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Adherence management for cancer patients on capecitabine: a prospective two-arm cohort study

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ARTICLE SUMMARY

Article Focus

- Adequate patient adherence to capecitabine, an orally administered prodrug of fluorouracil, is essential for treatment success. The early identification of potential non-adherers followed by adherence-enhancing measures may contribute to the effectiveness of oral anticancer drug therapy.
- This prospective, multi-centred observational cohort study aimed at the development and evaluation of a multiprofessional approach to assure adherence to capecitabine.
- It was hypothesized that adherence of initially adherent patients (≥90% adherence during the first cycle) would remain high over time without specific support and that initially non-adherent patients (<90% adherence during the first cycle) would benefit from specific adherence support.

Key Messages

- An early adherence screening effectively distinguishes between patients adhering and non-adhering to capecitabine.
- The provision of specific adherence support can enhance adherence of initially non-adherent patients.
- Initially adherent patients remain adherent for at least six cycles without specific support.

Strengths and Limitations

- Our approach is multiprofessional and needs-based utilising available resources for adherence management most efficiently.
- The relatively small sample size of initially non-adherent patients limits the validity of the observed results for this subgroup of patients.

ABSTRACT

Background: Capecitabine, an orally administered prodrug of fluorouracil, is administered twice daily for 14 days followed by a seven day rest period. Adequate patient adherence is essential for treatment success. The early identification of potential non-adherers followed by adherence-enhancing measures may contribute to the effectiveness of oral anticancer drug therapy.

Objective: To develop and evaluate a multiprofessional approach to assure adherence to capecitabine.

Methods: The study was conducted as a prospective, multi-centred observational cohort study. All participants received pharmaceutical care consisting of oral and written information. Daily adherence was defined as percentage of days with correctly administered capecitabine doses and assessed using electronic monitoring (MEMS®). According to their daily adherence during the first cycle, patients were identified as initially non-adherent (<90% adherence) or adherent (≥90% adherence). Initially non-adherent patients received additional adherence support.

Results: Seventy-three patients with various tumour entities were enrolled, 58 were initially adherent and 15 non-adherent. Median daily adherence of initially non-adherent patients increased from 85.7% to 97.6% during the observation period of six cycles. Throughout all cycles, median daily adherence of initially adherent patients was 100.0%. Daily adherence was not associated with socio-demographic and disease-related factors. No patient was non-persistent.

Conclusions: An early adherence screening effectively distinguishes between patients adhering and non-adhering to capecitabine. The provision of specific adherence support can enhance adherence of initially non-adherent patients, whereas initially adherent patients remain adherent for at least six cycles without specific support. Our needs-based approach helps to use available resources for adherence management efficiently.

INTRODUCTION

Cancer therapy has traditionally been dominated by intravenously administered agents.[1] However, oral anti-cancer drugs are increasingly used and more than one-quarter of all anti-cancer drugs currently under development are orally administered.[2 3] Oral anti-cancer therapies are highly accepted by patients based on obvious advantages, e.g. higher convenience, avoidance of venipuncture and paravasates, and greater patient autonomy.[2 4 5] However, these treatments are also associated with many challenges. Due to less intense contact between patient and health care providers, responsibilities in terms of managing the course of treatment are transferred to the patient such as monitoring of doses and toxicity.[2 6] In contrast to intravenously administered anti-cancer treatments, health care providers cannot always assume that patients are adherent which is, however, the key prerequisite for treatment success. Multidisciplinary patient care and specific patient education regarding all aspects of the treatment regimen are crucial to maintain adherence.[6–9]

Patients of the present study were treated with the chemotherapeutic agent capecitabine, an orally administered prodrug of cytotoxic fluorouracil (5 FU). Capecitabine has an improved tolerability and comparable efficacy compared with infusional or bolus 5 FU [10] and is frequently used in the treatment of breast, colorectal, and gastric cancer. Moreover, ovarian, pancreatic, or oesophageal tumours may be treated with capecitabine. Usually it is given in three-week cycles, twice per day for two weeks separated by 12 hours, followed by a one-week medication-free interval.[11]

Patient adherence to prescribed treatment regimens for chronic non-oncologic diseases accounts for 50% on average only.[12 13] Cancer patients' medication taking behaviour is presumed to be particularly adherent, since cancer is a life-threatening disease.[14–18] However, adherence rates of oral anti-cancer agents were reported to range from 16% to 100% depending on the drug and method of measurement.[15] Exact measurement of adherence is a challenge and existing methods are limited for various reasons. [19] Best estimation of adherence may be provided by electronic monitoring such as the medication event monitoring system (MEMS®).[20]

Several studies have been published investigating patient adherence to capecitabine. Partridge et al used MEMS® for adherence assessment in older women with early-stage breast cancer and defined adherence as the number of doses taken divided by doses expected. 75% of patients performed more than 80% of expected openings and were regarded as adherent. Average adherence was 78% across all cycles.[21 22] Winterhalder et al used participant self-reports in gastrointestinal and breast cancer patients. 91% (161/177) patients were found to be fully adherent, whereas only 9% (16/177) reported some kind of adherence error, i.e. any violation of the recommended regimen.[14] In 13 younger metastatic breast cancer patients, median adherence assessed using MEMS® was 96%. Adherence was defined as observed divided by expected

doses. Self-reported median adherence of 12 patients was 97%.[23] In 43 breast and colorectal cancer patients, self-reported non-adherence was 23.3%.[24] Furthermore, the effect of an intensified multidisciplinary pharmaceutical care programme on the adherence of cancer patients treated with capecitabine was investigated. Adherence was measured using MEMS® and defined as the percentage of days with correct medication taking behaviour. Patients who received pharmaceutical care showed a significantly higher mean daily adherence compared to the control group who received standard care (96.8% vs 87.2%, p=0.029).[25]

Thus, adherence rates of patients treated with capecitabine are relatively high compared to non-oncologic oral drugs but can still be increased by specific measures.[25] Conversely, this implies that only some patients treated with capecitabine are in need of an adherence-enhancing intervention and the limited resources could be used more efficiently. Certain patients manage their oral treatment regimen independently and do not benefit from a specialized patient care. In this study, we screened cancer patients for their adherence during their first capecitabine cycle to detect potential non-adherers. Initially adherent as well as non-adherent patients received basic pharmaceutical care and adverse event management. Specific adherence support was only applied to initially non-adherent patients.

The aim of the present study was to identify initially non-adherent patients and to investigate initially non-adherent and initially adherent patients' adherence over time. It was hypothesized that adherence of initially adherent patients would remain high over time without specific support and that initially non-adherent patients would benefit from specific adherence support.

METHODS

Study design

The study was conducted as a prospective, multi-centred, two-arm observational cohort study. One study arm consisted of patients classified as initially adherent (baseline daily adherence ≥90%), the other arm of initially non-adherent patients (baseline daily adherence <90%).

Study setting and sample

The study was conducted in two oncology outpatient wards and one oncology practice. Data were collected between July 2009 and March 2012. After the identification of eligibility by the collaborating oncologists, patients were asked to participate in the study. In case of acceptance, each participant signed a written informed consent. The study protocol considered a maximum observation period of six capecitabine cycles for every participant. The main inclusion criterion was the initiation of chemotherapy with capecitabine as single agent or combination therapy for treatment of cancer. Patients had to be capecitabine-naïve, at least 18 years old and able to speak, read and write German. Inclusion had to take place within two weeks after initiation of capecitabine treatment. Exclusion criteria implied any diagnosis of a disease or mental state compromising full understanding of purpose and course of the study. The ethics committee of the University of Bonn, Germany voted positively for this study.

Adherence measurement

Adherence to capecitabine treatment was assessed using the Medication Event Monitoring System (MEMS®, Aardex Group Ltd., Zug, Switzerland).[26] Every participant was provided with a MEMS® container and asked to use it for storage of capecitabine medication during study participation. The caps of the MEMS® containers recorded date and time of every opening. Patients were instructed to open the containers only when taking their capecitabine dose. In case of required refills, patients were requested to schedule refill and regular capecitabine intake at the same time in order to avoid additional openings. If this was not possible or in case of further extraordinary openings, patients were asked to note the respective information on a special documentation sheet. Since uncensored MEMS® data might overestimate non-adherence[27], adherence data were censored according to information derived from notes and interviews (e.g. exclusion of self-reported non-monitoring intervals or extra openings, and intake of doses taken from another source than MEMS®). Measurement ended after six completed capecitabine cycles or in case of premature treatment discontinuation.

Adherence analysis

Adherence was studied using medication taking profiles uploaded from the MEMS® monitors and patients' information concerning extraordinary incidents. 'Daily adherence' was selected as primary endpoint. It was defined as percentage of days with correctly administered capecitabine doses (number of days with correct drug intake divided by number of observed days). In the case of missing MEMS® data the corresponding days were not included in the analysis, i.e. the number of observed days was reduced accordingly. Adherence was assessed on days with drug intake as well as days during the rest period. A day was considered as adherent only, if two openings of the MEMS® monitor were recorded on a day during the drug intake period (dosing interval ≥6 hours) or if no openings were recorded during the rest period.

Basically, 'daily adherence' was calculated for every individual cycle (days with capecitabine intake plus therapy-free interval). Furthermore, adherence was calculated for the drug intake interval only excluding capecitabine-free days and referred to as 'daily intake adherence'. This was done in order to exclude the influence of the rest period on the adherence. Additionally, 'persistence' of drug intake was analysed. Duration of physician's capecitabine prescription was compared with the duration of the actual treatment by the participant.

For the classification of a participant as initially adherent or non-adherent, daily adherence was calculated for the intake period of the first cycle plus first day of the therapy-free interval. This parameter is referred to as 'baseline daily adherence'. A participant was classified as initially adherent (baseline daily adherence ≥90%) or initially non-adherent (baseline daily adherence <90%). Since no consensual standard for the definition of sufficient adherence exists[16], the threshold of 90% was defined empirically based on the results of an earlier research project[25]. If assessment of baseline adherence resulted in a participant being initially non-adherent, adherence support was provided before the start of the second intake period.

Modular medication management

In addition to standard care provided by physicians and nurses of the respective study centre, medication management consisted of three modules. These modules were provided by a registered pharmacist of the Department of Clinical Pharmacy at the University of Bonn, Germany. Every study participant received module 1 (basic pharmaceutical care) as well as module 2 (adverse event management). If a participant was initially non-adherent, module 3 (adherence support) was applied additionally.

Modules 1 and 2 were initiated after inclusion. Module 1 implied detailed medication history taking to perform drug-drug interaction checks and compile an individual medication plan. In case of identified drug-related problems, necessary changes of the medication were made in

collaboration with the responsible physician. Patients were educated in detail about the cytotoxic agent capecitabine, its mechanism of action and the individual dosing regimen. Further anti-cancer agents, supportive therapy and other agents taken regularly were also addressed. Patient counselling was supported by the provision of written information material. Within module 2, patients were educated regarding common adverse effects (eg, hand-foot syndrome and diarrhea). Prophylaxis, detection and treatment of adverse effects were discussed in detail. If patients took other drugs or were prescribed a concomitant anti-cancer treatment, they were counselled regarding the adverse effects of these drugs as well. An information brochure regarding prevention and management of adverse effects caused by chemotherapy supported oral counselling.

Module 3 contained a detailed discussion of the patient's individual adherence results on the basis of cycle 1 MEMS® data. Adherence support focussed on the identification of reasons for non-adherence to define a feasible adherence-enhancing strategy. Since various types of non-adherence exist, strategies to overcome individual barriers to adherence were designed individually. Strategies to improve unintentional non-adherence (eg due to forgetfulness) included treatment diaries or linking drug intake with a certain act of daily routine (cue dosing). In contrast, intentional non-adherence had to be approached in a completely different manner. If an adverse effect was the reason for not taking capecitabine, management and prevention of further adverse effects were addressed in accordance with module 2. Patients' expectations and experiences were included in all considerations. Moreover, an increase of the patient's awareness of the importance of adherence with capecitabine treatment was aimed. Routinely, beginning and end of the current and next capecitabine cycle were explicitly discussed. The content and course of the adherence-supporting session was adapted according to the patients' medication taking behaviour. If the participant showed a daily adherence <90%, the content of the first counselling session of module 3 was repeated and adherence-enhancing strategies were reassessed, discussed and adapted.

Personal follow-up visits took place at least once every cycle. Between scheduled appointments every participant had the possibility to reach individual advice in person, by telephone or by email.

Sample size calculation and statistical analysis

Sample size determination was conducted for the primary endpoint 'daily adherence'. Available adherence data[25] was analysed with regard to daily adherence of the participant's first capecitabine cycle. Regarding initially adherent patients a sample size of 45 was required to show with a power (1-β) of 80% that >75% of these patients remain being adherent (error of first kind (α) = 5%). The true population value of patients who persist being adherent was

assumed to account for >90%. Regarding initially non-adherent patients, a sample size of 30 patients was required to show with a power (1-β) of 80% that >80% of these patients become adherent after the adherence support (error of first kind (α) = 5%). The true population value of patients who became adherent was assumed to account for >95%. Finally a dropout rate of 20% was estimated so that a total sample size of 90 patients resulted (54 initially adherent and 36 initially non-adherent patients).

Data entry and statistical data analysis were carried out using Excel® 2007 (Microsoft, Redmond, USA) and SPSS® Version 20 (SPSS® Inc., Chicago, USA, Statistical Package for the Social Sciences). Appropriate descriptive statistics was used to characterise the patient population and summarise the study results. Data were mostly binary, nominal, ordinal, or failed to follow a normal distribution, thus non-parametric testing was utilised consistently. Differences regarding socio-demographic and disease-related characteristics between initially adherent and non-adherent patients were tested using the Fisher's exact test for nominal data. To explore the relationship between adherence and potential predictors of adherence, Spearman's rank correlation coefficient was used for comparing two continuous data sets and Mann-Whitney-U analysis was used for comparing continuous (not normally distributed) data with binary data sets

RESULTS

Participating oncologists assessed 97 patients for eligibility, 78 were enrolled in the study. Figure 1 provides a detailed overview of patient recruitment including reasons for exclusion and loss to follow-up. The main reason (seven out of eight refusals) for non-participation was perceived stress by the study in addition to their mentally and/or physically impaired condition. Since five patients were not capecitabine-naïve, two patients were not able to speak, read and write German and for four patients MEMS® use was not possible due to participation in another trial, they were not enrolled.

Patient characteristics

Seventy-three patients were analysed for baseline daily adherence, 58 were initially adherent and 15 initially non-adherent. Table 1 shows that there was no statistically significant difference between initially adherent and non-adherent patients regarding socio-demographic and disease-related characteristics. However, there was a significant difference in the therapy setting (p=0.021, Fisher's exact test).

Table 1: Socio-demographic and disease-related patient characteristics

Socio-demographic characteristics		initially adherent		initially non-adherent		P value
		n	%	n	%	
Classified age [years]	≤ 50	11	19.0	0	0.0	0.203
	51-60	15	25.9	6	40.0	
	61-70	17	29.3	3	20.0	
	71-80	10	17.2	5	33.3	
	> 80	5	8.6	1	6.7	
Sex	Female	44	75.9	10	66.7	0.516
	Male	14	24.1	5	33.3	
Number of additional drugs	≤ 5	45	77.6	10	66.7	0.514
	6-10	9	15.5	3	20.0	
	> 10	3	5.2	2	13.3	
	No answer	1	1.7	0	0.0	
Tumour entity	Breast cancer	21	36.2	7	46.7	0.818
	Colorectal cancer	25	43.1	7	46.7	
	Gastric cancer	3	5.2	0	0.0	
	Oesophageal cancer	1	1.7	1	6.7	
	Ovarian cancer	3	5.2	0	0.0	
	Cancer of unknown primary	1	1.7	0	0.0	
	Pancreatic cancer	3	5.2	0	0.0	
	Endometrial cancer	1	1.7	0	0.0	
Therapy regimen at inclusion[1, 2]	Cap	35	60.3	7	46.7	0.313
	Cap Beva	11	19.0	4	26.7	
	Cap Beva Ox	1	1.7	0	0.0	
	Cap Lap	1	1.7	0	0.0	
	Cap Ox	3	5.2	1	6.7	
	Cap Vin	1	1.7	1	6.7	
	Cap Mito	0	0.0	1	6.7	
	Cap Trastu Ox	0	0.0	1	6.7	
	Cap Fulve	2	3.4	0	0.0	
	Cap Vin Letro	1	1.7	0	0.0	
	Cap Trastu	3	5.2	0	0.0	
Treatment intention	curative	8	13.8	3	20.0	0.686
	palliative	50	86.2	12	80.0	
Classified time since diagnosis	< ½ year	15	25.9	4	26.7	0.712
	½ to 2 years	22	37.9	4	26.7	
	> 2 years	21	36.2	7	46.7	
Therapy setting	Oncology outpatient ward	51	87.9	9	60.0	0.021
	Oncology practice	7	12.1	6	40.0	

[1] Therapy regimens: **Cap** = capecitabine monotherapy; **Cap Beva** = capecitabine + bevacizumab; **Cap Beva Ox** = capecitabine + bevacizumab + oxaliplatin; **Cap Lap** = capecitabine + lapatinib: **Cap Ox** = capecitabine + oxaliplatin; **Cap Vin** = capecitabine + vinorelbine; **Cap Mito** = capecitabine + mitomycin; **Cap Trastu Ox** = capecitabine + trastuzumab + oxaliplatin; **Cap Fulve** = capecitabine + fulvestrant; **Cap Vin Letro** = capecitabine + vinorelbine + letrozole; **Cap Trastu** = capecitabine + trastuzumab

[2] Bisphosphonate and radiation therapies are not considered

Initially adherent patients

Initially adherent patients were observed for a median time of 119.0 days (range 21.0-152.0; IQR=69.8-126.0). During all observed cycles, a high percentage of these patients showed a daily adherence equal or greater 90% (Figure 2A). After the sixth cycle, 36 of 37 (97.3%, CI 88.8%-99.4%) initially adherent patients showed a daily adherence ≥90%. Since the CI does not include 75% it is shown with an error of the first kind of 5% that more than 75% of the initially adherent patients remained adherent after the modular medication management (without specific adherence support).

Figure 2B shows the same kind of data analysis for the daily intake adherence (excluding therapy-free interval). The fraction of initially adherent patients with a daily intake adherence ≥90% was lower compared to daily adherence reflecting that adherence is lower during intake than rest periods.

Figure 3 demonstrates that variability with regard to daily adherence increased from cycle 1 compared to further cycles. Median daily adherence was 100% in every cycle. Average daily adherence decreased from 98.9% in cycle 1 to 97.3% in cycle 6. Online table A provides more detailed information. Although initially adherent patients did not receive adherence support, the modular medication management led to a consistently high median daily adherence in a majority of these patients. Only in exceptional cases median daily adherence was observed to be lower than 90%. Individual daily adherence profiles of each patient over the observation period are provided in online figure A.

Online table A: Daily adherence of initially adherent patients (calculation based on intake and rest period)

	n	Mean [%]	Median [%]	SD [%]	Range [%]	IQR [%]
Cycle 1	58	98.9	100.0	2.1	93.3-100.0	100.0-100.0
Cycle 2	56	97.3	100.0	5.5	66.7-100.0	95.2-100.0
Cycle 3	48	97.2	100.0	4.9	75.0-100.0	95.2-100.0
Cycle 4	45	96.7	100.0	6.3	68.8-100.0	95.2-100.0
Cycle 5	40	97.4	100.0	4.7	80.0-100.0	95.2-100.0
Cycle 6	37	97.3	100.0	7.3	57.1-100.0	95.2-100.0

Initially non-adherent patients

Initially non-adherent patients were observed for a median time of 118.0 days (range 35.0-140.0; IQR=96.0-126.0). Figure 2A illustrates the percentage of patients who showed a daily adherence equal or greater than 90% during the different cycles. The results indicate a clear effect of adherence support. In cycle 2 the number of adherent patients was twice as high as in

cycle 1 and remained relatively constant in the later cycles. After completion of the sixth cycle, daily adherence of six out of eight (75.0%, CI 46.0%-91.3%) initially non-adherent patients accounted for ≥90%. Since the CI included 80% which was the cut-off value used for sample size determination of initially non-adherent patients, it could not be proven that >80% of initially non-adherent patients were adherent after the intervention.

Figure 2B shows the percentage of initially non-adherent patients with a daily intake adherence ≥90% over the cycles. In contrast to the initially adherent patients, the fractions of initially non-adherent patients exhibiting a daily adherence ≥90% and a daily intake adherence ≥90% did not exhibit major differences.

Median daily adherence increased from 85.7% in cycle 1 to 97.6% in cycle 6, see figure 4. Average daily adherence accounted for 80.8% during the first cycle and was found to be greater than 90% during the application of the adherence support module (online table B). Adherence varied widely between patients but also from cycle to cycle in the same patients. Online figure B shows individual daily adherence profiles of initially non-adherent patients during the course of the study calculated for intake plus rest period.

Online table B: Daily adherence of initially non-adherent patients (calculation based on intake and rest period)

	n	Mean [%]	Median [%]	SD [%]	Range [%]	IQR [%]
Cycle 1	15	80.8	85.7	17.6	28.6-92.9	85.0-90.5
Cycle 2	15	93.7	95.2	8.8	71.4-100.0	95.0-100.0
Cycle 3	13	90.7	95.2	13.6	59.1-100.0	90.5-100.0
Cycle 4	12	92.1	95.2	7.0	76.2-100.0	90.5-95.2
Cycle 5	12	92.7	95.2	7.2	79.2-100.0	88.1-97.6
Cycle 6	8	90.5	97.6	15.1	57.1-100.0	85.7-100.0

Potential predictors of adherence

There was no indication of an existing relationship between patients' daily adherence during the first cycle and their age (Spearman's r=0.009, p=0.941) or gender (p=0.891, Mann-Whitney-U test). In addition, there was not any significant association between daily adherence and any further socio-demographic and disease-related characteristics.

Persistence

All study patients were persistent during the whole period they were prescribed capecitabine chemotherapy. No patient performed an unauthorised discontinuation of his capecitabine treatment.

However, in 17 of the 58 initially adherent patients capecitabine therapy was discontinued prematurely by the physicians. In 12 patients this decision was taken due to tumour progression. Further reasons for therapy discontinuation were adverse drug reactions (hand-foot syndrome and haemolytic anemia), hospital admission, the toxicity of a co-administered drug, and the patient's wish to stop treatment. 36 patients completed six cycles as planned, two patients completed less than six capecitabine cycles as planned, one patient died after the completion of the third cycle and two patients quit their study participation during the second cycle.

In five of 15 initially non-adherent patients capecitabine therapy was discontinued prematurely due to tumour progression. Eight patients completed six capecitabine cycles as planned, one patient completed five cycles as planned, and one patient died during the second cycle.

DISCUSSION

In this study, we applied a systematic screening for non-adherent patients at an early stage of their capecitabine chemotherapy to provide a patient-tailored modular medication management. The results indicate that specific adherence support might improve adherence of initially non-adherent patients to capecitabine and that initially adherent patients' medication taking behaviour persists over time under basic pharmaceutical care and adverse event management.

Sample size of initially non-adherent patients

A major limitation of our study is the relatively small number of initially non-adherent patients. Instead of the required sample size of 30 initially non-adherent patients, only 15 patients could be enrolled during the study period. Previous data suggested a distribution of 60% initially adherent and 40% initially non-adherent patients.[25] The actual distribution within our patient population was 80% to 20%. This has to be considered before interpreting data of the initially non-adherent patients. However, a clear trend towards an improved adherence over time was observed. Further multicenter studies are needed to provide better generalisable findings.

Adherence screening

For the classification of patients as initially non-adherent or adherent, we used daily adherence of the first drug intake period plus the first day of the therapy-free interval assessed by MEMS®. Consideration of the whole capecitabine cycle would have provided a more complete picture of the participant's adherence during the first cycle. However, this was not feasible. To initiate adherence support before the start of cycle 2, an exact appointment on day 21 of the first cycle for group allocation would have been necessary. A belated start of the adherence supporting module would have biased the results of initially non-adherent patients.

Although our approach was suitable to discriminate between adhering and non-adhering patients it would be easier to identify non-adhering patients by means of possible predictors. With knowledge of adherence predictors a screening method without electronic monitoring could be developed, eg by a specific questionnaire. In general, numerous factors associated with non-adherence to oral anti-cancer drugs have been identified like eg side effects, forgetfulness, or disliking aspects of treatment.[20 28] On the basis of our data, it was not possible to derive significant information on adherence from socio-demographic or disease-related characteristics, eg age. Indeed, we observed that the three patients exhibiting the lowest baseline adherence during cycle 1 (28.6%, 57.1%, and 64.3%) were of a relatively old age (90, 75, and 79 years). However, from this result it cannot be concluded that adherence decreases with increasing age

as there were also elderly patients exhibiting high adherence. Our findings are in line with the findings of Partridge et al who did not find an association of adherence and age.[21] Furthermore, Bhattacharya et al did not identify significant associations between self-reported adherence to capecitabine and experience of side effects, beliefs about capecitabine, or satisfaction with information. However, the generalisability of that study was also limited by a relatively small sample size.[24] Therefore, larger multi-centre studies are necessary to identify precise predictors of non-adherence to capecitabine.

Effect of modular medication management

Adherence rates in our study were higher than those reported by Partridge et al who found an average overall adherence measured by MEMS® (defined as the number of doses taken divided by the number of doses prescribed) between 70% to 80%.[21] Analysing our data the same way, overall adherence values ranged between 98.2% and 100.5% in initially adherent patients and between 93.8% and 102.7% in initially non-adherent patients. This might be explained by the fact that every participant of the present study received two medication management modules during all six cycles. In case of initially non-adherent patients, the provided adherence support might have increased adherence additionally. This finding is consistent with previous results from our working group. Under the provision of intensified pharmaceutical care to 48 breast and colorectal cancer patients, the intervention group showed an increased mean overall adherence in comparison to the control group.[25] In line with previous results[21 25], non-persistence did not present a problem in our group of patients.

Daily adherence versus daily intake adherence

Daily adherence during the intake periods of each cycle was generally lower compared to daily adherence calculated on the basis of drug intake plus rest period. This implies that adherence to the regimen was better in the rest period when the drug should not be taken, i.e. not many patients took the drug by mistake. However, daily adherence calculated for the first intake interval plus the first day of the rest period in initially non-adherent patients was lower than daily adherence during the whole cycle or adherence during the intake interval alone. Eight of 15 patients took capecitabine one day too long, too short or completely ignored the break. From this finding we conclude that special attention has to be paid to the change of drug intake to drug-free days in the first capecitabine cycle. Patients have to be educated in detail regarding this particularity of capecitabine treatment.

Adherence management

Even though daily adherence could be improved in initially non-adherent patients, it has to be pointed out that this patient population did not reach the same adherence level as initially adherent patients. Moreover, inter-individual variability of adherence was higher. This finding suggests that a subgroup of patients with low adherence benefits from the adherence-enhancing intervention as suggested by Simons et al.[25] However, a certain number of patients cannot be reached and reveals a resistant medication taking behaviour. Reasons for intentional non-adherence in those patients were difficulties in swallowing tablets due to nausea and emesis caused by capecitabine (despite the provision of antiemetic prophylaxis and treatment), averseness to medication, or "compensating" intake for previous non-adherence during treatment break. Unintentional non-adherence was mainly based on forgetfulness. Further research should include a systematic approach to develop strategies for adherence management in those 'resistant' patients.

Conclusions

In summary, the results of this study demonstrate the potential of an early adherence screening for non-adherence and an individually applied modular medication management to use limited resources most efficiently. The provided adherence support improved adherence of initially non-adherent patients to oral chemotherapy. Moreover, the provision of basic pharmaceutical care and adverse event management was sufficient to maintain adherence in initially adherent patients for at least six cycles. The identification of potential predictors of adherence would facilitate the utilisation and broad application of the proposed adherence screening and modular medication management.

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Competing interests: All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that there have been no competing interests.

Patient consent: Obtained.

Ethics approval: This study was conducted with the approval of the ethics committee of the University of Bonn, Germany (consecutive number 042/09).

Contributorship statement: LK and UJ conceived the study design, substantially contributed to data analysis and interpretation, and drafted the manuscript. LK, YDK, PFS and CS were involved in the data collection and provision of multidisciplinary patient care. RF contributed substantially to statistical data analysis and interpretation. UJ is the guarantor. All authors critically reviewed the manuscript and gave their final approval for the version to be published.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: Extra data is available by emailing Ulrich Jaehde (u.jaehde@uni-bonn.de).

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE AND TABLE LEGENDS

Figure 1: Patient recruitment flow diagram

Figure 2: Percentage of patients exhibiting a **A** daily adherence ≥90% (during intake and rest periods) and a **B** daily intake adherence ≥90% (during the intake periods only)

Figure 3: Daily adherence of initially adherent patients during cycle 1 to 6

Figure 4: Daily adherence of initially non-adherent patients during cycle 1 to 6

Table 1: Socio-demographic and disease-related patient characteristics

Online figure A: Individual daily adherence of initially adherent patients during the course of the study; cycle 1: n=58, cycle 2: n=56, cycle 3: n=48, cycle 4: n=45, cycle 5: n=40, cycle 6: n=37, the black line represents median daily adherence

Online figure B: Individual daily adherence of initially non-adherent patients during the course of the study; cycle 1: n=15, cycle 2: n=15, cycle 3: n=13, cycle 4: n=12, cycle :5 n=12, cycle 6: n=8; the black line represents the median daily adherence

Online table A: Daily adherence of initially adherent patients (calculation based on intake and rest period)

Online table B: Daily adherence of initially non-adherent patients (calculation based on intake and rest period)

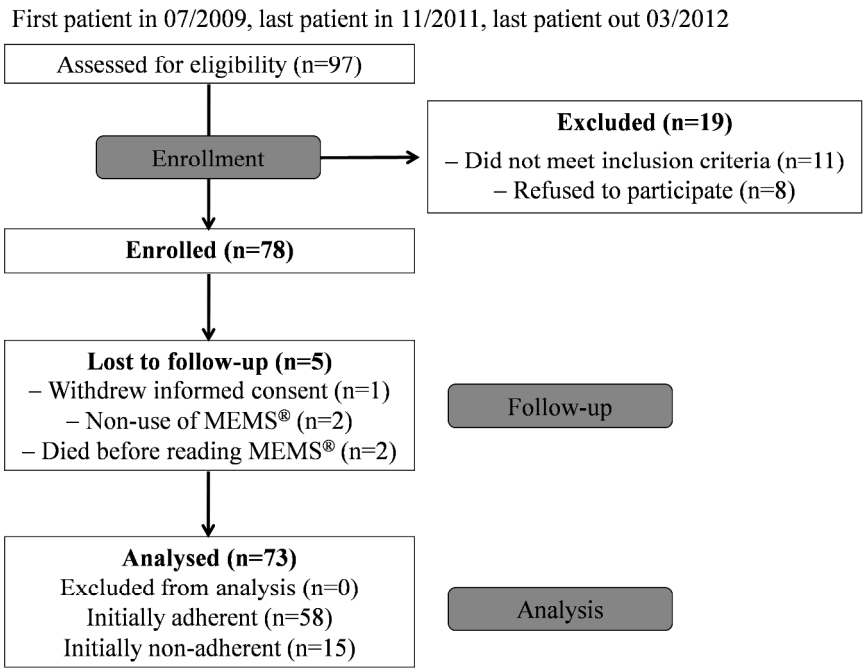

Fig. 1: Patient recruitment flow diagram
254x190mm (300 x 300 DPI)

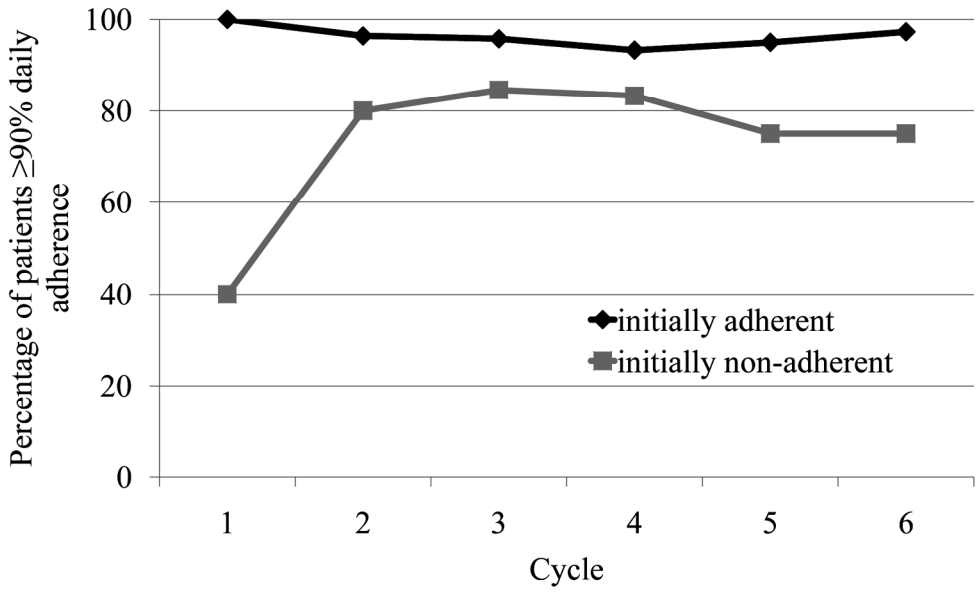

Fig. 2A: Percentage of patients exhibiting a daily adherence ≥90% (during intake and rest periods)
180x109mm (300 x 300 DPI)

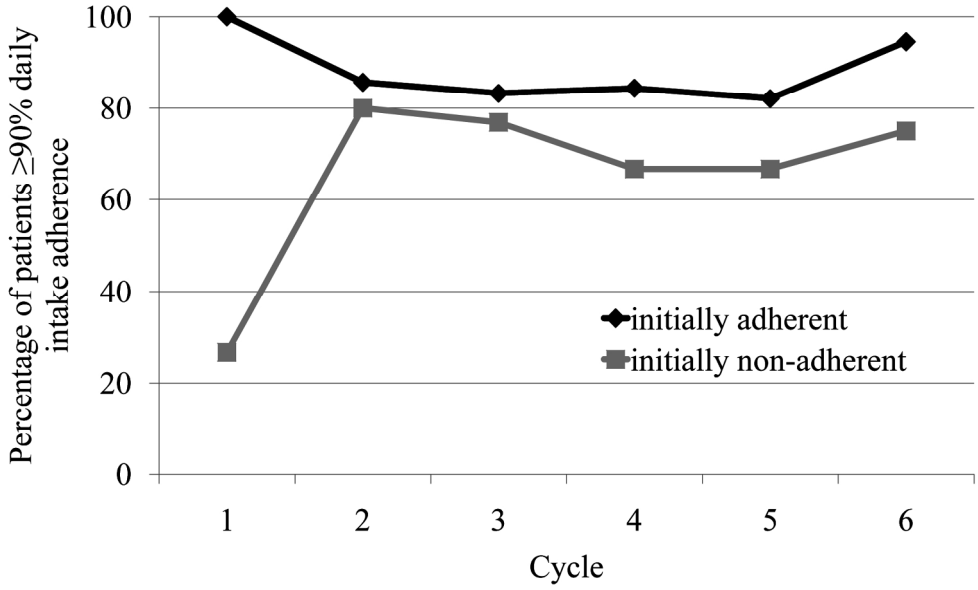

Fig. 2B: Percentage of patients exhibiting a daily intake adherence ≥90% (during the intake periods only)
180x109mm (300 x 300 DPI)

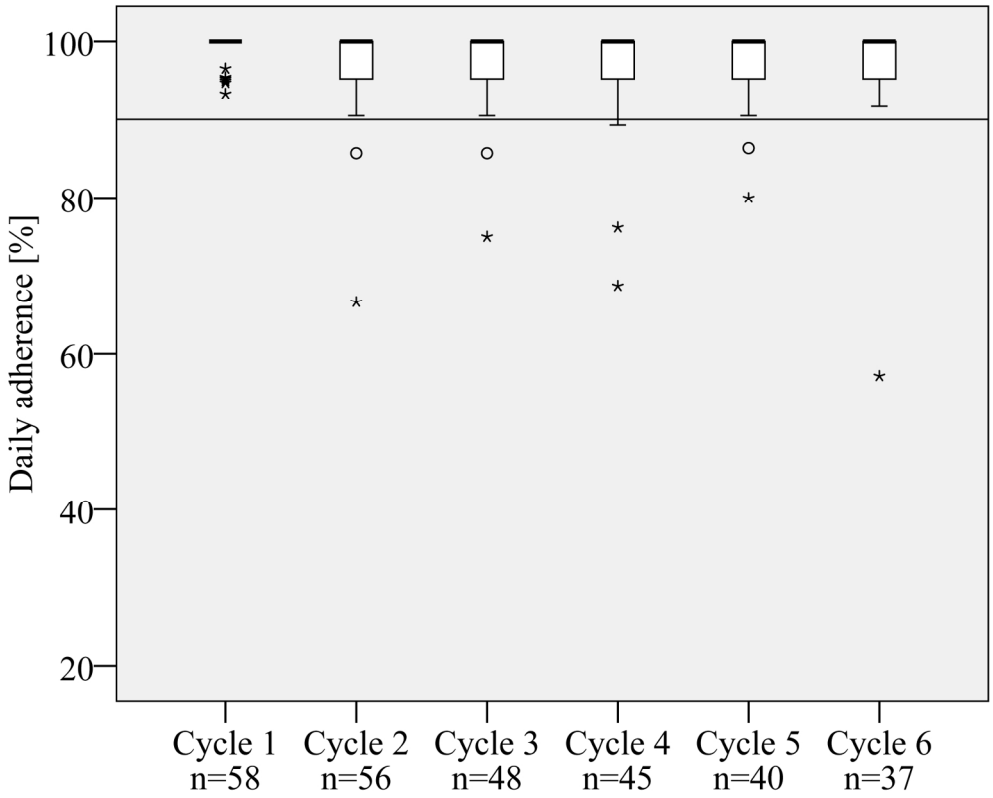

Fig. 3: Daily adherence of initially adherent patients during cycle 1 to 6
158x127mm (300 x 300 DPI)

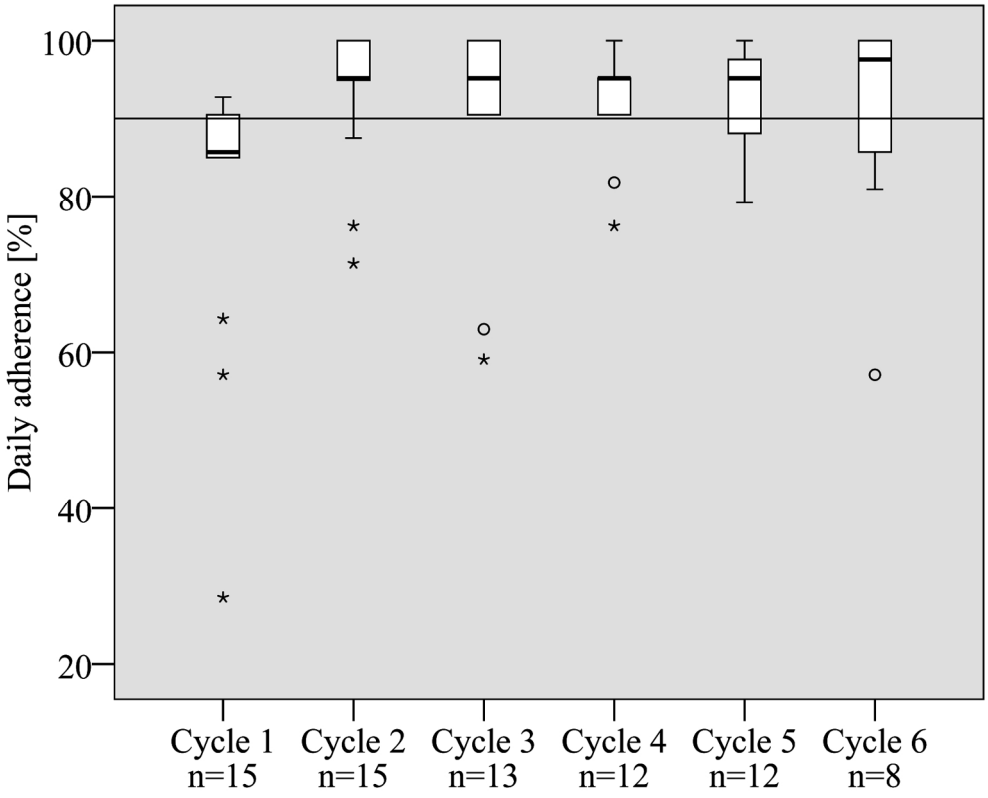

Fig. 4: Daily adherence of initially non-adherent patients during cycle 1 to 6
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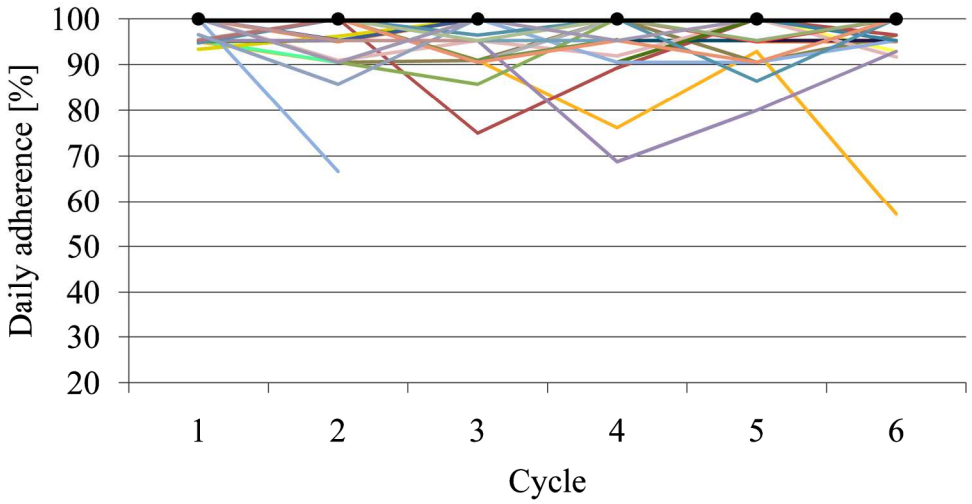
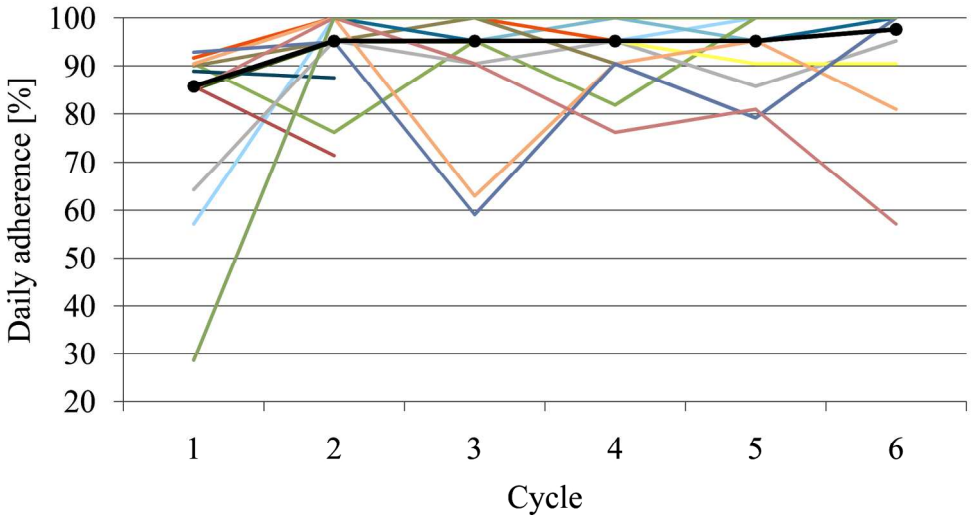


Online Fig. A: Individual daily adherence of initially adherent patients during the course of the study; cycle 1: n=58, cycle 2: n=56, cycle 3: n=48, cycle 4: n=45, cycle 5: n=40, cycle 6: n=37, the black line represents median daily adherence
180x94mm (300 x 300 DPI)



Online Fig. B: Individual daily adherence of initially non-adherent patients during the course of the study; cycle 1: n=15, cycle 2: n=15, cycle 3: n=13, cycle 4: n=12, cycle :5 n=12, cycle 6: n=8; the black line represents the median daily adherence
180x97mm (300 x 300 DPI)

STROBE statement - checklist of items that should be included in reports of observational studies

Krolop et al.
Adherence management for cancer patients on capecitabine: a prospective two-arm cohort study

	Item No	Recommendation	
Title and abstract			
	1	*(a)* Indicate the study's design with a commonly used term in the title or the abstract	OK
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	OK
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	OK
Objectives	3	State specific objectives, including any prespecified hypotheses	OK
Methods			
Study design	4	Present key elements of study design early in the paper	OK
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	OK
Participants	6	*(a) Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	OK
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	OK
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	OK
Bias	9	Describe any efforts to address potential sources of	Not

		bias	applicable
Study size	10	Explain how the study size was arrived at	OK
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	OK
Statistical methods	12	*(a)* Describe all statistical methods, including those used to control for confounding	OK
		(b) Describe any methods used to examine subgroups and interactions	OK
		(c) Explain how missing data were addressed	OK
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	*(a)* Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	OK
		(b) Give reasons for non-participation at each stage	OK
		(c) Consider use of a flow diagram	OK
Descriptive data	14*	*(a)* Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	OK
		(b) Indicate number of participants with missing data for each variable of interest	OK
		(c) Cohort study—Summarise follow-up time (eg average and total amount)	OK
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	OK
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(a) Give unadjusted estimates and, if applicable,	Not

		confounder adjusted estimates and their precision (eg 95% confidence interval). Make clear which confounders were adjusted for and why they were included	applicable
		(b) Report category boundaries when continuous variables were categorised	OK
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	OK
Discussion			
Key results	18	Summarise key results with reference to study objectives	OK
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	OK
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	OK
Generalisability	21	Discuss the generalisability (external validity) of the study results	OK
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	OK

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Adherence management for cancer patients on capecitabine: a prospective two-arm cohort study

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Adherence management for cancer patients on capecitabine: a prospective two-arm cohort study

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Key words: adherence, compliance, capecitabine, pharmaceutical care, oral chemotherapy

Word count: 4,308

ARTICLE SUMMARY

Article Focus

- Adequate patient adherence to capecitabine, an orally administered prodrug of fluorouracil, is essential for treatment success. The early identification of potential non-adherers followed by adherence-enhancing measures may contribute to the effectiveness of oral anticancer drug therapy.
- This prospective, multi-centred observational cohort study aimed to develop and evaluate a multiprofessional medication management to assure adherence to capecitabine.
- It was hypothesized that adherence of initially adherent patients (≥90% adherence during the first cycle) would remain high over time without specific support and that initially non-adherent patients (<90% adherence during the first cycle) would benefit from specific adherence support.

Key Messages

- An early adherence screening effectively distinguishes between patients adhering and non-adhering to capecitabine.
- The provision of specific adherence support is associated with enhanced adherence of initially non-adherent patients.
- Initially adherent patients remain adherent for at least six cycles without specific support implying that targeted support to those patients who benefit from it is a reasonable approach.

Strengths and Limitations

- Our approach is multiprofessional and needs-based utilising available resources for adherence management most efficiently.
- The relatively small sample size of initially non-adherent patients limits the validity of the observed results for this subgroup of patients.

ABSTRACT

Background: Capecitabine, an orally administered prodrug of fluorouracil, is administered twice daily for two weeks followed by one week off. Adequate patient adherence is essential for treatment success. The early identification of potential non-adherers followed by adherence-enhancing measures may contribute to the effectiveness of oral anticancer drug therapy.

Objective: To develop and evaluate a multiprofessional modular medication management to assure adherence to capecitabine.

Methods: The study was conducted as a prospective, multi-centred observational cohort study. All participants received pharmaceutical care consisting of oral and written information. Daily adherence was defined as percentage of days with correctly administered capecitabine doses and assessed using electronic monitoring (MEMS®). According to their daily adherence during the first cycle, patients were identified as initially non-adherent (<90% adherence) or adherent (≥90% adherence). Initially non-adherent patients received additional adherence support.

Results: Seventy-three patients with various tumour entities were enrolled, 58 were initially adherent and 15 non-adherent. Median daily adherence of initially non-adherent patients increased from 85.7% to 97.6% during the observation period of six cycles. Throughout all cycles, median daily adherence of initially adherent patients was 100.0%. Daily adherence was not associated with socio-demographic and disease-related factors. No patient was non-persistent.

Conclusions: An early adherence screening effectively distinguishes between patients adhering and non-adhering to capecitabine. The provision of specific adherence support is associated with enhanced adherence of initially non-adherent patients, whereas initially adherent patients remain adherent for at least six cycles without specific support. Our needs-based approach helps to use available resources for adherence management efficiently.

INTRODUCTION

Cancer therapy has traditionally been dominated by intravenously administered agents.[1] However, oral anti-cancer drugs are increasingly used and more than one-quarter of all anti-cancer drugs currently under development are orally administered.[2 3] Oral anti-cancer therapies are highly accepted by patients based on obvious advantages, e.g. higher convenience, avoidance of venipuncture and paravasates, and greater patient autonomy.[2 4 5] However, these treatments are also associated with many challenges. Due to less intense contact between patient and health care providers, responsibilities in terms of managing the course of treatment are transferred to the patient such as monitoring of doses and toxicity.[2 6] In contrast to intravenously administered anti-cancer treatments, health care providers cannot always assume that patients are adherent which is, however, the key prerequisite for treatment success. Multidisciplinary patient care and specific patient education regarding all aspects of the treatment regimen are crucial to maintain adherence.[6–9]

Patients of the present study were treated with the chemotherapeutic agent capecitabine, an orally administered prodrug of cytotoxic fluorouracil (5 FU). Capecitabine has an improved tolerability and comparable efficacy compared with infusional or bolus 5 FU [10] and is frequently used in the treatment of breast, colorectal, and gastric cancer. Moreover, ovarian, pancreatic, or oesophageal tumours may be treated with capecitabine. One capecitabine cycle consists of three weeks, two weeks of twice daily drug intake followed by seven days of break. [11]

Patient adherence to prescribed treatment regimens for chronic non-oncologic diseases accounts for 50% on average only.[12 13] Cancer patients' medication taking behaviour is presumed to be particularly adherent, since cancer is a life-threatening disease.[14–18] However, adherence rates of oral anti-cancer agents were reported to range from 16% to 100% depending on the drug and method of measurement.[15] Exact measurement of adherence is a challenge and existing methods are limited for various reasons.[19] Best estimation of adherence may be provided by electronic monitoring such as the medication event monitoring system (MEMS®).[20]

Several studies have been published investigating patient adherence to capecitabine. Partridge et al used MEMS® for adherence assessment in older women with early-stage breast cancer. Adherence was defined as the number of doses taken divided by the doses expected. 75% of the included patients were regarded as adherent, i.e. they performed more than 80% of the expected openings. Mean adherence accounted for 78% across all cycles.[21 22] Winterhalder et al used participant self-reports to explore adherence in gastrointestinal and breast cancer patients. Any violation of the recommended treatment regimen, according to their diary entries, during the duration of the capecitabine treatment was considered as non-adherence. 91% (161/177) patients were found to be fully adherent, whereas only 9% (16/177) reported some kind of adherence error.[14] The adherence of 13 younger metastatic breast cancer patients was assessed using

MEMS® and the median accounted for 96%. Adherence was defined as observed doses divided by expected doses. Self-reported adherence was assessed additionally and the median was 97% (n=12).[23] Self-reported non-adherence of 43 breast and colorectal cancer patients was 23.3%.[24] Furthermore, the effect of an intensified multidisciplinary pharmaceutical care programme consisting of a combination of written and spoken information on the adherence of cancer patients treated with capecitabine was investigated. Adherence was measured using MEMS® and defined as the percentage of days with correct medication taking behaviour. Patients who received pharmaceutical care showed a significantly higher mean daily adherence compared to the control group who received standard care (96.8% vs 87.2%, p=0.029).[25]

Thus, adherence rates of patients treated with capecitabine are relatively high compared to non-oncologic oral drugs but can still be increased by specific measures.[25] Conversely, this implies that only some patients treated with capecitabine are in need of an adherence-enhancing intervention and the limited resources could be used more efficiently. Certain patients manage their oral treatment regimen independently and do not benefit from specialized patient care. Therefore, we chose a modular medication management approach in this study. Cancer patients were screened for their adherence during their first capecitabine cycle to detect potential non-adherers. Initially adherent as well as non-adherent patients received basic pharmaceutical care and adverse event management. Specific adherence support was only applied to initially non-adherent patients.

According to the recently published taxonomy for describing and defining adherence to medications[26], this study primarily addressed the implementation element of adherence. The aim was to identify initially non-adherent patients and to investigate initially non-adherent and initially adherent patients' adherence over time. It was hypothesized that adherence of initially adherent patients would remain high over time without specific support and that initially non-adherent patients would benefit from specific adherence support.

METHODS

Study design

The study was conducted as a prospective, multi-centred, two-arm observational cohort study. One study arm consisted of patients classified as initially adherent (baseline daily adherence ≥90%), the other arm of initially non-adherent patients (baseline daily adherence <90%).

Study setting and sample

The study was conducted in two oncology outpatient wards and one oncology practice. Data were collected between July 2009 and March 2012. After the identification of eligibility by the collaborating oncologists, the study pharmacist asked the patients if they were willing to participate in the study. In case of acceptance, each participant signed a written informed consent. The study protocol considered a maximum observation period of six capecitabine cycles for every participant. The main inclusion criterion was the initiation of chemotherapy with capecitabine as single agent or combination therapy for treatment of cancer. Patients had to be capecitabine-naïve, at least 18 years old and able to speak, read and write German. Inclusion had to take place within two weeks after initiation of capecitabine treatment. Exclusion criteria implied any diagnosis of a disease or mental state compromising full understanding of purpose and course of the study. The ethics committee of the University of Bonn, Germany voted positively for this study.

Adherence measurement

Adherence to capecitabine treatment was assessed using the Medication Event Monitoring System (MEMS®, Aardex Group Ltd., Zug, Switzerland).[27] Every participant was provided with a MEMS® container and asked to use it for storage of capecitabine medication during study participation. For ethical reasons patients were informed about the fact that their adherence was being monitored. The caps of the MEMS® containers recorded date and time of every opening. Patients were instructed to open the containers only when taking their capecitabine dose. In case of required refills, patients were requested to schedule refill and regular capecitabine intake at the same time in order to avoid additional openings. If this was not possible or in case of further extraordinary openings, patients were asked to note the respective information on a special documentation sheet. Since uncensored MEMS® data might overestimate non-adherence[28], adherence data were censored according to information derived from notes and interviews (e.g. exclusion of self-reported non-monitoring intervals or extra openings, and intake of doses taken

from another source than MEMS®). Measurement ended after six completed capecitabine cycles or in case of premature treatment discontinuation.

Adherence analysis

Adherence was studied using medication taking profiles uploaded from the MEMS® monitors and patients' information concerning extraordinary incidents. 'Daily adherence' was selected as primary endpoint. It was defined as percentage of days with correctly administered capecitabine doses (number of days with correct drug intake divided by number of observed days). In the case of missing MEMS® data the corresponding days were not included in the analysis, i.e. the number of observed days was reduced accordingly. Adherence was assessed on days with drug intake as well as days during the rest period. A day was considered as adherent only, if two openings of the MEMS® monitor were recorded on a day during the drug intake period (dosing interval ≥6 hours) or if no openings were recorded during the rest period.

Different measures of adherence were used. 'Daily adherence' was calculated for every individual cycle on the basis of days with and without drug intake. Furthermore, 'daily intake adherence' was calculated for every individual cycle on the basis of the drug intake interval only. This was done in order to exclude the influence of the intake-free interval on the adherence. Additionally, 'persistence' of drug intake was analysed. Duration of physician's capecitabine prescription was compared with the duration of the actual treatment by the participant.

For the classification of a participant as initially adherent or non-adherent, daily adherence was calculated for the intake period of the first cycle plus first day of the therapy-free interval. This parameter is referred to as 'baseline daily adherence'. A participant was classified as initially adherent (baseline daily adherence ≥90%) or initially non-adherent (baseline daily adherence <90%). Since no consensual standard for the definition of sufficient adherence exists[16], the threshold of 90% was defined empirically based on the results of an earlier research project[25]. If assessment of baseline adherence resulted in a participant being initially non-adherent, adherence support was provided before the start of the second intake period.

Modular medication management

In addition to standard care provided by physicians and nurses of the respective study centre, medication management consisted of three modules. A detailled literature search was conducted to identify most valuable components of pharmaceutical care and adherence enhancement. On the basis of the reviewed literature the modules were developed, discussed and adapted. Every study participant received module 1 (basic pharmaceutical care) as well as module 2 (adverse

event management). These modules were provided by a registered pharmacist of the Department of Clinical Pharmacy at the University of Bonn, Germany, in collaboration with the attending physicians and nurses. If a participant was initially non-adherent, the pharmacist delivered module 3 (adherence support) to the patient additionally.

Modules 1 and 2 were initiated after inclusion. Module 1 implied detailed medication history taking to perform drug-drug interaction checks and compile an individual medication plan. In case of identified drug-related problems, necessary changes of the medication were made in collaboration with the responsible physician. Patients were educated in detail about the cytotoxic agent capecitabine, its mechanism of action and the individual dosing regimen. Further anti-cancer agents, supportive therapy and other agents taken regularly were also addressed. Patient counselling was supported by the provision of written information material. Within module 2, patients were educated regarding common adverse effects (eg, hand-foot syndrome and diarrhea). Prophylaxis, detection and treatment of adverse effects were discussed in detail. If patients took other drugs or were prescribed a concomitant anti-cancer treatment, they were counselled regarding the adverse effects of these drugs as well. An information brochure regarding prevention and management of adverse effects caused by chemotherapy supported oral counselling.

Since feeding back to the patients electronically compiled adherence data has been demonstrated to be an effective approach to enhance adherence[29], module 3 contained a detailed discussion of the patient's individual adherence results on the basis of cycle 1 MEMS® data. Adherence support focussed on the identification of reasons for non-adherence to define a feasible adherence-enhancing strategy. Since various types of non-adherence exist, strategies to overcome individual barriers to adherence were designed individually. Strategies to improve unintentional non-adherence (eg due to forgetfulness) included treatment diaries or linking drug intake with a certain act of daily routine (cue dosing). In contrast, intentional non-adherence had to be approached in a completely different manner. If an adverse effect was the reason for not taking capecitabine, management and prevention of further adverse effects were addressed in accordance with module 2. Patients' expectations and experiences were included in all considerations. Moreover, an increase of the patient's awareness of the importance of adherence with capecitabine treatment was aimed. Routinely, beginning and end of the current and next capecitabine cycle were explicitly discussed. The content and course of the adherence-supporting session was adapted according to the patients' medication taking behaviour. If the participant showed a daily adherence <90%, the content of the first counselling session of module 3 was repeated and adherence-enhancing strategies were reassessed, discussed and adapted.

Personal follow-up visits took place at least once every cycle. Between scheduled appointments every participant had the possibility to reach individual advice in person, by telephone or by email.

Sample size calculation and statistical analysis

Sample size calculations were based on one-sided exact binomial tests and conducted for the primary endpoint 'daily adherence'. Available adherence data[25] was analysed with regard to daily adherence of the participant's first capecitabine cycle. Regarding initially adherent patients a sample size of 45 was required to show with a power (1-β) of 80% that >75% of these patients remain being adherent (type I error(α) = 5%). The true population value of patients who persist being adherent was assumed to account for >90%. Regarding initially non-adherent patients, a sample size of 30 patients was required to show with a power (1-β) of 80% that >80% of these patients become adherent after the adherence support (type I error (α) = 5%). The true population value of patients who became adherent was assumed to account for >95%. Finally a dropout rate of 20% was estimated so that a total sample size of 90 patients resulted (54 initially adherent and 36 initially non-adherent patients).Data entry and statistical data analysis were carried out using Excel® 2007 (Microsoft, Redmond, USA) and SPSS® Version 20 (SPSS® Inc., Chicago, USA, Statistical Package for the Social Sciences). Appropriate descriptive statistics was used to characterise the patient population and summarise the study results. Data were mostly binary, nominal, ordinal, or failed to follow a normal distribution, thus non-parametric testing was utilised consistently. Differences regarding socio-demographic and disease-related characteristics between initially adherent and non-adherent patients were tested using the Fisher's exact test for nominal data. To explore the relationship between adherence and potential predictors of adherence, Spearman's rank correlation coefficient was used for comparing two continuous data sets and Mann-Whitney-U analysis was used for comparing continuous (not normally distributed) data with binary data sets.

RESULTS

During the data collection period participating oncologists assessed in total 97 patients for eligibility, 78 were enrolled in the study. Figure 1 provides a detailed overview of patient recruitment including reasons for exclusion and loss to follow-up. The main reason (seven out of eight refusals) for non-participation was perceived stress by the study in addition to their mentally and/or physically impaired condition. Since five patients were not capecitabine-naïve, two patients were not able to speak, read and write German and for four patients MEMS® use was not possible due to participation in another trial, they were not enrolled.

Patient characteristics

Seventy-three patients were analysed for baseline daily adherence, 58 (79.5%) were initially adherent and 15 (20.5%) initially non-adherent. Table 1 shows that there was no statistically significant difference between initially adherent and non-adherent patients regarding socio-demographic and disease-related characteristics. However, there was a significant difference in the therapy setting (p=0.021, Fisher's exact test).

Table 1: Socio-demographic and disease-related patient characteristics

Socio-demographic characteristics		initially adherent		initially non-adherent		P value
		n	%	n	%	
Classified age [years]	≤ 50	11	19.0	0	0.0	0.203
	51-60	15	25.9	6	40.0	
	61-70	17	29.3	3	20.0	
	71-80	10	17.2	5	33.3	
	> 80	5	8.6	1	6.7	
Sex	Female	44	75.9	10	66.7	0.516
	Male	14	24.1	5	33.3	
Number of additional drugs (excluding PRN drugs)	≤ 5	45	77.6	10	66.7	0.514
	6-10	9	15.5	3	20.0	
	> 10	3	5.2	2	13.3	
	No answer	1	1.7	0	0.0	
Tumour entity	Breast cancer	21	36.2	7	46.7	0.818
	Colorectal cancer	25	43.1	7	46.7	
	Gastric cancer	3	5.2	0	0.0	
	Oesophageal cancer	1	1.7	1	6.7	
	Ovarian cancer	3	5.2	0	0.0	
	Cancer of unknown primary	1	1.7	0	0.0	
	Pancreatic cancer	3	5.2	0	0.0	
	Endometrial cancer	1	1.7	0	0.0	
Therapy regimen at inclusion	Monotherapy	35	60.3	7	46.7	0.339
	Combination therapy	23	39.7	8	53.3	
Treatment intention	curative	8	13.8	3	20.0	0.686
	palliative	50	86.2	12	80.0	
Classified time since diagnosis	< ½ year	15	25.9	4	26.7	0.712
	½ to 2 years	22	37.9	4	26.7	
	> 2 years	21	36.2	7	46.7	
Therapy setting	Oncology outpatient ward	51	87.9	9	60.0	0.021
	Oncology practice	7	12.1	6	40.0	

Initially adherent patients

Initially adherent patients were observed for a median time of 119.0 days (range 21.0-152.0; IQR=69.8-126.0). During all observed cycles, a high percentage of these patients showed a daily adherence equal or greater 90% (Figure 2A). After the sixth cycle, 36 of 37 (97.3%, CI 88.8%-99.4%) initially adherent patients showed a daily adherence ≥90%. Since the CI does not include 75% it is shown with a type I error of 5% that more than 75% of the initially adherent patients remained adherent after the modular medication management (without specific adherence support).

Figure 2B shows the same kind of data analysis for the daily intake adherence (excluding therapy-free interval). The fraction of initially adherent patients with a daily intake adherence

≥90% was lower compared to daily adherence reflecting that adherence is lower during intake than rest periods.

Figure 3 demonstrates that variability with regard to daily adherence increased from cycle 1 compared to further cycles. Median daily adherence was 100% in every cycle. Mean daily adherence decreased from 98.9% in cycle 1 to 97.3% in cycle 6. Online table A provides more detailed information. Although initially adherent patients did not receive specific adherence support, a consistently high median daily adherence in a majority of these patients was observed. Only in exceptional cases median daily adherence was observed to be lower than 90%. Individual daily adherence profiles of each patient over the observation period are provided in online figure A.

Initially non-adherent patients

Initially non-adherent patients were observed for a median time of 118.0 days (range 35.0-140.0; IQR=96.0-126.0). Figure 2A illustrates the percentage of patients who showed a daily adherence equal or greater than 90% during the different cycles. Adherence increased in association with the specific support provided. In cycle 2 the percentage of adherent patients was 80.0% (12/15) compared to 40.0% (6/15) in cycle 1 and it ranged between 75.0 % and 84.6% in the following cycles 3 to 6. After completion of the sixth cycle, daily adherence of six out of eight (75.0%, CI 46.0%-91.3%) initially non-adherent patients accounted for ≥90%. Since the CI included 80% which was the cut-off value used for sample size determination of initially non-adherent patients, it could not be proven that >80% of initially non-adherent patients were adherent after the intervention.

Figure 2B shows the percentage of initially non-adherent patients with a daily intake adherence ≥90% over the cycles. In contrast to the initially adherent patients, the fractions of initially non-adherent patients exhibiting a daily adherence ≥90% and a daily intake adherence ≥90% did not exhibit major differences.

Median daily adherence increased from 85.7% in cycle 1 to 97.6% in cycle 6, see figure 4. Mean daily adherence accounted for 80.8% during the first cycle and was found to be greater than 90% during the application of the adherence support module (online table B). Adherence varied widely between patients but also from cycle to cycle in the same patients. Online figure B shows individual daily adherence profiles of initially non-adherent patients during the course of the study calculated for intake plus rest period.

Potential predictors of adherence

There was no indication of an existing relationship between patients' daily adherence during the first cycle and their age (Spearman's r=0.009, p=0.941) or gender (p=0.891, Mann-Whitney-U test). In addition, there was not any significant association between daily adherence and any further socio-demographic and disease-related characteristics.

Persistence

All study patients were persistent during the whole period they were prescribed capecitabine chemotherapy. No patient performed an unauthorised discontinuation of his capecitabine treatment.

However, in 17 of the 58 (29.3%) initially adherent patients capecitabine therapy was discontinued prematurely by the physicians. In 12 patients this decision was taken due to tumour progression. Further reasons for therapy discontinuation were adverse drug reactions (hand-foot syndrome and haemolytic anemia), hospital admission, the toxicity of a co-administered drug, and the patient's wish to stop treatment. 36 (62.1%) patients completed six cycles as planned, two patients (3.4%) completed less than six capecitabine cycles as planned, one patient (1.7%) died after the completion of the third cycle and two patients quit their study participation during the second cycle.

In five of 15 (33.3%) initially non-adherent patients capecitabine therapy was discontinued prematurely due to tumour progression. Eight patients (53.3%) completed six capecitabine cycles as planned, one patient (6.7%) completed five cycles as planned, and one patient died during the second cycle.

DISCUSSION

In this study, we applied a systematic screening for non-adherent patients at an early stage of their capecitabine chemotherapy to provide a patient-tailored modular medication management. The results indicate that specific adherence support might improve adherence of initially non-adherent patients to capecitabine and that initially adherent patients' medication taking behaviour persists over time under basic pharmaceutical care and adverse event management.

Sample size of initially non-adherent patients

A major limitation of our study is the relatively small number of initially non-adherent patients. Instead of the required sample size of 30 initially non-adherent patients, only 15 patients could be enrolled during the study period. Previous data suggested a distribution of 60% initially adherent and 40% initially non-adherent patients.[25] The actual distribution within our patient population was 80% to 20%. This has to be considered before interpreting data of the initially non-adherent patients. However, a clear trend towards an improved adherence over time was observed. Further multicenter studies are needed to provide better generalisable findings.

Adherence screening

For the classification of patients as initially non-adherent or adherent, we used daily adherence of the first drug intake period plus the first day of the therapy-free interval assessed by MEMS®. Consideration of the whole capecitabine cycle would have provided a more complete picture of the participant's adherence during the first cycle. However, this was not feasible. To initiate adherence support before the start of cycle 2, an exact appointment on day 21 of the first cycle for group allocation would have been necessary. A belated start of the adherence supporting module would have biased the results of initially non-adherent patients.

Our approach using the gold standard of adherence assessment was suitable to discriminate between adhering and non-adhering patients. In theory it would be less costly and labour intensive to identify non-adhering patients alternatively by means of possible predictors, eg by a specific questionnaire. In general, numerous factors associated with non-adherence to oral anti-cancer drugs have been identified like eg side effects, forgetfulness, or disliking aspects of treatment.[20 30] On the basis of our data, it was, however, not possible to derive significant information on adherence from socio-demographic or disease-related characteristics, eg age. Indeed, we observed that the three patients exhibiting the lowest baseline adherence during cycle 1 (28.6%, 57.1%, and 64.3%) were of a relatively old age (90, 75, and 79 years). However, from this result it cannot be concluded that adherence decreases with increasing age

as there were also elderly patients exhibiting high adherence. Our findings are in line with the findings of Partridge et al who did not find an association of adherence and age.[21] Furthermore, Bhattacharya et al did not identify significant associations between self-reported adherence to capecitabine and experience of side effects, beliefs about capecitabine, or satisfaction with information. However, the generalisability of that study was also limited by a relatively small sample size.[24] Therefore, larger multi-centre studies are necessary to identify precise predictors of non-adherence to capecitabine.

Effect of modular medication management

Adherence rates in our study were higher than those reported by Partridge et al who found an average overall adherence measured by MEMS® (defined as the number of doses taken divided by the number of doses prescribed) between 70% to 80%.[21] Analysing our data the same way, overall adherence values ranged between 98.2% and 100.5% in initially adherent patients and between 93.8% and 102.7% in initially non-adherent patients. High adherence results in this study might be explained by the fact that every participant of the present study received two pharmaceutical care modules during all six cycles. Regardless the specific adherence support, elements of module 1 and 2, such as an individual medication plan and patient counselling regarding prophylaxis, detection and treatment of adverse effects, might have had a beneficial effect on adherence of both initially adherent and initially non-adherent patients as shown previously[25].

However, in case of initially non-adherent patients, the provided adherence support might have increased adherence additionally. This finding is consistent with previous results from our working group. Under the provision of intensified pharmaceutical care to 48 breast and colorectal cancer patients, the intervention group showed an increased mean overall adherence in comparison to the control group.[25] In line with previous results [21 25 25], non-persistence did not present a problem in our group of patients.

Daily adherence versus daily intake adherence

Daily adherence during the intake periods of each cycle was generally lower compared to daily adherence calculated on the basis of drug intake plus rest period. This implies that adherence to the regimen was better in the rest period when the drug should not be taken, i.e. not many patients took the drug by mistake. However, eight of 15 (53.3%) patients took capecitabine one day too long, too short or completely ignored the break. From this finding we conclude that special attention has to be paid to the change of drug intake to drug-free days in the first capecitabine cycle. Patients have to be educated in detail regarding this particularity of the

capecitabine treatment regimen. The attending health care provider should inform the patient exactly on the dates of the intake-free period. Written notes can serve as mnemonic devices. Future studies should further facilitate the development of appropriate adherence parameters in order to improve the reflection of the longitudinal aspect of adherence data.

Adherence management

Even though daily adherence could be improved in initially non-adherent patients, it has to be pointed out that this patient population did not reach the same adherence level as initially adherent patients. Moreover, inter-individual variability of adherence was higher. This finding suggests that a subgroup of patients with low adherence benefits from the adherence-enhancing intervention as suggested by Simons et al.[25] However, a certain number of patients cannot be reached and reveals a resistant medication taking behaviour. Reasons for intentional non-adherence in those patients were difficulties in swallowing tablets due to nausea and emesis caused by capecitabine (despite the provision of antiemetic prophylaxis and treatment), averseness to medication, or "compensating" intake for previous non-adherence during treatment break. Unintentional non-adherence was mainly based on forgetfulness. Further research should include a systematic approach to develop strategies for adherence management in those 'resistant' patients. The adherence of intentionally non-adherent patients could be enhanced by means of advanced educational interventions. Behavioural interventions such as medication dosette boxes or alarm clocks could be used more extensively in the adherence enhancement of unintentionally non-adherent patients.

Conclusions

In summary, the results of this study demonstrate the potential of an early adherence screening for non-adherence and an individually applied modular medication management to use limited resources most efficiently. The provided adherence support is associated with enhanced adherence of initially non-adherent patients to oral chemotherapy. Moreover, the provision of basic pharmaceutical care and adverse event management was sufficient to maintain adherence in initially adherent patients for at least six cycles. The identification of potential predictors of adherence would facilitate the utilisation and broad application of the proposed adherence screening and modular medication management.

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Competing interests: All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that there have been no competing interests.

Patient consent: Obtained.

Ethics approval: This study was conducted with the approval of the ethics committee of the University of Bonn, Germany (consecutive number 042/09).

Contributorship statement: LK and UJ conceived the study design, substantially contributed to data analysis and interpretation, and drafted the manuscript. LK, YDK, PFS and CS were involved in the data collection and provision of multidisciplinary patient care. RF contributed substantially to statistical data analysis and interpretation. UJ is the guarantor. All authors critically reviewed the manuscript and gave their final approval for the version to be published.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: Extra data is available by e-mailing Ulrich Jaehde (u.jaehde@uni-bonn.de).

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE AND TABLE LEGENDS

Figure 1: Patient recruitment flow diagram

Figure 2: Percentage of patients exhibiting a **A** daily adherence ≥90% (during intake and rest periods) and a **B** daily intake adherence ≥90% (during the intake periods only)

Figure 3: Daily adherence of initially adherent patients during cycle 1 to 6 (the median is represented by the black band in every box; bottom and top of each box are the first and third quartiles; circles are 1.5-3 times the box height away from the box; stars are >3 times the box height away from the box)

Figure 4: Daily adherence of initially non-adherent patients during cycle 1 to 6 (the median is represented by the black band in every box; bottom and top of each box are the first and third quartiles; circles are 1.5-3 times the box height away from the box; stars are >3 times the box height away from the box)

Table 1: Socio-demographic and disease-related patient characteristics

Online figure A: Individual daily adherence of initially adherent patients during the course of the study, each different coloured line represents one patient, the black line represents median daily adherence; cycle 1: n=58, cycle 2: n=56, cycle 3: n=48, cycle 4: n=45, cycle 5: n=40, cycle 6: n=37

Online figure B: Individual daily adherence of initially non-adherent patients during the course of the study, each different coloured line represents one patient, the black line represents median daily adherence; cycle 1: n=15, cycle 2: n=15, cycle 3: n=13, cycle 4: n=12, cycle :5 n=12, cycle 6: n=8

Online table A: Daily adherence of initially adherent patients (calculation based on intake and rest period)

Online table B: Daily adherence of initially non-adherent patients (calculation based on intake and rest period)

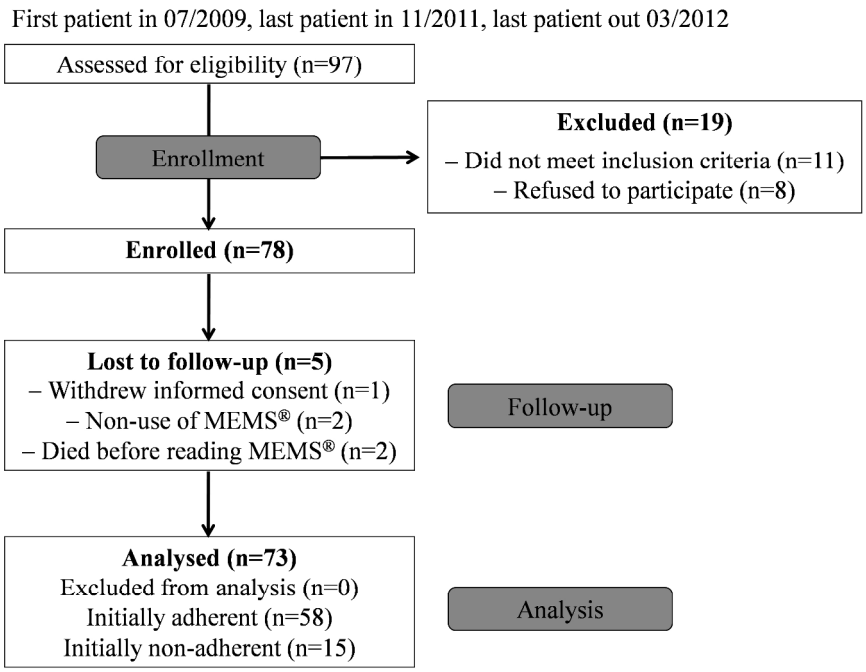

Fig. 1: Patient recruitment flow diagram
254x190mm (300 x 300 DPI)

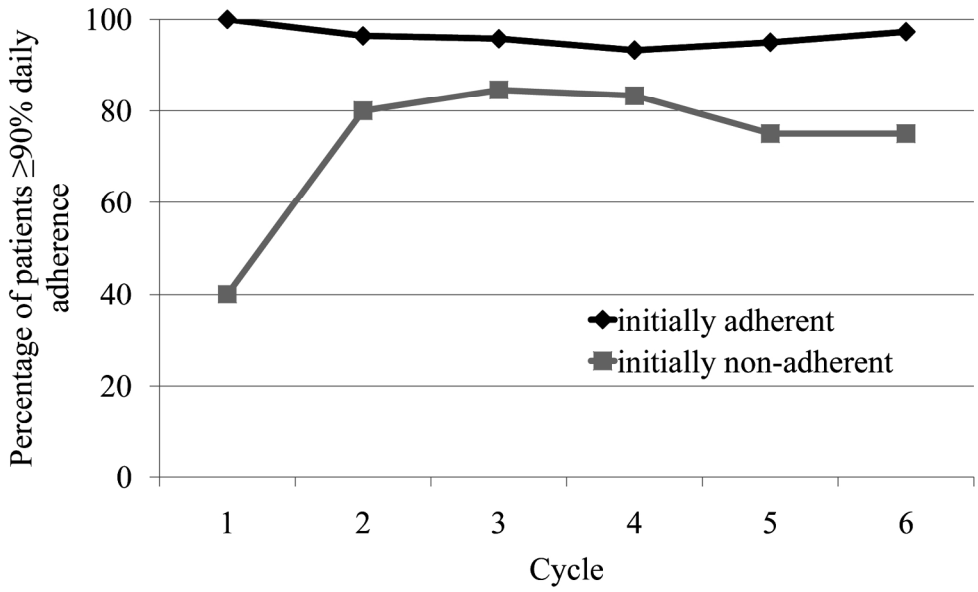

Fig. 2A: Percentage of patients exhibiting a daily adherence ≥90% (during intake and rest periods)
180x109mm (300 x 300 DPI)

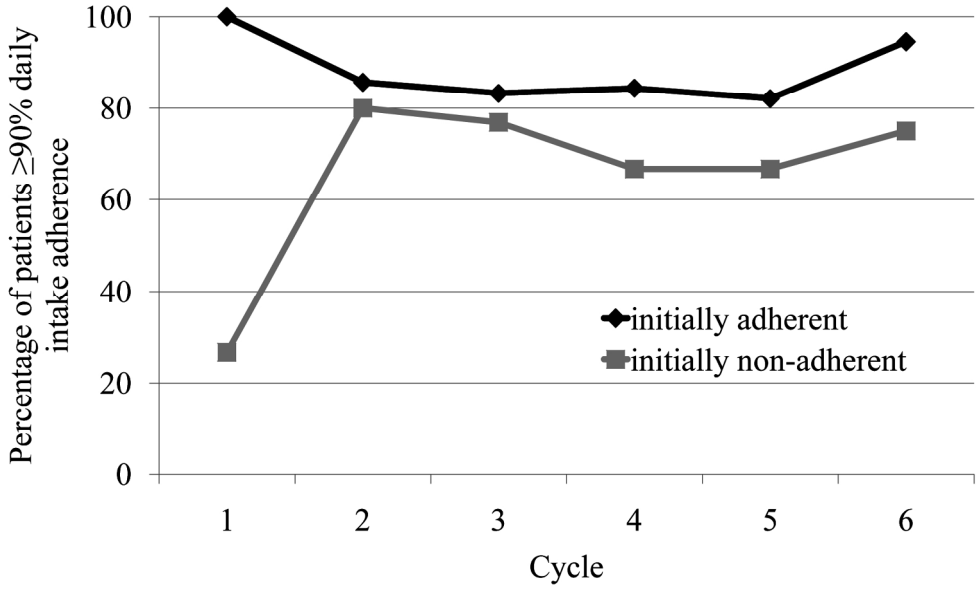

Fig. 2B: Percentage of patients exhibiting a daily intake adherence ≥90% (during the intake periods only)
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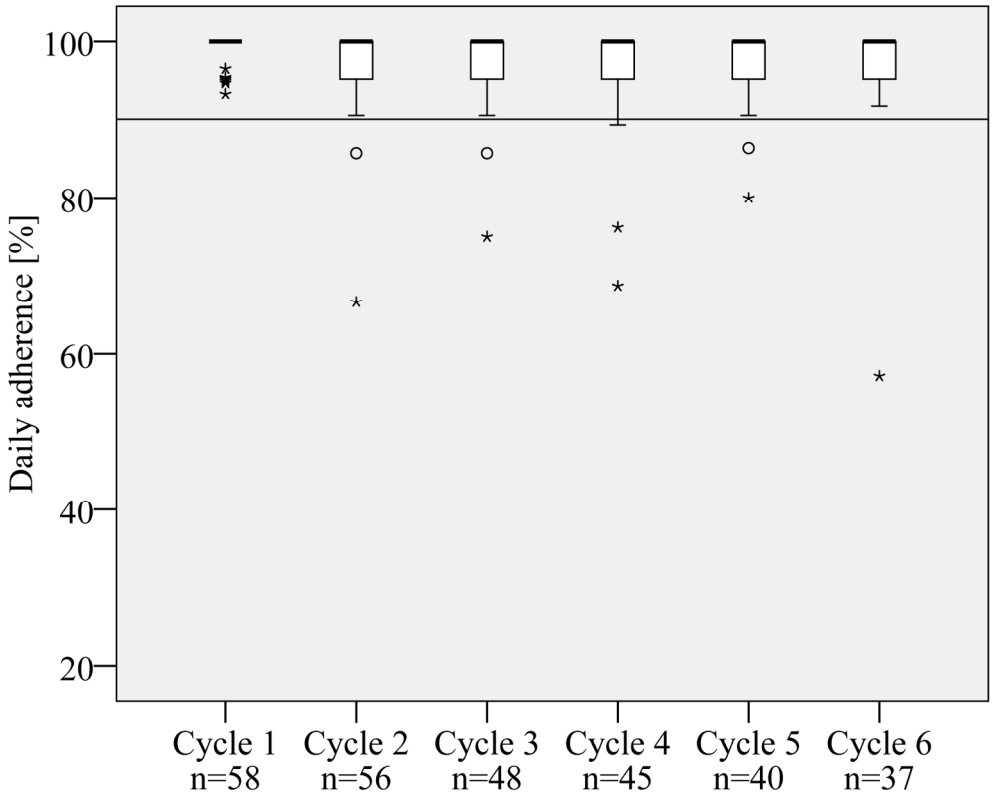

Fig. 3: Daily adherence of initially adherent patients during cycle 1 to 6
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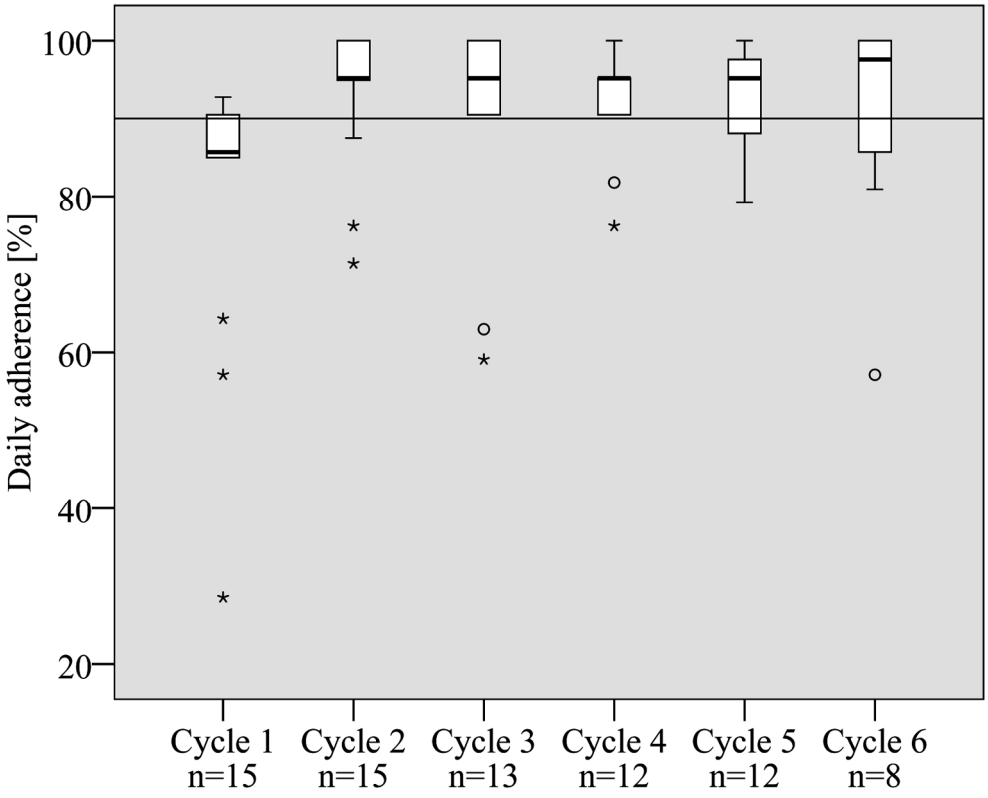
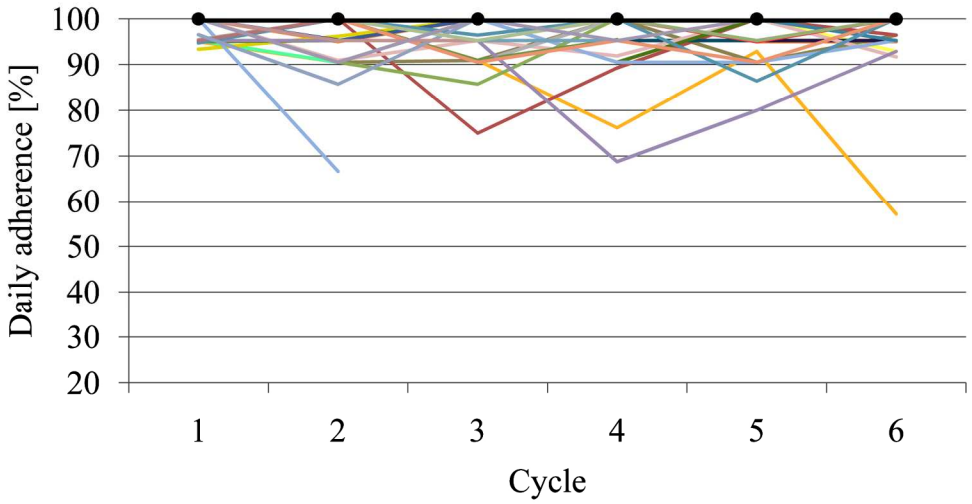
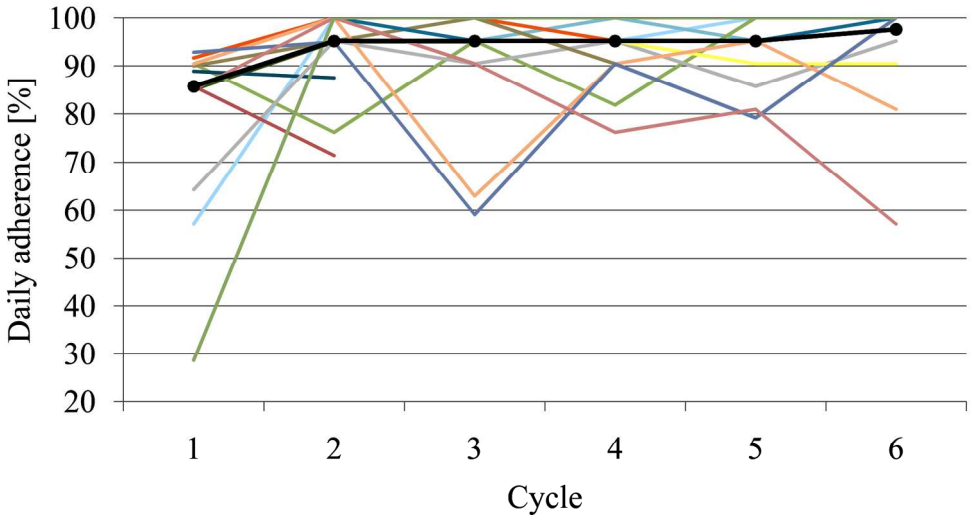


Fig. 4: Daily adherence of initially non-adherent patients during cycle 1 to 6
158x127mm (300 x 300 DPI)



Online Fig. A: Individual daily adherence of initially adherent patients during the course of the study; cycle 1: n=58, cycle 2: n=56, cycle 3: n=48, cycle 4: n=45, cycle 5: n=40, cycle 6: n=37, the black line represents median daily adherence
180x94mm (300 x 300 DPI)



Online Fig. B: Individual daily adherence of initially non-adherent patients during the course of the study; cycle 1: n=15, cycle 2: n=15, cycle 3: n=13, cycle 4: n=12, cycle :5 n=12, cycle 6: n=8; the black line represents the median daily adherence
180x97mm (300 x 300 DPI)

Adherence management for cancer patients on capecitabine: a prospective two-arm cohort study

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ARTICLE SUMMARY

Article Focus

- Adequate patient adherence to capecitabine, an orally administered prodrug of fluorouracil, is essential for treatment success. The early identification of potential non-adherers followed by adherence-enhancing measures may contribute to the effectiveness of oral anticancer drug therapy.
- This prospective, multi-centred observational cohort study aimed ~~at the~~to develop~~ment~~ and ~~evaluation~~ evaluate ~~of~~ a multiprofessional ~~approach~~ medication management to assure adherence to capecitabine.
- It was hypothesized that adherence of initially adherent patients (≥90% adherence during the first cycle) would remain high over time without specific support and that initially non-adherent patients (<90% adherence during the first cycle) would benefit from specific adherence support.

Key Messages

- An early adherence screening effectively distinguishes between patients adhering and non-adhering to capecitabine.
- The provision of specific adherence support ~~can enhance~~is associated with enhanced adherence of initially non-adherent patients.
- Initially adherent patients remain adherent for at least six cycles without specific support implying that targeted support to those patients who benefit from it is a reasonable approach.

Strengths and Limitations

- Our approach is multiprofessional and needs-based utilising available resources for adherence management most efficiently.
- The relatively small sample size of initially non-adherent patients limits the validity of the observed results for this subgroup of patients.

ABSTRACT

Background: Capecitabine, an orally administered prodrug of fluorouracil, is administered twice daily for ~~14 days~~two weeks followed by ~~a seven day rest period~~one week off. Adequate patient adherence is essential for treatment success. The early identification of potential non-adherers followed by adherence-enhancing measures may contribute to the effectiveness of oral anticancer drug therapy.

Objective: To develop and evaluate a multiprofessional ~~approach~~ modular medication management to assure adherence to capecitabine.

Methods: The study was conducted as a prospective, multi-centred observational cohort study. All participants received pharmaceutical care consisting of oral and written information. Daily adherence was defined as percentage of days with correctly administered capecitabine doses and assessed using electronic monitoring (MEMS®). According to their daily adherence during the first cycle, patients were identified as initially non-adherent (<90% adherence) or adherent (≥90% adherence). Initially non-adherent patients received additional adherence support.

Results: Seventy-three patients with various tumour entities were enrolled, 58 were initially adherent and 15 non-adherent. Median daily adherence of initially non-adherent patients increased from 85.7% to 97.6% during the observation period of six cycles. Throughout all cycles, median daily adherence of initially adherent patients was 100.0%. Daily adherence was not associated with socio-demographic and disease-related factors. No patient was non-persistent.

Conclusions: An early adherence screening effectively distinguishes between patients adhering and non-adhering to capecitabine. The provision of specific adherence support ~~can~~ is associated with enhanced adherence of initially non-adherent patients, whereas initially adherent patients remain adherent for at least six cycles without specific support. Our needs-based approach helps to use available resources for adherence management efficiently.

INTRODUCTION

Cancer therapy has traditionally been dominated by intravenously administered agents.[1] However, oral anti-cancer drugs are increasingly used and more than one-quarter of all anti-cancer drugs currently under development are orally administered.[2 3] Oral anti-cancer therapies are highly accepted by patients based on obvious advantages, e.g. higher convenience, avoidance of venipuncture and paravasates, and greater patient autonomy.[2 4 5] However, these treatments are also associated with many challenges. Due to less intense contact between patient and health care providers, responsibilities in terms of managing the course of treatment are transferred to the patient such as monitoring of doses and toxicity.[2 6] In contrast to intravenously administered anti-cancer treatments, health care providers cannot always assume that patients are adherent which is, however, the key prerequisite for treatment success. Multidisciplinary patient care and specific patient education regarding all aspects of the treatment regimen are crucial to maintain adherence.[6–9]

Patients of the present study were treated with the chemotherapeutic agent capecitabine, an orally administered prodrug of cytotoxic fluorouracil (5 FU). Capecitabine has an improved tolerability and comparable efficacy compared with infusional or bolus 5 FU [10] and is frequently used in the treatment of breast, colorectal, and gastric cancer. Moreover, ovarian, pancreatic, or oesophageal tumours may be treated with capecitabine. One capecitabine cycle consists of three weeks, two weeks of twice daily drug intake followed by seven days of break. ~~Usually it is given in three-week cycles, twice per day for two weeks separated by 12 hours, followed by a one-week medication-free interval.~~[11]

Patient adherence to prescribed treatment regimens for chronic non-oncologic diseases accounts for 50% on average only.[12 13] Cancer patients' medication taking behaviour is presumed to be particularly adherent, since cancer is a life-threatening disease.[14–18] However, adherence rates of oral anti-cancer agents were reported to range from 16% to 100% depending on the drug and method of measurement.[15] Exact measurement of adherence is a challenge and existing methods are limited for various reasons.[19] Best estimation of adherence may be provided by electronic monitoring such as the medication event monitoring system (MEMS®).[20]

Several studies have been published investigating patient adherence to capecitabine. Partridge et al used MEMS® for adherence assessment in older women with early-stage breast cancer. ~~and defined adherence~~ Adherence was defined as the number of doses taken divided by the doses expected. 75% of the included patients were regarded as adherent, i.e. they performed more than 80% of the expected openings ~~and were regarded as adherent~~. ~~Average~~ Mean adherence ~~was~~ accounted for 78% across all cycles.[21 22] Winterhalder et al used participant self-reports to explore adherence in gastrointestinal and breast cancer patients. ~~–~~Any violation of the recommended treatment regimen, according to their diary entries, during the duration of the

capecitabine treatment was considered as non-adherence. 91% (161/177) patients were found to be fully adherent, whereas only 9% (16/177) reported some kind of adherence error~~, i.e. any violation of the recommended regimen~~.[14] ~~In 13 younger metastatic breast cancer patients, median~~ The adherence of 13 younger metastatic breast cancer patients was assessed using MEMS® ~~was~~ and the median accounted for 96%. Adherence was defined as observed doses divided by expected doses. Self-reported ~~median~~ adherence was assessed additionally and the median ~~of 12 patients~~ was 97% (n=12).[23] ~~In 43 breast and colorectal cancer patients, S~~self-reported non-adherence of 43 breast and colorectal cancer patients was 23.3%.[24] Furthermore, the effect of an intensified multidisciplinary pharmaceutical care programme consisting of a combination of written and spoken information on the adherence of cancer patients treated with capecitabine was investigated. Adherence was measured using MEMS® and defined as the percentage of days with correct medication taking behaviour. Patients who received pharmaceutical care showed a significantly higher mean daily adherence compared to the control group who received standard care (96.8% vs 87.2%, p=0.029).[25]

Thus, adherence rates of patients treated with capecitabine are relatively high compared to non-oncologic oral drugs but can still be increased by specific measures.[25] Conversely, this implies that only some patients treated with capecitabine are in need of an adherence-enhancing intervention and the limited resources could be used more efficiently. Certain patients manage their oral treatment regimen independently and do not benefit from ~~a~~ specialized patient care. Therefore, we chose a modular medication management approach in this study. ~~In this study, we screened~~ Cancer patients were screened for their adherence during their first capecitabine cycle to detect potential non-adherers. Initially adherent as well as non-adherent patients received basic pharmaceutical care and adverse event management. Specific adherence support was only applied to initially non-adherent patients.

According to the recently published taxonomy for describing and defining adherence to medications[26], this study primarily addressed the implementation element of adherence. The aim ~~of the present study~~ was to identify initially non-adherent patients and to investigate initially non-adherent and initially adherent patients' adherence over time. It was hypothesized that adherence of initially adherent patients would remain high over time without specific support and that initially non-adherent patients would benefit from specific adherence support.

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METHODS

Study design

The study was conducted as a prospective, multi-centred, two-arm observational cohort study. One study arm consisted of patients classified as initially adherent (baseline daily adherence ≥90%), the other arm of initially non-adherent patients (baseline daily adherence <90%).

Study setting and sample

The study was conducted in two oncology outpatient wards and one oncology practice. Data were collected between July 2009 and March 2012. After the identification of eligibility by the collaborating oncologists, the study pharmacist asked the patients ~~were asked~~ if they were willing to participate in the study. In case of acceptance, each participant signed a written informed consent. The study protocol considered a maximum observation period of six capecitabine cycles for every participant. The main inclusion criterion was the initiation of chemotherapy with capecitabine as single agent or combination therapy for treatment of cancer. Patients had to be capecitabine-naïve, at least 18 years old and able to speak, read and write German. Inclusion had to take place within two weeks after initiation of capecitabine treatment. Exclusion criteria implied any diagnosis of a disease or mental state compromising full understanding of purpose and course of the study. The ethics committee of the University of Bonn, Germany voted positively for this study.

Adherence measurement

Adherence to capecitabine treatment was assessed using the Medication Event Monitoring System (MEMS®, Aardex Group Ltd., Zug, Switzerland).[27] Every participant was provided with a MEMS® container and asked to use it for storage of capecitabine medication during study participation. For ethical reasons patients were informed about the fact that their adherence was being monitored. The caps of the MEMS® containers recorded date and time of every opening. Patients were instructed to open the containers only when taking their capecitabine dose. In case of required refills, patients were requested to schedule refill and regular capecitabine intake at the same time in order to avoid additional openings. If this was not possible or in case of further extraordinary openings, patients were asked to note the respective information on a special documentation sheet. Since uncensored MEMS® data might overestimate non-adherence[28], adherence data were censored according to information derived from notes and interviews (e.g. exclusion of self-reported non-monitoring intervals or extra openings, and intake of doses taken

from another source than MEMS®). Measurement ended after six completed capecitabine cycles or in case of premature treatment discontinuation.

Adherence analysis

Adherence was studied using medication taking profiles uploaded from the MEMS® monitors and patients' information concerning extraordinary incidents. 'Daily adherence' was selected as primary endpoint. It was defined as percentage of days with correctly administered capecitabine doses (number of days with correct drug intake divided by number of observed days). In the case of missing MEMS® data the corresponding days were not included in the analysis, i.e. the number of observed days was reduced accordingly. Adherence was assessed on days with drug intake as well as days during the rest period. A day was considered as adherent only, if two openings of the MEMS® monitor were recorded on a day during the drug intake period (dosing interval ≥6 hours) or if no openings were recorded during the rest period.

Different measures of adherence were used. ~~Basically,~~ 'D~~d~~aily adherence' was calculated for every individual cycle on the basis of ~~(~~days with and without drug intake~~therapy-free interval)~~. Furthermore, 'daily intake adherence' was calculated for every individual cycle on the basis of ~~for~~ the drug intake interval only ~~and referred to as 'daily intake adherence'~~. This was done in order to exclude the influence of the ~~rest period~~intake-free interval on the adherence. Additionally, 'persistence' of drug intake was analysed. Duration of physician's capecitabine prescription was compared with the duration of the actual treatment by the participant.

For the classification of a participant as initially adherent or non-adherent, daily adherence was calculated for the intake period of the first cycle plus first day of the therapy-free interval. This parameter is referred to as 'baseline daily adherence'. A participant was classified as initially adherent (baseline daily adherence ≥90%) or initially non-adherent (baseline daily adherence <90%). Since no consensual standard for the definition of sufficient adherence exists[16], the threshold of 90% was defined empirically based on the results of an earlier research project[25]. If assessment of baseline adherence resulted in a participant being initially non-adherent, adherence support was provided before the start of the second intake period.

Modular medication management

In addition to standard care provided by physicians and nurses of the respective study centre, medication management consisted of three modules. A detailled literature search was conducted to identify most valuable components of pharmaceutical care and adherence enhancement. On the basis of the reviewed literature the modules were developed, discussed and adapted.~~These modules were provided by a registered pharmacist of the Department of Clinical Pharmacy at~~

~~the University of Bonn, Germany.~~ Every study participant received module 1 (basic pharmaceutical care) as well as module 2 (adverse event management). These modules were provided by a registered pharmacist of the Department of Clinical Pharmacy at the University of Bonn, Germany, in collaboration with the attending physicians and nurses. If a participant was initially non-adherent, the pharmacist delivered module 3 (adherence support) ~~was applied~~to the patient additionally.

Modules 1 and 2 were initiated after inclusion. Module 1 implied detailed medication history taking to perform drug-drug interaction checks and compile an individual medication plan. In case of identified drug-related problems, necessary changes of the medication were made in collaboration with the responsible physician. Patients were educated in detail about the cytotoxic agent capecitabine, its mechanism of action and the individual dosing regimen. Further anti-cancer agents, supportive therapy and other agents taken regularly were also addressed. Patient counselling was supported by the provision of written information material. Within module 2, patients were educated regarding common adverse effects (eg, hand-foot syndrome and diarrhea). Prophylaxis, detection and treatment of adverse effects were discussed in detail. If patients took other drugs or were prescribed a concomitant anti-cancer treatment, they were counselled regarding the adverse effects of these drugs as well. An information brochure regarding prevention and management of adverse effects caused by chemotherapy supported oral counselling.

Since feeding back to the patients electronically compiled adherence data has been demonstrated to be an effective approach to enhance adherence[29], ~~M~~module 3 contained a detailed discussion of the patient's individual adherence results on the basis of cycle 1 MEMS® data. Adherence support focussed on the identification of reasons for non-adherence to define a feasible adherence-enhancing strategy. Since various types of non-adherence exist, strategies to overcome individual barriers to adherence were designed individually. Strategies to improve unintentional non-adherence (eg due to forgetfulness) included treatment diaries or linking drug intake with a certain act of daily routine (cue dosing). In contrast, intentional non-adherence had to be approached in a completely different manner. If an adverse effect was the reason for not taking capecitabine, management and prevention of further adverse effects were addressed in accordance with module 2. Patients' expectations and experiences were included in all considerations. Moreover, an increase of the patient's awareness of the importance of adherence with capecitabine treatment was aimed. Routinely, beginning and end of the current and next capecitabine cycle were explicitly discussed. The content and course of the adherence-supporting session was adapted according to the patients' medication taking behaviour. If the participant showed a daily adherence <90%, the content of the first counselling session of module 3 was repeated and adherence-enhancing strategies were reassessed, discussed and adapted.

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Personal follow-up visits took place at least once every cycle. Between scheduled appointments every participant had the possibility to reach individual advice in person, by telephone or by email.

Sample size calculation and statistical analysis

Sample size ~~determination~~ calculations were based on one-sided exact binomial tests ~~was~~ and conducted for the primary endpoint 'daily adherence'. Available adherence data[25] was analysed with regard to daily adherence of the participant's first capecitabine cycle. Regarding initially adherent patients a sample size of 45 was required to show with a power (1-β) of 80% that >75% of these patients remain being adherent (type I error ~~of first kind~~ (α) = 5%). The true population value of patients who persist being adherent was assumed to account for >90%. Regarding initially non-adherent patients, a sample size of 30 patients was required to show with a power (1-β) of 80% that >80% of these patients become adherent after the adherence support (type I error ~~of first kind~~ (α) = 5%). The true population value of patients who became adherent was assumed to account for >95%. Finally a dropout rate of 20% was estimated so that a total sample size of 90 patients resulted (54 initially adherent and 36 initially non-adherent patients).

Data entry and statistical data analysis were carried out using Excel® 2007 (Microsoft, Redmond, USA) and SPSS® Version 20 (SPSS® Inc., Chicago, USA, Statistical Package for the Social Sciences). Appropriate descriptive statistics was used to characterise the patient population and summarise the study results. Data were mostly binary, nominal, ordinal, or failed to follow a normal distribution, thus non-parametric testing was utilised consistently. Differences regarding socio-demographic and disease-related characteristics between initially adherent and non-adherent patients were tested using the Fisher's exact test for nominal data. To explore the relationship between adherence and potential predictors of adherence, Spearman's rank correlation coefficient was used for comparing two continuous data sets and Mann-Whitney-U analysis was used for comparing continuous (not normally distributed) data with binary data sets.

RESULTS

During the data collection period pParticipating oncologists assessed in total 97 patients for eligibility, 78 were enrolled in the study. Figure 1 provides a detailed overview of patient recruitment including reasons for exclusion and loss to follow-up. The main reason (seven out of eight refusals) for non-participation was perceived stress by the study in addition to their mentally and/or physically impaired condition. Since five patients were not capecitabine-naïve, two patients were not able to speak, read and write German and for four patients MEMS® use was not possible due to participation in another trial, they were not enrolled.

Patient characteristics

Seventy-three patients were analysed for baseline daily adherence, 58 (79.5%) were initially adherent and 15 (20.5%) initially non-adherent. Table 1 shows that there was no statistically significant difference between initially adherent and non-adherent patients regarding socio-demographic and disease-related characteristics. However, there was a significant difference in the therapy setting (p=0.021, Fisher's exact test).

Table 1: Socio-demographic and disease-related patient characteristics

Socio-demographic characteristics		initially adherent		initially non-adherent		P value
		n	%	n	%	
Classified age [years]	≤ 50	11	19.0	0	0.0	0.203
	51-60	15	25.9	6	40.0	
	61-70	17	29.3	3	20.0	
	71-80	10	17.2	5	33.3	
	> 80	5	8.6	1	6.7	
Sex	Female	44	75.9	10	66.7	0.516
	Male	14	24.1	5	33.3	
Number of additional drugs (excluding PRN drugs)	≤ 5	45	77.6	10	66.7	0.514
	6-10	9	15.5	3	20.0	
	> 10	3	5.2	2	13.3	
	No answer	1	1.7	0	0.0	
Tumour entity	Breast cancer	21	36.2	7	46.7	0.818
	Colorectal cancer	25	43.1	7	46.7	
	Gastric cancer	3	5.2	0	0.0	
	Oesophageal cancer	1	1.7	1	6.7	
	Ovarian cancer	3	5.2	0	0.0	
	Cancer of unknown primary	1	1.7	0	0.0	
	Pancreatic cancer	3	5.2	0	0.0	
	Endometrial cancer	1	1.7	0	0.0	
Therapy regimen at inclusion[1, 2]	Monotherapy	35	60.3	7	46.7	0.339
	Combined therapy	23	39.7	8	53.3	0.313
	~~Cap Beva~~	~~11~~	~~19.0~~	~~4~~	~~26.7~~	
	~~Cap Beva Ox~~	~~1~~	~~1.7~~	~~0~~	~~0.0~~	
	~~Cap Lap~~	~~1~~	~~1.7~~	~~0~~	~~0.0~~	
	~~Cap Ox~~	~~3~~	~~5.2~~	~~1~~	~~6.7~~	
	~~Cap Vin~~	~~1~~	~~1.7~~	~~1~~	~~6.7~~	
	~~Cap Mito~~	~~0~~	~~0.0~~	~~1~~	~~6.7~~	
	~~Cap Trastu Ox~~	~~0~~	~~0.0~~	~~1~~	~~6.7~~	
	~~Cap Fulve~~	~~2~~	~~3.4~~	~~0~~	~~0.0~~	
	~~Cap Vin Letro~~	~~1~~	~~1.7~~	~~0~~	~~0.0~~	
	~~Cap Trastu~~	~~3~~	~~5.2~~	~~0~~	~~0.0~~	
Treatment intention	curative	8	13.8	3	20.0	0.686
	palliative	50	86.2	12	80.0	
Classified time since diagnosis	< ½ year	15	25.9	4	26.7	0.712
	½ to 2 years	22	37.9	4	26.7	
	> 2 years	21	36.2	7	46.7	
Therapy setting	Oncology outpatient ward	51	87.9	9	60.0	0.021
	Oncology practice	7	12.1	6	40.0	

[1] ~~Therapy regimens: **Cap** = capecitabine monotherapy; **Cap Beva** = capecitabine + bevacizumab; **Cap Beva Ox** = capecitabine + bevacizumab + oxaliplatin; **Cap Lap** = capecitabine + lapatinib; **Cap Ox** = capecitabine + oxaliplatin; **Cap Vin** = capecitabine + vinorelbine; **Cap Mito** = capecitabine + mitomycin; **Cap Trastu Ox** = capecitabine + trastuzumab + oxaliplatin; **Cap Fulve** = capecitabine + fulvestrant; **Cap Vin Letro** = capecitabine + vinorelbine + letrozole; **Cap Trastu** = capecitabine + trastuzumab~~

[2] ~~Bisphosphonate and radiation therapies are not considered~~

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Initially adherent patients

Initially adherent patients were observed for a median time of 119.0 days (range 21.0-152.0; IQR=69.8-126.0). During all observed cycles, a high percentage of these patients showed a daily adherence equal or greater 90% (Figure 2A). After the sixth cycle, 36 of 37 (97.3%, CI 88.8%-99.4%) initially adherent patients showed a daily adherence ≥90%. Since the CI does not include 75% it is shown with a~~n~~ type I error ~~of the first kind~~ of 5% that more than 75% of the initially adherent patients remained adherent after the modular medication management (without specific adherence support).

Figure 2B shows the same kind of data analysis for the daily intake adherence (excluding therapy-free interval). The fraction of initially adherent patients with a daily intake adherence ≥90% was lower compared to daily adherence reflecting that adherence is lower during intake than rest periods.

Figure 3 demonstrates that variability with regard to daily adherence increased from cycle 1 compared to further cycles. Median daily adherence was 100% in every cycle. ~~Average~~ Mean daily adherence decreased from 98.9% in cycle 1 to 97.3% in cycle 6. Online table A provides more detailed information. Although initially adherent patients did not receive specific adherence support, ~~the modular medication management led to~~ a consistently high median daily adherence in a majority of these patients was observed. Only in exceptional cases median daily adherence was observed to be lower than 90%. Individual daily adherence profiles of each patient over the observation period are provided in online figure A.

Online table A: Daily adherence of initially adherent patients (calculation based on intake and rest period)

	n	Mean [%]	Median [%]	SD [%]	Range [%]	IQR [%]
Cycle 1	58	98.9	100.0	2.1	93.3-100.0	100.0-100.0
Cycle 2	56	97.3	100.0	5.5	66.7-100.0	95.2-100.0
Cycle 3	48	97.2	100.0	4.9	75.0-100.0	95.2-100.0
Cycle 4	45	96.7	100.0	6.3	68.8-100.0	95.2-100.0
Cycle 5	40	97.4	100.0	4.7	80.0-100.0	95.2-100.0
Cycle 6	37	97.3	100.0	7.3	57.1-100.0	95.2-100.0

Initially non-adherent patients

Initially non-adherent patients were observed for a median time of 118.0 days (range 35.0-140.0; IQR=96.0-126.0). Figure 2A illustrates the percentage of patients who showed a daily adherence equal or greater than 90% during the different cycles. Adherence increased in association with the specific support provided. ~~The results indicate a clear effect of adherence support.~~ In cycle 2 the ~~number of~~ percentage of adherent patients was 80.0% (12/15) compared

to 40.0% (6/15) ~~twice as high as~~ in cycle 1 and it ranged between 75.0 % and 84.6% in the following cycles 3 to 6~~remained relatively constant in the later cycles~~. After completion of the sixth cycle, daily adherence of six out of eight (75.0%, CI 46.0%-91.3%) initially non-adherent patients accounted for ≥90%. Since the CI included 80% which was the cut-off value used for sample size determination of initially non-adherent patients, it could not be proven that >80% of initially non-adherent patients were adherent after the intervention.

Figure 2B shows the percentage of initially non-adherent patients with a daily intake adherence ≥90% over the cycles. In contrast to the initially adherent patients, the fractions of initially non-adherent patients exhibiting a daily adherence ≥90% and a daily intake adherence ≥90% did not exhibit major differences.

Median daily adherence increased from 85.7% in cycle 1 to 97.6% in cycle 6, see figure 4. ~~Average~~ Mean daily adherence accounted for 80.8% during the first cycle and was found to be greater than 90% during the application of the adherence support module (online table B). Adherence varied widely between patients but also from cycle to cycle in the same patients. Online figure B shows individual daily adherence profiles of initially non-adherent patients during the course of the study calculated for intake plus rest period.

Online table B: Daily adherence of initially non-adherent patients (calculation based on intake and rest period)

	n	Mean [%]	Median [%]	SD [%]	Range [%]	IQR [%]
Cycle 1	15	80.8	85.7	17.6	28.6-92.9	85.0-90.5
Cycle 2	15	93.7	95.2	8.8	71.4-100.0	95.0-100.0
Cycle 3	13	90.7	95.2	13.6	59.1-100.0	90.5-100.0
Cycle 4	12	92.1	95.2	7.0	76.2-100.0	90.5-95.2
Cycle 5	12	92.7	95.2	7.2	79.2-100.0	88.1-97.6
Cycle 6	8	90.5	97.6	15.1	57.1-100.0	85.7-100.0

Potential predictors of adherence

There was no indication of an existing relationship between patients' daily adherence during the first cycle and their age (Spearman's r=0.009, p=0.941) or gender (p=0.891, Mann-Whitney-U test). In addition, there was not any significant association between daily adherence and any further socio-demographic and disease-related characteristics.

Persistence

All study patients were persistent during the whole period they were prescribed capecitabine chemotherapy. No patient performed an unauthorised discontinuation of his capecitabine treatment.

However, in 17 of the 58 (29.3%) initially adherent patients capecitabine therapy was discontinued prematurely by the physicians. In 12 patients this decision was taken due to tumour progression. Further reasons for therapy discontinuation were adverse drug reactions (hand-foot syndrome and haemolytic anemia), hospital admission, the toxicity of a co-administered drug, and the patient's wish to stop treatment. 36 (62.1%) patients completed six cycles as planned, two patients (3.4%) completed less than six capecitabine cycles as planned, one patient (1.7%) died after the completion of the third cycle and two patients quit their study participation during the second cycle.

In five of 15 (33.3%) initially non-adherent patients capecitabine therapy was discontinued prematurely due to tumour progression. Eight patients (53.3%) completed six capecitabine cycles as planned, one patient (6.7%) completed five cycles as planned, and one patient died during the second cycle.

DISCUSSION

In this study, we applied a systematic screening for non-adherent patients at an early stage of their capecitabine chemotherapy to provide a patient-tailored modular medication management. The results indicate that specific adherence support might improve adherence of initially non-adherent patients to capecitabine and that initially adherent patients' medication taking behaviour persists over time under basic pharmaceutical care and adverse event management.

Sample size of initially non-adherent patients

A major limitation of our study is the relatively small number of initially non-adherent patients. Instead of the required sample size of 30 initially non-adherent patients, only 15 patients could be enrolled during the study period. Previous data suggested a distribution of 60% initially adherent and 40% initially non-adherent patients.[25] The actual distribution within our patient population was 80% to 20%. This has to be considered before interpreting data of the initially non-adherent patients. However, a clear trend towards an improved adherence over time was observed. Further multicenter studies are needed to provide better generalisable findings.

Adherence screening

For the classification of patients as initially non-adherent or adherent, we used daily adherence of the first drug intake period plus the first day of the therapy-free interval assessed by MEMS®. Consideration of the whole capecitabine cycle would have provided a more complete picture of the participant's adherence during the first cycle. However, this was not feasible. To initiate adherence support before the start of cycle 2, an exact appointment on day 21 of the first cycle for group allocation would have been necessary. A belated start of the adherence supporting module would have biased the results of initially non-adherent patients.

~~Although o~~Our approach using the gold standard of adherence assessment was suitable to discriminate between adhering and non-adhering patients. ~~-~~In theory it would be less costly and labour intensive to identify non-adhering patients alternatively by means of possible predictors~~-~~ ~~With knowledge of adherence predictors a screening method without costly and labour intensive electronic monitoring could be developed~~, eg by a specific questionnaire. In general, numerous factors associated with non-adherence to oral anti-cancer drugs have been identified like eg side effects, forgetfulness, or disliking aspects of treatment.[20 30] On the basis of our data, it was, however, not possible to derive significant information on adherence from socio-demographic or disease-related characteristics, eg age. Indeed, we observed that the three patients exhibiting the lowest baseline adherence during cycle 1 (28.6%, 57.1%, and 64.3%) were of a relatively

old age (90, 75, and 79 years). However, from this result it cannot be concluded that adherence decreases with increasing age as there were also elderly patients exhibiting high adherence. Our findings are in line with the findings of Partridge et al who did not find an association of adherence and age.[21] Furthermore, Bhattacharya et al did not identify significant associations between self-reported adherence to capecitabine and experience of side effects, beliefs about capecitabine, or satisfaction with information. However, the generalisability of that study was also limited by a relatively small sample size.[24] Therefore, larger multi-centre studies are necessary to identify precise predictors of non-adherence to capecitabine.

Effect of modular medication management

Adherence rates in our study were higher than those reported by Partridge et al who found an average overall adherence measured by MEMS® (defined as the number of doses taken divided by the number of doses prescribed) between 70% to 80%.[21] Analysing our data the same way, overall adherence values ranged between 98.2% and 100.5% in initially adherent patients and between 93.8% and 102.7% in initially non-adherent patients. ~~This~~ High adherence results in this study might be explained by the fact that every participant of the present study received two pharmaceutical care ~~medication management~~ modules during all six cycles. Regardless the specific adherence support, elements of module 1 and 2, such as an individual medication plan and patient counselling regarding ~~-~~prophylaxis, detection and treatment of adverse effects, might have had a beneficial effect on adherence of both initially adherent and initially non-adherent patients as shown previously[25].

However, i~~I~~n case of initially non-adherent patients, the provided adherence support might have increased adherence additionally. This finding is consistent with previous results from our working group. Under the provision of intensified pharmaceutical care to 48 breast and colorectal cancer patients, the intervention group showed an increased mean overall adherence in comparison to the control group.[25] In line with previous results [21 25 25], non-persistence did not present a problem in our group of patients.

Daily adherence versus daily intake adherence

Daily adherence during the intake periods of each cycle was generally lower compared to daily adherence calculated on the basis of drug intake plus rest period. This implies that adherence to the regimen was better in the rest period when the drug should not be taken, i.e. not many patients took the drug by mistake. However, ~~daily adherence calculated for the first intake interval plus the first day of the rest period in initially non-adherent patients was lower than daily adherence during the whole cycle or adherence during the intake interval alone. E~~eight of

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15 (53.3%) patients took capecitabine one day too long, too short or completely ignored the break. From this finding we conclude that special attention has to be paid to the change of drug intake to drug-free days in the first capecitabine cycle. Patients have to be educated in detail regarding this particularity of the capecitabine treatment regimen. The attending health care provider should inform the patient exactly on the dates of the intake-free period. Written notes can serve as mnemonic devices. Future studies should further facilitate the development of appropriate adherence parameters in order to improve the reflection of the longitudinal aspect of adherence data.

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Adherence management

Even though daily adherence could be improved in initially non-adherent patients, it has to be pointed out that this patient population did not reach the same adherence level as initially adherent patients. Moreover, inter-individual variability of adherence was higher. This finding suggests that a subgroup of patients with low adherence benefits from the adherence-enhancing intervention as suggested by Simons et al.[25] However, a certain number of patients cannot be reached and reveals a resistant medication taking behaviour. Reasons for intentional non-adherence in those patients were difficulties in swallowing tablets due to nausea and emesis caused by capecitabine (despite the provision of antiemetic prophylaxis and treatment), averseness to medication, or "compensating" intake for previous non-adherence during treatment break. Unintentional non-adherence was mainly based on forgetfulness. Further research should include a systematic approach to develop strategies for adherence management in those 'resistant' patients. The adherence of intentionally non-adherent patients could be enhanced by means of advanced educational interventions. Behavioural interventions such as medication dosette boxes or alarm clocks could be used more extensively in the adherence enhancement of unintentionally non-adherent patients.

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Conclusions

In summary, the results of this study demonstrate the potential of an early adherence screening for non-adherence and an individually applied modular medication management to use limited resources most efficiently. The provided adherence support ~~improved~~ is associated with enhanced adherence of initially non-adherent patients to oral chemotherapy. Moreover, the provision of basic pharmaceutical care and adverse event management was sufficient to maintain adherence in initially adherent patients for at least six cycles. The identification of potential predictors of adherence would facilitate the utilisation and broad application of the proposed adherence screening and modular medication management.

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Competing interests: All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that there have been no competing interests.

Patient consent: Obtained.

Ethics approval: This study was conducted with the approval of the ethics committee of the University of Bonn, Germany (consecutive number 042/09).

Contributorship statement: LK and UJ conceived the study design, substantially contributed to data analysis and interpretation, and drafted the manuscript. LK, YDK, PFS and CS were involved in the data collection and provision of multidisciplinary patient care. RF contributed substantially to statistical data analysis and interpretation. UJ is the guarantor. All authors critically reviewed the manuscript and gave their final approval for the version to be published.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: Extra data is available by emailing Ulrich Jaehde (u.jaehde@uni-bonn.de).

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE AND TABLE LEGENDS

Figure 1: Patient recruitment flow diagram

Figure 2: Percentage of patients exhibiting a **A** daily adherence ≥90% (during intake and rest periods) and a **B** daily intake adherence ≥90% (during the intake periods only)

Figure 3: Daily adherence of initially adherent patients during cycle 1 to 6 (the median is represented by the black band in every box; bottom and top of each box are the first and third quartiles; circles are 1.5-3 times the box height away from the box; stars are >3 times the box height away from the box)

Figure 4: Daily adherence of initially non-adherent patients during cycle 1 to 6 (the median is represented by the black band in every box; bottom and top of each box are the first and third quartiles; circles are 1.5-3 times the box height away from the box; stars are >3 times the box height away from the box)

Table 1: Socio-demographic and disease-related patient characteristics

Online figure A: Individual daily adherence of initially adherent patients during the course of the study~~:~~, each different coloured line represents one patient, the black line represents median daily adherence; cycle 1: n=58, cycle 2: n=56, cycle 3: n=48, cycle 4: n=45, cycle 5: n=40, cycle 6: n=37~~, the black line represents median daily adherence~~

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Online figure B: Individual daily adherence of initially non-adherent patients during the course of the study~~:~~, each different coloured line represents one patient, the black line represents median daily adherence; cycle 1: n=15, cycle 2: n=15, cycle 3: n=13, cycle 4: n=12, cycle :5 n=12, cycle 6: n=8~~; the black line represents the median daily adherence~~

Online table A: Daily adherence of initially adherent patients (calculation based on intake and rest period)

Online table B: Daily adherence of initially non-adherent patients (calculation based on intake and rest period)

STROBE statement - checklist of items that should be included in reports of observational studies

Krolop et al.
Adherence management for cancer patients on capecitabine: a prospective two-arm cohort study

	Item No	Recommendation	
Title and abstract			
	1	*(a)* Indicate the study's design with a commonly used term in the title or the abstract	OK
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	OK
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	OK
Objectives	3	State specific objectives, including any prespecified hypotheses	OK
Methods			
Study design	4	Present key elements of study design early in the paper	OK
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	OK
Participants	6	*(a) Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	OK
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	OK
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	OK
Bias	9	Describe any efforts to address potential sources of	Not

		bias	applicable
Study size	10	Explain how the study size was arrived at	OK
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	OK
Statistical methods	12	*(a)* Describe all statistical methods, including those used to control for confounding	OK
		(b) Describe any methods used to examine subgroups and interactions	OK
		(c) Explain how missing data were addressed	OK
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	*(a)* Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	OK
		(b) Give reasons for non-participation at each stage	OK
		(c) Consider use of a flow diagram	OK
Descriptive data	14*	*(a)* Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	OK
		(b) Indicate number of participants with missing data for each variable of interest	OK
		(c) Cohort study—Summarise follow-up time (eg average and total amount)	OK
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	OK
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(a) Give unadjusted estimates and, if applicable,	Not

		confounder adjusted estimates and their precision (eg 95% confidence interval). Make clear which confounders were adjusted for and why they were included	applicable
		(b) Report category boundaries when continuous variables were categorised	OK
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	OK
Discussion			
Key results	18	Summarise key results with reference to study objectives	OK
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	OK
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	OK
Generalisability	21	Discuss the generalisability (external validity) of the study results	OK
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	OK

Online table A: Daily adherence of initially adherent patients (calculation based on intake and rest period)

	n	Mean [%]	Median [%]	SD [%]	Range [%]	IQR [%]
Cycle 1	58	98.9	100.0	2.1	93.3-100.0	100.0-100.0
Cycle 2	56	97.3	100.0	5.5	66.7-100.0	95.2-100.0
Cycle 3	48	97.2	100.0	4.9	75.0-100.0	95.2-100.0
Cycle 4	45	96.7	100.0	6.3	68.8-100.0	95.2-100.0
Cycle 5	40	97.4	100.0	4.7	80.0-100.0	95.2-100.0
Cycle 6	37	97.3	100.0	7.3	57.1-100.0	95.2-100.0

Online table B: Daily adherence of initially non-adherent patients (calculation based on intake and rest period)

	n	Mean [%]	Median [%]	SD [%]	Range [%]	IQR [%]
Cycle 1	15	80.8	85.7	17.6	28.6-92.9	85.0-90.5
Cycle 2	15	93.7	95.2	8.8	71.4-100.0	95.0-100.0
Cycle 3	13	90.7	95.2	13.6	59.1-100.0	90.5-100.0
Cycle 4	12	92.1	95.2	7.0	76.2-100.0	90.5-95.2
Cycle 5	12	92.7	95.2	7.2	79.2-100.0	88.1-97.6
Cycle 6	8	90.5	97.6	15.1	57.1-100.0	85.7-100.0