	p=0.684
Mid-treatment	21	34.2	24	21.8	p=0.753
Economic impact					
Initiation	18	34.6	14	32.0	p=0.740
Mid-treatment	15	27.4	9	24.4	p=0.511
Overall symptomatic scale					
Initiation	10	9.4	11	10.1	p=0.841
Mid-treatment	15	13.6	18	17.1	p=0.468
Overall health status					
Initiation	65	16.2	68	14.0	p=0.682
Mid-treatment	69	15.3	66	16.7	p=0.663

*p < 0.05.

When analyzing the changes perceived by patients throughout their treatment, there were clinically relevant differences regarding the basal value in both patient arms. Patients on FOLFOX presented a clinically relevant worsening in daily activities, constipation and insomnia. Worsening was considered "moderate" for the first two items, and "high" for the last one. There was also a worsening classified as "small", and therefore not clinically relevant, for the following items: fatigue, nausea, vomiting, dyspnea and diarrhea. When analyzing patients on XELOX, a clinically relevant worsening was observed, and "moderate" in daily activities, constipation, fatigue, nausea, vomiting, anorexia and diarrhea. There was also a worsening considered "small" in economic impact; and therefore, not clinically relevant.

No differences were found in any patient group for these items: physical function, cognitive function, social function, and pain. Regarding the functional scale, symptomatic scale, and overall health scale, there was worsening in the second for both groups, but it was not clinically relevant in any, the change was considered "small"; there was no variation in the other two, with no differences found in any of the patient groups throughout adjuvant treatment.

Discussion

In this study, it was observed that patients treated with XELOX were worse emotionally at week 12 of treatment than those treated with FOLFOX, and presented worsening in fatigue, nausea, vomiting, anorexia and diarrhea.

In comparison with other studies already published, these have demonstrated that patients on FOLFOX presented higher incidence of insomnia and dyspnea vs. XELOX[4,13]. The study by Comella P et al. in patients with metastatic CRC (mCRC) showed an improvement in insomnia throughout treatment in patients on FOLFOX, and worsening in dyspnea with XELOX[14]. Regarding the studies by Lin JK et al. and Comella P et al., it should be highlighted that patients on FOLFOX presented an improvement in social function in the first one, and improvement on cognitive function and pain in the second one; while in the second study, there was an improvement in the constipation item for mCRC patients on XELOX[4,14].

Regarding anorexia, the study by Chen HH et al. found differences between both regimens, because patients on FOLFOX presented a higher incidence of anorexia both at treatment initiation and at 12 weeks[15]. In our study, it was observed that there was no worsening in said item throughout adjuvancy with FOLFOX, while there was worsening with XELOX. This difference can be due to the patient profile in each study, because the study by Chen HH et al. analyzed patients diagnosed with mCRC, who presented a higher basal incidence of anorexia than nmCRC patients[15].

Finally, the main limitation of the study was its sample size; this fact limits the ability to draw statistically significant conclusions. A larger randomized study could be conducted in order to confirm these results.

Contribution to the scientific literature

Colorectal cancer is the most frequent neoplasia in the digestive system, and its control is currently one of the priorities within public health, given the mortality and morbidity caused. Quality of Life is becoming increasingly considered in Oncology, and it is important to analyze it in order to have a better understanding of the impact of chemotherapy treatment on patient results and, therefore, selecting one chemotherapy regimen over another. To this aim, it is innovative to compare the quality

of life associated with the FOLFOX and XELOX regimens in patients with non-metastatic colorectal carcinoma. The quality of life in patients treated with XELOX seems to be worse than that of patients treated with FOLFOX. The highest worsening presented throughout their treatment in the emotional situation of patients on XELOX was caused by a higher perception of fatigue, nausea, vomiting, anorexia and diarrhea. Therefore, at the time of selecting one chemotherapy regimen over another, the quality of life associated with each chemotherapy regimen must be taken into account, besides the patients' performance status, their lifestyle, age and education level.

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Author notes

Author of correspondence Correo electrónico: julia.sanchez.gundin@gmail.com (Julia Sánchez Gundín).

Conflict of interest declaration

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