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ORIGINAL ARTICLE

Adherence to capecitabine in preoperative treatment of stage II and III rectal cancer: do we need to worry?

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Background: Preoperative oral capecitabine plus radiotherapy has been progressively adopted in oncology units to provide more convenient care to patients with rectal cancer, but little is known about adherence to this therapy.

Patients and methods: Prospective, multicentre observational study in six hospitals in metropolitan Barcelona (Spain), in patients with stage II and III rectal cancer. Assessment of adherence was based on the medical report in the clinical history, a patient questionnaire and a pill count in the pharmacy service upon finalization of treatment. Patients were considered adherent if they had taken 80%–110% of the prescribed treatment. We evaluated clinical variables, adverse effects, anxiety and depression (using the hospital anxiety depression scale [HADS]), and quality of life (EORTC QLQ-30). We analysed adherence-associated variables using a logistic regression model and concordance between adherence measures by means of the modified Kappa index.

Results: We included 119 participants. Adherence measures showed little concordance between the assessment methods used: adherence was 100% according to the clinical history, 83.2% according to self-report and 67.9% according to the pill count. In the multivariable analysis, the most relevant variable associated with non-adherence was anxiety prior to treatment (adjusted odds ratio [ORa] 6.96, 95% confidence interval [CI] 1.48, 32.7). We did not observe any relevant association between adherence and clinical variables and baseline quality of life parameters.

Conclusions: Adherence to short-term oral neoadjuvant treatment in rectal cancer may be a clinical problem, and it should be acknowledged and systematically evaluated by clinicians during treatment. The limited concordance between different measures of adherence highlights the challenges in monitoring it and the need to use different approaches to assess its impact in clinical practice.

Key words: adherence, rectal cancer, oral chemotherapy, quality of life, HAD

Introduction

Combination radiochemotherapy for stage II and III rectal cancer is a therapeutic standard [1], with oral capecitabine normally administered as an adjunct to radiotherapy, but this option also raises the question of therapeutic adherence.

Adherence is the degree to which patient behaviour corresponds to the therapeutic recommendations agreed on with the treating physician [2]. One very relevant aspect of research on therapeutic adherence is its measurement, as there is no validated instrument that helps to standardise its quantification [2]. In fact, the results of different evaluations on adherence depend in part on how it is assessed [3], with a considerable variety of methods to choose from [4].

One little-studied area in adherence research is preoperative treatment for rectal cancer with capecitabine. The fact that this is

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a short-term, oral treatment given prior to surgery suggests that adherence should be high [5]. The aim of this study is to evaluate adherence in this clinical situation in a prospective, multi-hospital cohort, using different methods to measure adherence.

Patients and methods

This was a prospective study and included patients diagnosed with incident, stage II and III rectal cancer, with an indication for treatment with capecitabine and radiotherapy as a neoadjuvant treatment to surgical intervention. Six hospitals in the Barcelona area participated between June 2012 and March 2014. Patients signed informed consent upon enrolment, and the study was approved by the Ethics Clinical Research Committee at the Bellvitge Hospital. Participants were followed up throughout the neoadjuvant treatment (5–6 weeks) or until definitive suspension of treatment due to disease progression, toxicity or patient decision. We excluded patients participating in clinical trials. Assuming an 80% adherence rate to the treatment in our population, we calculated needing a sample size of 102 to estimate adherence with 95% confidence and a precision of ± 5%. We anticipated a replacement rate of 10%.

Variables and source of data were obtained using the following: The review of the clinical record was the source for information on tumour characteristics, stage and treatment. The questionnaire on patient-reported symptoms and adverse effects consisted of a specific list, revised by the investigating clinicians. Participants also responded to questions about comorbidities and the number of medicines they were taking in addition to the chemotherapy.

The Simplified Medication Adherence Questionnaire (SMAQ) [6] elicited information about participants' habits for taking medication, propensity to skip doses, timetables, adverse effects, omissions at the weekend and quantification over the previous week. Specially trained medical professionals administered the questionnaire. We categorised patients as non-adherent if their response to one or more questions on adherence was negative. The average pill count on dispensed and returned medication was carried out in the hospital pharmacy during planned appointments for prescription refills. Adherence was calculated from the number of pills prescribed, the pills returned and the days of treatment. Patients were categorised as adherent if they took ≥ 80% [7].

We evaluated participants' emotional state (depression and anxiety) using HADS, which is self-administered and has been validated in our country [8]. We also used the EORTC QLQ-C30, a validated tool for assessing quality of life in cancer patients over the previous week; it consists of 30 questions or items related to physical, emotional, social and functional aspects [9].

To analyse the determinants of non-adherence to oral treatment, we calculated the odds ratio (OR) and its 95% confidence interval (CI) using non-conditional logistic regression models. In order to predict adherence, we have restricted the statistical analysis to pre-treatment variables. Each variable whose univariate test has shown a P value of less than 0.25 were adjusted for clinical variables (age, sex and stage) [10]. The degree of concordance between the three methods used to measure adherence was estimated using the modified Kappa statistic [11]. We used the SPSS statistical package (version 21.0).

Results

One hundred nineteen participants were included in the study. Supplementary Figure S1 (available at *Annals of Oncology* online) presents the flow chart for participants during the course of the study.

Table 1 shows the characteristics of the patients. There were 76.3% of these with comorbidity; hypertension was the most frequent condition. All patients received concomitant radiotherapy,

Table 1. Description of the study sample participants characteristics

		N (%)
Sex	Men	76 (63.9)
	Women	43 (36.1)
Age at diagnosis	Mean (SD)	64.7 (10.0)
	<55	20 (16.8)
	55–64	37 (31.1)
	65–74	47 (39.5)
	≥75	15 (12.6)
BMI at diagnosis	Mean (SD)	28.5 (11.1)
	Normal weight	35 (29.4)
	Overweight	44 (370)
	Obese	31 (26.1)
	Missing	9 (7.5)
Karnosfky grade (%)	Mean (SD)	90.7 (11.2)
ECOG grade	0	40 (33.6)
	1	66 (55.5)
	2	1 (0.8)
	Missing	12 (10.1)
Clinical stage	IIA	12 (10.1)
	IIIA	11 (9.2)
	IIIB	54 (45.4)
	IIIC	42 (35.3)
Educational level[a]	Illiterate	17 (14.4)
	Primary school education	61 (51.7)
	Secondary school education	19 (16.1)
	Higher education	12 (10.2)
	Missing	9 (7.6)
Person(s) administering medication[a]	Patient	95 (80.5)
	Family	8 (6.8)
	Patient and family	13 (11.0)
	Missing	2 (1.7)
Comorbidity[a] (multiple choice)	No	28 (23.7)
	Yes	90 (76.3)
	Cardiopathy	9 (10.0)
	High blood pressure	61 (67.8)
	Diabetes	21 (23.3)
	High cholesterol	47 (52.2)
	Depression	14 (15.6)
	Others	18 (20.0)
Polymedication[a]	0	17 (14.4)
	1–4	77 (65.3)
	5–10	22 (186)
	+ 10	2 (1.7)
Radiotherapy[b]		118 (100.0)
Total dose applied	45 Gy	56 (47.5)
	50.4 Gy	57 (48.3)
	Others	5 (4.2)
Temporary interruption of treatment	Yes	25 (21.2)
	No	93 (78.8)
Chemotherapy[b]		118 (100.0)
Temporary interruption of treatment	Yes	7 (5.9)
	No	111 (94.1)
Definitive suspension of treatment	Yes	5 (4.2)
	No	113 (95.8)
Reason for discontinuing treatment	Toxicity	4 (80.0)
	Other: perforated duodenal ulcer	1 (20.0)

[a]Participant-report questionnaire ($N = 118$).
[b]Review of the clinical record—follow-up ($N = 118$).

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and 116 finally underwent surgery; the other 2 patients could not due to disease progression. With regard to capecitabine treatment, this was temporarily interrupted in seven patients (5.9%) and definitively in five (4.2%) due to toxicity.

Table 2. Description of adherence measures

	% Adherence	Concordance	
		Physician report	SMAQ
Physician report	100		
SMAQ	83.2	N=1070.82[a]	
Refill hospital pharmacy	67.9	N=1090.56[a]	N=102 0.40[a]

Interpretation of Kappa: <0: poor; 0.01–0.20: slight; 0.21–0.40: fair; 0.41–0 60: moderate; 0.61–0.80: substantial; 0.81–0.99: almost perfect.
[a]Concordance: alternative chance-corrected statistic to kappa.

Overall, physicians' reports did not include any mention of non-adherence, whereas adherence was 83.2% according to the SMAQ questionnaire and 67.9% according to the pill count in the hospital pharmacy. Thus, the degree of concordance was very high between the clinical history and the SMAQ but more moderate with the pill count (Table 2).

The univariable and multivariable analyses with the different independent variables in relation to adherence (measured by pill count) are presented in Table 3, along with the percentage of adherents according to the categories of each variable. In the multivariable analysis, we did not observe an association between adherence and any of the demographic or disease-related variables. With regard to the HADS, we observed that participants with low levels of anxiety at treatment initiation were seven times as adherent as participants with high levels (OR 6.96, 95% CI 1.48, 32.70). There was also a significant, although lower magnitude, association for depression and anxiety together; participants with a higher global score at treatment initiation were less adherent (Table 3). The EORTC QLQ-30 pre-treatment did not bring to light any significant association for global quality of life.

Table 3. Association between adherence (pill count) and pre-treatment study variables: prevalence and odds ratio

N=109		N (% adherents)	OR (95% CI)	ORa (95% CI)
Sex	Men	69 (63.8)		1
	Women	40 (75.0)	1.71 (0.72–4.06)	2.14 (0.80–5.73)
Age at diagnosis	≤54	19 (52.6)	1	1
	55–64	33 (75.8)	2.81 (0.85–9.36)	2.95 (0 78–11.2)
	≥65	57 (68.4)	1.95 (0.68–5.63)	1.77 (0.56–5.57)
Clinical stage	II–IIIA	22 (68.2)	1	1
	IIIB–IIIC	87 (67.8)	0.98 (0.36–2.68)	0.90 (0.28–2.86)
Patholog cal stage	0	18 (72.2)	1	1
		29 (75.9)	1.21 (0.32–4.60)	1.12 (0.25–5.00)
	II	29 (62.1)	0.63 (0.18–2.25)	0.60 (0.13–2.72)
	III	29 (65.5)	0.73 (0.20–0.264)	1.13 (0.27–4.72)
	IV	2 (100.0)		
Tumour site	Distal rectum	33 (72.7)	1	1
	Middle rectum	42 (61.9)	0.61 (0.23–1.64)	0.26 (0.07–1.00)
	Proximal rectum	32 (75.0)	1.13 (0.37–3.41)	0.89 (0.23–3.51)
Symptoms at diagnosis, clinical history	None	2 (100.0)		
	1–2	48 (72.9)	1	
	+3	59 (62.7)	0.63 (0.27–1.43)	0.34 (0.11 a 1.02)
Symptoms at diagnosis	Rectal bleeding	86 (67.4)	0.91 (0.34–2.45)	0.64 (0.20–2.08)
	Rectal tenesmus	49 (65.3)	0.81 (0.36–1.81)	0.97 (0.38–2.49)
	Constipation	19 (73.7)	1.40 (0.0.46–4.25)	1.69 (0.44–6.43)
	Abdominal pain	22 (59.1)	0.62 (0.23–1.62)	0.59 (0.16–2.13)
	Constitutional syndrome	12 (50.0)	0.43 (0.13–1.43)	0 21 (0.04–1.00)
Polymedication	0	16 (68.8)	1	1
	1–4	70 (68.6)	0.99 (0.31–3.20)	0.97 (0.25–3.72)
	5–10	20 (70.0)	1.06 (0.26–4.41)	0.85 (0.16–4.43)
	+ 10	2 (0.0)		
HADS anxiety (scale 0–21)	No symptoms of anxiety (<8 points)	70 (75.7)	3.64 (1.07–12.3)	6.96 (1.48–32.7)
	Bordeline (8–10 points)	25 (56.0)	1.48 (0.39–5.71)	1.70 (0.31–9.40)
	Symptoms of anxiety (≥11 points)	13 (46.2)		
HADS depression (scale 0–21)	No symptoms of depression (<8 points)	101 (69.3)	1	1
	Borderline (8–10 points)	3 (66.7)	0.89 (0.08–10.1)	1.08 (0.07 – 17.7)
	Symptoms of depression (>11 points)	4 (25.0)	0.15 (0.02–1.48)	0.15 (0.01 – 1.66)

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Table 3. *Continued*

N=109		*N* (% adherents)	OR (95% CI)	ORa (95% CI)
		Mean (SD)	OR (95% CI)	ORa (95% CI)
HADS		8.3 (5.6)	0.92 (0.86–0.98)	0.89 (0.82–0.97)
EORTC QLQ-C30, mean (SD) (scale 0–100)	Global quality of life	75.5 (16.4)	1.02 (1.00–1.04)	1.02 (0.99–1.04)
	Physical function	94.2 (9.8)	1.03 (1.00–1.06)	1.04 (1.00–1.08)
	Social function	92.2 (14.5)	1.00 (0.98–1.03)	1.01 (0.97–1.04)
	Emotional function	78.2 (18.7)	1.01 (0.99–1.03)	1.02 (0.99–1.04)
	Cognitive function	92.9 (12.1)	1.02 (1.00–1.04)	1.03 (1.00–1.05)
	Role function	95.0 (14.4)	1.02 (1.00–1.04)	1.01 (0.98–1.04)
	Fatigue	12.2 (17.2)	0.98 (0.96–1.00)	0.98 (0.95–1.00)
	Nausea and vomiting	1.1 (5.1)	0.95 (0.90–1.00)	0.93 (0.87–0.99)
	Pain	12.1 (16.3)	0.98 (0.96–1.00)	0.98 (0.95–1.00)
	Dyspnoea	4.1 (11.0)	1.00 (0.97–1.03)	1.00 (0.97–1.03)
	Insomnia	24.2 (31.6)	1.00 (0.99–1.01)	1.00 (0.98–1.02)
	Loss of appetite	7.3 (16.0)	0.98 (0.96–1.00)	0.98 (0.95–1.00)
	Constipation	15.5 (25.5)	0.99 (0.98–1.01)	0.99 (0.97–1.01)
	Diarrhoea	16.9 (24.9)	0.98 (0.97–1.00)	0.99 (0.97–1.01)
	Economic impact	13.7 (19.9)	0.98 (0.96–1.00)	0.97 (0.95–1.00)

OR, odds ratio; ORa, odds ratio adjusted for sex, age at diagnosis and clinical stage; CI, confidence interval.

Discussion

The main finding of this study is the different result for adherence to preoperative chemotherapy with capecitabine in the context of radiochemotherapy for rectal cancer, according to the method of assessment. Adherence varied from 100% (clinical history) to 83.2% (self-report) to 67.9% (pill count). We know that self-report tends to overestimate adherence compared to indirect methods that do not depend on patient opinion [12], in part due to social desirability bias [13], wherein patients respond in the way they believe will please the health professional evaluating them. Patients and professionals may also have different perceptions regarding what adherence means.

The data on adherence observed in this study are consistent with the range of values observed in previous studies [4]. In a sample of 24 participants with rectal cancer, Figueiredo [14] measured adherence by means of pill count, finding that 94.3% were adherent. In a single-site intervention study, evaluating the impact of pharmaceutical care, also in 24 participants with colorectal cancer, Simmons et al. [15] observed an adherence rate of 87.2% in the control group and 96.8% in the intervention group, using electronic monitoring as the method of assessment. Bhattachayn et al. [16] measured adherence with self-report in colorectal and breast cancer patients, reporting a 72.7% rate of adherence, while an intervention study in Germany [17] observed a rate of 79.5% in the pre-intervention phase, using electronic monitoring. Globally, these data are similar to those we obtained when using self-report, and better than those obtained through pill counts. Our results show the need for health professionals to systematically evaluate therapeutic adherence as a routine part of the treatment process, once the reliability of the assessment method has been checked [18]. Our failure to identify any predictive factors that would allow us to define a subgroup of patients at high risk for non-adherence, underlines the importance of systematic evaluation in all patients. Indeed, the association between sociodemographic or disease-related variables and poor adherence shows mixed results in recent literature reviews [4]. However, we did find a clear association for anxiety at treatment initiation, suggesting that this is a clinically manageable risk factor to take into account when detected.

Some studies have shown how to improve adherence through pharmaceutical care and education strategies [17], and they also explore patient concerns about their disease, the need to have better information about it, the potential adverse effects of treatment and how to manage them [16]. These strategies, combined with discussions with patients about the medical aspects related to treatment and the disease prognosis, may be useful in reducing non-adherence to capecitabine.

Some limitations of this study should be considered when interpreting results. Physician-reported adherence was measured by means of a review of the data recorded in the clinical history. However, this could lead to an underestimation of their capacity to detect a problem. In addition, our exclusion of patients involved in clinical trials could have eliminated a group of patients with different characteristics and hypothetically greater adherence. On the other hand, one noteworthy feature of this study, which attests to its representativeness to usual clinical practice, is its multicentre design and its complete lack of attrition.

All in all, we observed notable differences in adherence according to the measurement technique in rectal cancer patients who were candidates for treatment with radical intent with preoperative radiochemotherapy. Health professionals should assess adherence problems with the patient during the consultation, especially the presence of anxiety at treatment initiation, in order to identify patients at risk of non-adherence. Pharmacists could also monitor the pill count at the end of the treatment and inform the physician about any adherence problems observed.

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Disclosure

The authors have declared no conflicts of interest.

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Key Message

Adherence to short-term oral neoadjuvant capecitabine in rectal cancer patients could be a clinical problem, and it should be acknowledged and assessed by health professionals during treatment. [AQ7]