Indonesian Journal of Pharmacy

VOL 33 (1) 2022: 22–33 | REVIEW ARTICLE

Effect of Pharmacist Interventions on Medication Adherence to Capecitabine in Patients with Cancer: A Systematic Review

Atika Wahyu Puspitasari[1,2], Susi Ari Kristina[3*], Satibi[3], and Yayi Suryo Prabandari[4]

1. Doctoral Program in Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281
2. Faculty of Pharmacy, Universitas Indonesia, Jakarta, Indonesia, 16424
3. Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281
4. Department of Public Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281

Info Article

Submitted: 02-08-2021
Revised: 06-11-2021
Accepted: 25-03-2022

*Corresponding author
Susi Ari Kristina

Email:
susiari_k@ugm.ac.id

ABSTRACT

Oral chemotherapy poses challenges regarding patient medication adherence. Pharmacists play a vital role in supporting medication adherence to achieve the effectiveness of therapy. This review aimed to evaluate the impact of pharmacist interventions on medication adherence in patients with cancer taking capecitabine. The literature was systematically reviewed using Scopus, ScienceDirect, Sage Journal, Springer Link, PubMed, and Google Scholar. Key text words included "adherence, pharmacist intervention, capecitabine, oral chemotherapy, and cancer." We collected original articles published from January 2010 to June 2021 in English that reported pharmacist interventions to enhance capecitabine adherence in adult patients with cancer and assessed adherence rates pre- and post-intervention. Two independent researchers extracted data relevant to inclusion criteria and determined the methodological quality of studies using the Joanna Briggs Institute Critical Appraisal Checklist Tools. A total of 4179 articles were retrieved, of which five were eligible for review. The most common pharmacist intervention strategy was a combination of patient education, with oral and written information provided. Components of patient education were the characteristics of capecitabine, including its mechanism of action, side effects, and their management; current therapeutic regimen; importance of adherence; and risk of non-adherence. Pharmacist interventions provide beneficial impacts on medication adherence, beliefs about medication, and tolerability of side effects. The findings suggest that pharmacist interventions support medication adherence improvement and highlight the role of pharmacist interventions in pharmaceutical oncology care services. Further studies are necessary to assess pharmacist interventions' long-term effects and clinical outcomes.

Keywords: Capecitabine, Oral chemotherapy, Pharmacist, Adherence, Cancer

INTRODUCTION

The development of oral cancer agents has now increased significantly (Battis *et al*., 2017). The use of these agents in clinical practice provides greater patient preference over intravenous infusion because of convenience (Greer *et al*., 2020; McCue *et al*., 2014). However, the disadvantages of these drugs are their bioavailability because of malabsorption, inter- and intra-individual pharmacokinetic variability, and adherence issues (Saux *et al*., 2018).

The oral chemotherapeutic agent of this study was capecitabine, which is widely used to treat metastatic breast and colorectal cancer as a single or a combination therapy (Timmers *et al*., 2012; Walko *et al*., 2005). Capecitabine is a 5-fluorouracil (5-FU) prodrug. It has shown efficacy and safety comparable to 5-FU (Hefner *et al*., 2018;

Reigner *et al*., 2001; Schellens, 2007; Timmers *et al*., 2012; Wagstaff *et al*., 2003; Walko *et al*., 2005). However, capecitabine has a complex dosing schedule. Capecitabine is taken on specific days of a cycle. Capecitabine is taken 30 minutes after meals at 12-hour intervals for 14 days, followed by a 1-week drug-free period. Capecitabine is often associated with a high incidence of side effects similar to 5-FU, including nausea, vomiting, diarrhea, stomatitis, fatigue, and hand–foot syndrome (Bauchner *et al*., 2001; Lam & Fresco, 2015; Sardi *et al*., 2017; Schneider *et al*., 2011).

As a home-based therapy, capecitabine is administered without supervision or less intense contact from healthcare providers; hence, it poses challenges regarding medication adherence (Bassan *et al*., 2014; Eek *et al*., 2016; McCue *et al*., 2014; Wood, 2012). Treatment adherence is a critical aspect of achieving therapeutic success, optimal patient outcomes, and health-related quality of life (Felton *et al*., 2016; Lam & Fresco, 2015; Spoelstra & Given, 2011). Medication adherence is defined as a person's behavior in taking medication, following a diet, and implementing lifestyle changes according to agreed recommendations from healthcare providers (World Health Organization, 2003). Treatment adherence can be influenced by several factors, such as factors related to patients, therapy, disease, healthcare systems, and socioeconomic status (World Health Organization, 2003).

Non-adherence to capecitabine potentially leads to disease progression, increased morbidity, and decreased overall survival (Kovacic *et al*., 2017). A systematic review reported that capecitabine adherence rates varied between 51.2% and 100%, depending on the method of measurement and the definition of adequate adherence (Puspitasari *et al*., 2021). A pharmacist is one member of an oncology care team who plays a role in supporting and maximizing patient adherence to oral chemotherapy (Acharya *et al*., 2013; Felton *et al*., 2016; Plevin *et al*., 2010; Wick & Elswick, 2018). Pharmacists should monitor adherence and resolve any medication-taking problem, including non-adherence (Aslani *et al*., 2019). Pharmacists have been integrated in such teams because of their expertise, skill, and strong knowledge of medicines (Colombo *et al*., 2017; Felton *et al*., 2016).

Various studies on pharmacist interventions to improve adherence in patients with cancer using capecitabine oral chemotherapy have been carried out. However, currently, no systematic review has been explicitly published regarding the effectiveness of pharmacist interventions on capecitabine adherence. To address this gap, the objective of this systematic review was to synthesize available evidence on the effectiveness of pharmacist interventions in treatment adherence in patients with cancer receiving capecitabine.

MATERIAL AND METHODS

We conducted a systematic review of the published literature through Scopus, ScienceDirect, Sage Journal, Springer Link, PubMed, and Google Scholar. The search strategy used keywords related to adherence, pharmacist intervention, capecitabine, oral chemotherapy, and cancer (Appendix 1).

The screening was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. We screened relevant articles based on the title, index term, and abstract. We reviewed full-text articles according to the predefined inclusion criteria. Two research members (AW, SA) independently assessed eligible studies and discussed any discrepancies to achieve agreement.

We selected articles if they met the following inclusion criteria: Patients: Adults, outpatients, and patients with cancer (≥ 18 years) receiving capecitabine; Medication: capecitabine; Exposure: pharmacist intervention for promoting adherence to capecitabine; Outcome: quantitative patient adherence rate before and after the intervention; Study type: randomized controlled trial (RCT), non-randomized control trial, prospective observational study, and quasi-experimental study; Published in the English language; Published in the period 2010–2021; Accessible as full-text articles.

Articles were excluded if the intervention description was not clear, and if they were reviews, letters to the editor, editorials, or commentaries. Data were extracted from eligible articles, including lead author, year of publication, country, research design, follow-up duration, type of cancer, sample size, adherence measurement method, intervention description, control group, parameters measured, and study results. At least one other reviewer confirmed the data extraction process. Two investigators (AW/SA or AW/SAT) discussed any point of inconsistency to reach an agreement.

Appendix 1. Search terms on the database

Database	Search Terms
Scopus	adherence OR compliance OR concordance OR non-adherence OR non-compliance OR non-adherence OR non-compliance OR "non adherence" OR "non compliance" AND pharmacist OR pharmacy OR "pharmacist intervention" OR "pharmaceutical care" AND capecitabine OR "prodrug 5 fluorouracil" AND "oral chemotherapy" OR therapy OR treatment OR medication AND cancer OR malignancy OR carcinoma
Science Direct	adherence OR compliance AND pharmacist OR "pharmacist intervention" AND capecitabine OR "prodrug 5 fluorouracil" AND "oral chemotherapy" AND cancer OR malignancy
Sage Journal	adherence OR compliance OR concordance OR non-adherence OR non-compliance OR non-adherence OR non-compliance OR "non-adherence" OR "non-compliance" AND pharmacist OR pharmacy OR "pharmacist intervention" OR "pharmaceutical care" AND capecitabine OR "prodrug 5 fluorouracil" AND "oral chemotherapy" OR therapy OR treatment OR medication AND cancer OR malignancy OR carcinoma
Springer Link	adherence OR compliance OR concordance OR non-adherence OR non-compliance OR non-adherence OR non-compliance OR "non-adherence" OR "non-compliance" AND pharmacist OR pharmacy OR "pharmacist intervention" OR "pharmaceutical care" AND capecitabine OR "prodrug 5 fluorouracil" AND "oral chemotherapy" OR therapy OR treatment OR medication AND cancer OR malignancy OR carcinoma
PubMed	adherence OR compliance OR concordance OR non-adherence OR non-compliance OR non-adherence OR non-compliance OR "non-adherence" OR "non-compliance" AND pharmacist OR pharmacy OR "pharmacist intervention" OR "pharmaceutical care" AND capecitabine OR "prodrug 5 fluorouracil" AND "oral chemotherapy" OR therapy OR treatment OR medication AND cancer OR malignancy OR carcinoma
Google Scholar	adherence OR compliance OR concordance OR non-adherence OR non-compliance OR non-adherence OR non-compliance OR "non-adherence" OR "non-compliance" AND pharmacist OR pharmacy OR "pharmacist intervention" OR "pharmaceutical care" AND capecitabine OR "prodrug 5 fluorouracil" AND "oral chemotherapy" OR therapy OR treatment OR medication AND cancer OR malignancy OR carcinoma

We evaluated the quality and risk of bias for each included study using the Joanna Briggs Institute Critical Appraisal Checklist Tools (https://jbi.global/critical-appraisal-tools) for RCTs (13 criteria) and non-randomized experimental studies (9 criteria). Each checklist criterion was rated as yes, no, unclear, or not applicable. Two authors (AW/SA or AW/SAT or AW/YS) independently assessed the study quality. Any discrepancy in the assessing process was discussed and resolved by the review team.

RESULT AND DISCUSSION

A total of 4194 articles were identified from an online database. We excluded articles because of duplication (n=27), they were not related to pharmacist intervention for improving capecitabine adherence (n=4142), they reported only overviews of adherence of capecitabine (n=20), they were qualitative studies (n=5) or a case report (n=1), they did not measure the adherence rate (n=5), they provided capecitabine intervention led by non-pharmacists (n=2), and they did not measure the adherence rate before pharmacist intervention (n=2). Five research articles related to pharmacist interventions to improve adherence in patients with cancer taking capecitabine *met all* inclusion criteria for review (Figure 1).

The critical appraisal results of the quality and risk of bias for each study included are described in Appendices 2 and 3, including an RCT and four non-randomized experimental studies. All studies received more than 50% "yes" in the checklist. One RCT study was not blinded and did not explain the data analysis. Meanwhile, in non-randomized experimental studies, three studies did not use a control group. A study did not clearly inform the validation score and the reliability test of the measurement tools used.

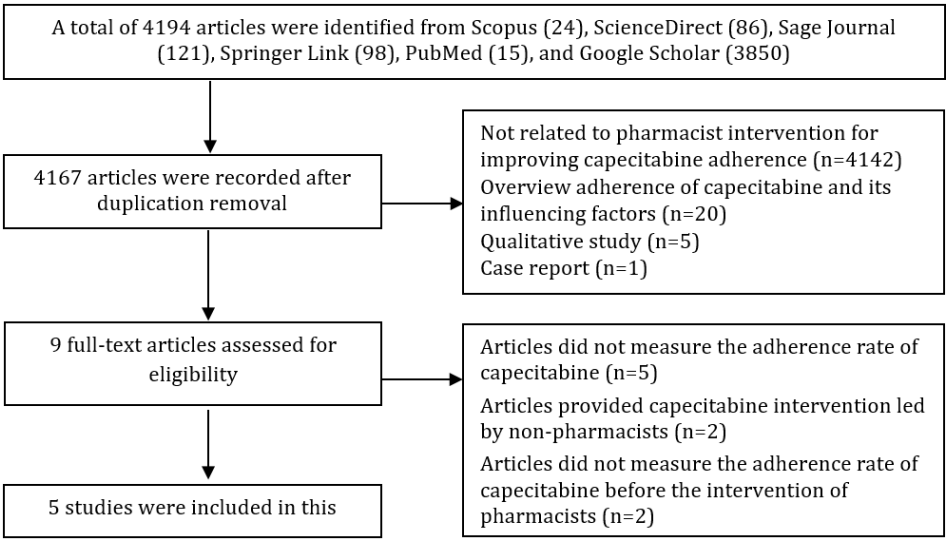

Figure 1. The flowchart of the selection process

Table I. Descriptions of pharmacist interventions

Author, year	Country	Study design	Observation period	Type of cancer	Sample size	Adherence measurement
Simons *et al.,* 2011	Germany	Cohort with a control group, multicentered, and non-randomized	126 days	Colorectal and breast cancer	48	MEMS™
Krolop *et al.,* 2013	Germany	Two-arm observational cohort, multicentered	6 cycles	Diverse cancer	73	MEMS™
Eldeib *et al.,* 2018	Egypt	RCT, single centered	During treatment periods	Metastatic colorectal or gastric cancer	44	Pill count
Birand *et al.,* 2019	Northern Cyprus	Before–after, single centered	3 cycles	Diverse cancer	81	Morisky Green Levine Test 2018
Vacher *et al.,* 2020	France	Before–after, single centered	6 cycles	Colorectal or breast cancer	55	MEMS™

RCT, randomized control trial; MEMS, medication event monitoring system

All studies were published in English between 2011 and 2020 and were conducted in Germany (Krolop *et al*., 2013; Simons *et al*., 2011), Northern Cyprus (Birand *et al*., 2019), Egypt (Eldeib *et al*., 2019), and France (Vacher *et al*., 2020). Several studies used a multicenter cohort study design, with (Simons *et al*., 2011) or without (Krolop *et al*., 2013) control groups. Two other studies used a single-center before–after study design (Birand *et al*., 2019; Vacher *et al*., 2020) and one study used a single-center RCT (Eldeib *et al*., 2019) (Table I).

Most studies used face-to-face educational interventions combined with written information (Birand *et al*., 2019; Krolop *et al*., 2013; Simons *et al*., 2011; Vacher *et al*., 2020). A study used weekly telephone-based follow-up (Eldeib *et al*., 2019). Pharmacist education to patients included the patient treatment plan (Birand *et al*., 2019; Krolop *et al*., 2013), information on the drug's mechanism of action (Krolop *et al*., 2013; Simons *et al*., 2011; Vacher *et al*., 2020), side effects, and their management (Birand *et al*., 2019; Eldeib *et al*., 2019; Simons *et al*., 2011; Vacher *et al*., 2020),

Appendix 2. The methodological quality assessment of studies (RCT)

JBI Critical Appraisal Checklist for randomized controlled trials	Eldeib *et al*., 2018
1. Was true randomization used for assignment of participants to treatment groups?	Y, but not sufficient
2. Was allocation to treatment groups concealed?	N
3. Were treatment groups similar at the baseline?	Y
4. Were participants blind to treatment assignment?	N
5. Were those delivering treatment blind to treatment assignment?	N
6. Were outcome assessors blind to treatment assignment?	N
7. Were treatment groups treated identically other than the intervention of	Y
8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Y
9. Were participants analyzed in the groups to which they were randomized?	Y
10. Were outcomes measured in the same way for treatment groups?	Y
11. Were outcomes measured in a reliable way?	Y
12. Was appropriate statistical analysis used?	Unclear
13. Was the trial design appropriate for the topic, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Y

JBI, Joanna Briggs Institute; RCT Randomized control trial

current therapeutic regimen (Krolop *et al*., 2013; Simons *et al*., 2011), importance of adherence (Birand *et al*., 2019; Eldeib *et al*., 2019; Simons *et al*., 2011), risk of non-adherence (Simons *et al*., 2011), supportive therapy (Krolop *et al*., 2013), rational drug use (Birand *et al*., 2019), and when a patient missed a dose (Vacher *et al*., 2020) and when a patient referred to a doctor (Vacher *et al*., 2020). In addition, two studies involved the role of pharmacists in identifying drug interactions (Krolop *et al*., 2013; Simons *et al*., 2011) or drug–drug-related problems and collaborating with responsible doctors when therapeutic changes were needed (Krolop *et al*., 2013). Studies in this review also reported personal follow-up visits at least once every cycle and individual advice by telephone or email (Krolop *et al*., 2013), reviews of patient adherence by asking them directly (Eldeib *et al*., 2019), and allowing the patient to call the pharmacist to obtain information and support about management side effects (Birand *et al*., 2019) (Table II).

The duration of the intervention varied from three to six cycles (Birand *et al*., 2019; Krolop *et al*., 2013; Simons *et al*., 2011; Vacher *et al*., 2020), and one study reported monitoring the intervention during the treatment period (Eldeib *et al*., 2019). The outcome parameters measured varied between studies. Measuring adherence was the primary outcome in all studies. Other outcomes assessed include beliefs about medication (Birand *et al*., 2019), toxicities (Eldeib *et al*., 2019), tumor response (Eldeib *et al*., 2019), survival assessment (Eldeib *et al*., 2019), and health service utilization (Eldeib *et al*., 2019). The researchers used various adherence measurement methods both subjectively and objectively, including the electronic medication event monitoring system (MEMS™) (Krolop *et al*., 2013; Simons *et al*., 2011; Vacher *et al*., 2020), pill count (Eldeib *et al*., 2019), and the 2018 Morisky Green Levine Test (Birand *et al*., 2019).

Pharmacist interventions significantly improved the mean daily adherence in the intervention group (p=0.029) (Simons *et al*., 2011), the probability of patients still taking capecitabine in the intervention group (p=0.019) (Simons *et al*., 2011), the median adherence in the certain cycle (p=0.046), the tolerability of certain adverse effects in the certain cycle in the intervention group (Eldeib *et al*., 2019), and the mean patient necessity–concern balance score (p=0.0001) (Birand *et al*., 2019). In some studies, overall patients' adherence between the two groups showed no significant differences (Eldeib *et al*., 2019; Simons *et al*., 2011).

Table II. Components of pharmacist interventions

Author, year	Pharmacist intervention	Component of intervention	Control group description	Outcomes measures	Result
Simons *et al.*, 2011	Pharmaceutical care service consists of written and oral information by two registered pharmacists.	1. The pharmacist delivered information about characteristics of capecitabine, including mechanism of action, possible adverse events and their management, explanation of individual treatment regiment, importance of adherence, and risk of non-adherence. 2. Drug interaction checking 3. Giving written dosing schedule	Standard care	Adherence	Overall adherence increased but did not differ significantly in the two groups (p=0.069). The mean daily adherence was significantly higher in the intervention group (p=0.029). The probability of patients still taking capecitabine was 48% in the control group and 83% in the intervention group (p=0.019).
Krolop *et al.*, 2013	Pharmaceutical care service consists of a combination of written and oral information.	Patients received three medication management modules provided by a registered pharmacy, personal follow-up visits at least once every cycle, and individual advice by telephone or email. Module 1 consists of basic pharmaceutical care (detailed medication history) to check drug–drug interaction and compile an individual medication plan. If drug–drug-related problems are identified, the responsible doctor and pharmacist will collaborate to make necessary changes The pharmacist also educated the patient about the action mechanism and individual dosing regimen of capecitabine, supportive therapy, and other medication regularly taken. Module 2 consists of adverse event management for capecitabine, and other drugs taken. Module 3 consists of adherence support to a patient who was initially non-adherent.	NA	Adherence	Median daily adherence of initially non-adherent patients increased from 85.7% to 97.6% during the observation period of six cycles. All patients were persistent.

Eldeib *et al.*, 2018	Weekly telephone-based follow-up and NCI standard care	Patients received weekly phone calls from the principal investigator during the therapy period. Follow-up phone calls included assessment of adverse effects and management strategies (nonpharmacological and pharmacological treatment), reinforcement about adherence, and reviewing patient adherence by asking patient directly	NCI standard care (standard information about capecitabine and capecitabine toxicity, individualized drug regimen.)	1. Adherence 2. Toxicities 3. Health service utilization 4. Tumor response 5. Survival assessment	Overall patients' adherence in the intervention group was higher but not statistically different (p=0.354). The intervention group showed a statistically significantly higher median adherence than the control group on a specific cycle (p=0.046) The intervention group demonstrated statistically better tolerability of side effects in specific cycles than the control group.
Birand *et al.*, 2019	Patient education by clinical oncology pharmacist (face-to-face and written information)	Education about patient treatment plan, rational drug use, serious and common side effects, and their management, the importance of medication adherence The patient called the pharmacist by telephone to get information and support regarding side effect management.	NA	Medication adherence Beliefs about medications	Pharmacist education improved the mean patient necessity–concern balance scores by two-fold significantly (p <0,0001). 74 (91.4%) patients were adherent after the intervention.
Vacher *et al.*, 2020	Therapeutic education program every 3 cycles for 90 minutes by a pharmacist trained in therapeutic education (oral and written information)	Educational diagnosis, knowledge about treatment, such as role and mechanism of action, schedule, side effect management, when patient missed the dose, and referring to the doctor.	NA	Adherence	Therapeutic education program for non-adherent patients improved their adherence score by 17.8% and led 60% of these patients to become adherent.

NCI, National Cancer Institute

Appendix 3. The methodological quality assessment of studies (non-randomized studies)

JBI Critical Appraisal Checklist for randomized controlled trials	**Simons *et al.*, 2011**	**Krolop *et al.*, 2013**	**Birand *et al.*, 2019**	**Vacher *et al.*, 2020**
Is it clear in the study what is the "cause" and what is the "effect" (i.e., there is no confusion about which variable comes first)?	Y	Y	Y	Y
Were the participants included in any similar comparisons?	Y	Y	Y	Y
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Y	Y	Y	Y
Was there a control group?	Y	N	N	N
Were there multiple measurements of the outcome both pre- and post the intervention/exposure?	Y	Y	Y	Y
Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Y	Y	Y	N
Were the outcomes of participants included in any comparisons measured in the same way?	Y	Y	Y	Y
Were outcomes measured in a reliable way?	Y	Y	Unclear	Y
Was appropriate statistical analysis used?	Y	Y	Y	Y

JBI, Joanna Briggs Institute; RCT Randomized control trial

Research limitations in most studies were the small sample size (Eldeib *et al*., 2019; Krolop *et al*., 2013; Simons *et al*., 2011), single-center studies (Birand *et al*., 2019; Eldeib *et al*., 2019), and lack of blinding (Eldeib *et al*., 2019; Simons *et al*., 2011). Other limitations were reported, such as a non-randomized study design (Simons *et al*., 2011), the absence of a control group (Birand *et al*., 2019), and reporting and recall bias (Birand *et al*., 2019). One study did not convey its study limitations (Vacher *et al*., 2020).

Pharmacists are an essential part of the oncology service team because of their expertise and specialized knowledge of cancer therapy. Pharmacists' vital roles are to maximize the benefits of treatment and to minimize toxicity (Coutsouvelis *et al*., 2020). This systematic review describes the characteristics and evaluates the impact of pharmacist interventions on adherence to capecitabine in patients with cancer. The challenge of assessing pharmacist interventions with different strategies provides various results and makes it difficult to identify the most effective role of pharmacists. However, we could summarize some findings to guide future studies.

The types of cancer most assessed in studies are breast and colorectal cancer as these cancers have a high incidence of cases. Breast cancer is the most common worldwide (24.5%), followed by colorectal cancer (9.45%) (Sung *et al*., 2021). Capecitabine is used as first-line therapy in patients with metastatic breast and colorectal cancer (Schellens, 2007; Walko *et al*., 2005).

The measuring adherence used in studies varied because there is no gold standard. The MEMS was used in most studies to assess treatment adherence. The MEMS is an objective method that can minimize manipulation by patients. However, the MEMS is expensive, so it is not always feasible in daily practice, and it is challenging to ensure that pills are taken at the appropriate time of day as prescribed. Additionally, the open cap indicates that the drug is being taken, making it challenging to track medication ingestion (Anghel *et al*., 2019; McCue *et al*., 2014). Pill count is another objective measurement method used in one of the studies. On the other hand, the self-reported questionnaire is a subjective method that tends to overestimate patient bias because of recall memory. However, this method is simple and inexpensive, and provides real-time feedback, so it is used more often in clinical settings (Lam & Fresco, 2015; McCue *et al*., 2014). The different method of adherence measurement in these studies affects the adherence threshold. Therefore, determining a uniform adherence threshold is needed to estimate the adherence level accurately and to provide better evidence (Lam & Fresco, 2015).

In this review, the most common pharmacist intervention was patient education by providing written and oral information. Patient education is one of the integrated roles of pharmacists in outpatient clinic settings (Coutsouvelis *et al*.,

2020). Patient education is a vital domain to improve knowledge and enforce medication adherence. The educational program also supports patients' involvement in their health, provides a discussion forum, and builds patients' self-efficacy in their drug-taking behavior. A continuous interaction with patients provides an opportunity to identify adherence barriers and potential strategies to resolve them (Zullig *et al*., 2015).

The education components were generally focused on the patients' knowledge of their medication, including the characteristics of capecitabine, such as its mechanism of action, side effects, and management; current therapeutic regimen; importance of adherence; and risk of non-adherence. Education about the disease and regimen is the key to supporting medication-taking behavior and improving medication adherence (Lin *et al*., 2017). Education increases knowledge to understand what drugs patients are taking, following prescribed behavior, and the importance of medication adherence for their health. The educational content provided must be using language that is easy to understand and following the level of health literacy (Costa *et al*., 2015; Zullig *et al*., 2015).

In addition to patient education, some studies also involved pharmacists' role in identifying drug- or drug–drug-related problems and collaborating with responsible doctors when therapeutic changes were necessary. As members of a multidisciplinary team, pharmacists can optimize drug therapy in patients with cancer. These pharmacists' roles are fundamental in pharmacotherapy management (Lopez-martin *et al*., 2014). Patients with cancer have a high risk of suffering from drug interactions because of the large numbers of drugs required to treat their cancer, including cytotoxic agents and supportive therapy, such as antiemetics, antibiotics, analgesics, and others (Chen & Cheung, 2014).

Pharmacist interventions showed a beneficial impact on medication adherence. Pharmacist interventions significantly improved the mean daily adherence (p=0.029) (Simons *et al*., 2011), the probability of patients still taking capecitabine (p=0.019) (Simons *et al*., 2011), and the median adherence in the specific cycle (p=0.046) (Eldeib *et al*., 2019) in the intervention group. In addition, pharmacist interventions significantly enhanced the tolerability of certain adverse effects in the certain cycle (Eldeib *et al*., 2019) and the mean patient necessity–concern balance score (p=0.0001) (Birand *et al*., 2019) in an intervention group. Likewise, a literature review on the impact of outpatient oncology pharmacists concluded that they contributed positively to assessing medication adherence, understanding of medications, improved symptom control, patient satisfaction, and improved patient quality of life (Maleki *et al*., 2019).

In some studies, overall patient adherence between the two groups was not significantly different. This could have been due to the level of capecitabine adherence that tends to be high at the beginning of the study. The presence of the Hawthorne effect might also cause this phenomenon. Patients in the control group were aware that their medication adherence was being assessed. In addition, a single component intervention can be a possible reason. Interventions without providing personalized care have little or limited effect on medication adherence. Integrated interventions that include education, case management, and behavioral support, such as reminders, can improve medication adherence (Hajj *et al*., 2018; Viswanathan *et al*., 2012).

Limitations reported in most studies are small sample sizes and single-center studies. These results were less representative, so the generalizability of the studies was limited (Bhattacharya *et al*., 2012). In addition, the small sample size might have masked statistical significance, so it might have caused potential data interpretation errors. Therefore, further multicenter studies in various countries and regions are necessary to characterize the impacts of pharmacist interventions. Another limitation in some studies is the lack of blinding, a non-randomized design, and no control group that can be considered a potential source of bias (Colombo *et al*., 2017). The use of self-reported measuring adherence led to overestimation or underestimation. Therefore, subjective and objective assessments are recommended to minimize bias (Lam & Fresco, 2015).

The limitation of this systematic review is that research on pharmacist interventions on capecitabine adherence is limited. In addition, the differences in study design, method of measuring adherence, and follow-up duration between studies resulted in the results of pharmacist interventions being not directly comparable. The impact of pharmacist interventions on physiological parameters or health outcomes was limited. Additionally, this review includes only

articles published in English, so there is potential for publication bias.

CONCLUSION

This review shows that pharmacists support medication adherence improvement in adult patients with cancer taking capecitabine. Pharmacist interventions in improving medication adherence generally included patient education by providing written and oral information. Further studies are needed to assess pharmacist interventions' long-term effects and clinical outcomes. Finding new and innovative interventions is also necessary to increase the efficiency and cost-effectiveness of pharmacist interventions.

ACKNOWLEDGMENT

Doctoral Dissertation Research Grant, Ministry of Research and Technology/National Agency for Research and Innovation, Republic of Indonesia.

REFERENES

Acharya, A. S., Prakash, A., Saxena, P., & Nigam, A. (2013). Sampling: why and how of it? *Indian Journal of Medical Specialities*, 4(2), 3–7. https://doi.org/10.7713/ijms.2013.0032

Anghel, L. A., Farcas, A. M., & Oprean, R. N. (2019). An overview of the common methods used to measure treatment adherence. *Medicine and Pharmacy Reports*, 92(2), 117–122. https://doi.org/10.15386/mpr-1201

Bassan, F., Peter, F., Houbre, B., Brennstuhl, M. J., Costantini, M., Speyer, E., & Tarquinio, C. (2014). Adherence to oral antineoplastic agents by cancer patients: Definition and literature review. *European Journal of Cancer Care*, 23(1), 22–35. https://doi.org/10.1111/ecc.12124

Bauchner, H., Osganian, S., Smith, K., & Triant, R. (2001). Improving parent knowledge about antibiotics: A video intervention. *Pediatrics*, 108(4), 845–850. https://doi.org/10.1542/peds.108.4.845

Bhattacharya, D., Easthall, C., Willoughby, K. A., Small, M., & Watson, S. (2012). Capecitabine non-adherence: Exploration of magnitude, nature and contributing factors. *Journal of Oncology Pharmacy Practice*, 18(3), 333–342. https://doi.org/10.1177/1078155211436022

Birand, N., Bosnak, A. S., Diker, O., Abdikarim, A., & Basgut, B. (2019). The role of the pharmacist in improving medication beliefs and adherence in cancer patients. *Journal of Oncology Pharmacy Practice*, 25(8), 1916–1926. https://doi.org/10.1177/1078155219831377

Chen, L., & Cheung, W. Y. (2014). Potential Drug Interactions in Patients with a History of Cancer. *Current Oncology*, 21(2), 212–220.

Colombo, L. R. P., Aguiar, P. M., Lima, T. M., & Storpirtis, S. (2017). The effects of pharmacist interventions on adult outpatients with cancer: A systematic review. *Journal of Clinical Pharmacy and Therapeutics*, 42(4), 414–424. https://doi.org/10.1111/jcpt.12562

Costa, E., Giardini, A., Savin, M., Menditto, E., Lehane, E., Laosa, O., & Pecorelli, S. (2015). Interventional tools to improve medication adherence : review of literature. *Patient Preference and Adherence*, 9(1), 1303–1314.

Coutsouvelis, J., Adams, J., Dip, G., Bortz, H., Chau, M., Chiang, K., Foo, J., Ibrahim, K., Kerr, K., O'Connor, S., Powell, M., Rowan, G., Siderov, J., Tey, A., Tran, J., Vasileff, H., & Munro, C. (2020). Standard of practice in oncology and haematology for pharmacy services. *Journal of Pharmacy Practice and Research*, 50, 528–545. https://doi.org/10.1002/jppr.1686

Eek, D., Krohe, M., Mazar, I., Horsfield, A., Pompilus, F., Friebe, R., & Shields, A. L. (2016). Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: A review of the literature. *Patient Preference and Adherence*, 10, 1609–1621. https://doi.org/10.2147/PPA.S106629

Eldeib, H. K., Abbassi, M. M., Hussein, M. M., Salem, S. E., & Sabry, N. A. (2019). The Effect of Telephone-Based Follow-Up on Adherence, Efficacy, and Toxicity of Oral Capecitabine-Based Chemotherapy. *Telemedicine and E-Health*, 25(6), 462–470. https://doi.org/10.1089/tmj.2018.0077

Felton, M. A., Van Londen, G. J., & Marcum, Z. A. (2016). Medication adherence to oral cancer therapy: The promising role of the pharmacist. *Journal of Oncology Pharmacy Practice*, 22(2), 378–381. https://doi.org/10.1177/1078155214559114

Hajj, M. S. el, Jaam, M. J., & Awaisu, A. (2018). Effect of pharmacist care on medication adherence and cardiovascular outcomes among patients post-acute coronary syndrome: A systematic review. *Research in Social and Administrative Pharmacy*, 14(6), 507–520.

Hefner, J., Berberich, S., Lanvers, E., Sanning, M., Steimer, A. K., & Kunzmann, V. (2018). Patient–doctor relationship and adherence to capecitabine in outpatients of a german comprehensive cancer center. *Patient Preference and Adherence*, 12, 1875–1887. https://doi.org/10.2147/PPA.S169354

Krikorian, S., Pories, S., Tataronis, G., Caughey, T., Chervinsky, K., Lotz, M., Shen, A. H., & Weissmann, L. (2019). Adherence to oral chemotherapy: Challenges and opportunities. *Journal of Oncology Pharmacy Practice*, 25(7), 1590–1598. https://doi.org/10.1177/1078155218800384

Krolop, L., Ko, Y., Schwindt, P. F., Schumacher, C., Fimmers, R., & Jaehde, U. (2013). Adherence management for patients with cancer taking capecitabine : a prospective two-arm cohort study. *BMJ Open*, 3(7), e003139. https://doi.org/10.1136/bmjopen-2013-003139

Lam, W. Y., & Fresco, P. (2015). Medication Adherence Measures: An Overview. *BioMed Research International*, 217047.

Lin, C., Clark, R., Tu, P., Bosworth, H. B., Zullig, L. L., Lin, C., & Clark, R. (2017). Breast cancer oral anti-cancer medication adherence : a systematic review of psychosocial motivators and barriers. *Breast Cancer Research and Treatment*, 165(2), 247–260. https://doi.org/10.1007/s10549-017-4317-2

Lopez-martin, C., Siles, M. G., Alcaide-Garcia, J., & Felipe, V. F. (2014). Role of clinical pharmacists to prevent drug interactions in cancer outpatients : a single-centre experience. *International Journal of Clinical Pharmacy*, 36(6), 1251–1259. https://doi.org/10.1007/s11096-014-0029-4

Maleki, S., Alexander, M., Fua, T., Liu, C., Rischin, D., & Lingaratnam, S. (2019). A systematic review of the impact of outpatient clinical pharmacy services on medication-related outcomes in patients receiving anticancer therapies. *Journal of Oncology Pharmacy Practice*, 25(1), 130–139. https://doi.org/10.1177/1078155218783814

McCue, D. A., Lohr, L. K., & Pick, A. M. (2014). Improving adherence to oral cancer therapy in clinical practice. *Pharmacotherapy*, 34(5), 481–494. https://doi.org/10.1002/phar.1399

Puspitasari, A. W., Kristina, S. A. R. I., & Prabandari, Y. S. (2021). Overview of Adherence and Influencing Factors to Capecitabine In Cancer Patients : Systematic Review. *International Journal of Pharmaceutical Research*, 13(1), 3106–3118.

Reigner, B., Blesch, K., & Weidekamm, E. (2001). Clinical Pharmacokinetics of Capecitabine. *Clinical Pharmacokinetics*, 40(2), 85–104.

Sardi, L., Idri, A., & Fernández-Alemán, J. L. (2017). A systematic review of gamification in e-Health. *Journal of Biomedical Informatics*, 71, 31–48. https://doi.org/10.1016/j.jbi.2017.05.011

Schellens, J. (2007). Clinical Pharmacology : Concise Drug Reviews Capecitabine. *The Oncologist,* 12, 152–155. https://doi.org/10.1634/theoncologist.12-2-152

Schneider, S. M., Hess, K., & Gosselin, T. (2011). Interventions to Promote Adherence with Oral Agents. *Seminars in Oncology Nursing*, 27(2), 133–141. https://doi.org/10.1016/j.soncn.2011.02.005

Simons, S., Ringsdorf, S., Braun, M., Mey, U. J., Schwindt, P. F., Ko, Y. D., Schmidt-Wolf, I., Kuhn, W., & Jaehde, U. (2011). Enhancing adherence to capecitabine chemotherapy by means of multidisciplinary pharmaceutical care. *Supportive Care in Cancer*, 19(7), 1009–1018. https://doi.org/10.1007/s00520-010-0927-5

Spoelstra, S. L., & Given, C. W. (2011). Assessment and Measurement of Adherence to Oral Antineoplastic Agents. *Seminars in Oncology Nursing*, 27(2), 116–132. https://doi.org/10.1016/j.soncn.2011.02.004

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020 : GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, 71, 209-249. https://doi.org/10.3322/caac.21660

Timmers, L., Swart, E. L., Boons, C. C. L. M., Mangnus, D., van de Ven, P. M., Peters, G. J., Boven, E., & Hugtenburg, J. G. (2012). The use of capecitabine in daily practice: A study on adherence and patients' experiences. *Patient Preference and Adherence,* 6, 741–748. https://doi.org/10.2147/PPA.S36757

Vacher, L., Thivat, E., Poirier, C., Mouret-Reynier, M. A., Chollet, P., Devaud, H., Dubray-Longeras, P., Kwiatkowski, F., Durando, X., van Praagh-Doreau, I., & Chevrier, R. (2020). Improvement in adherence to Capecitabine and Lapatinib by way of a therapeutic education program. *Supportive Care in Cancer,* 28(7), 3313–3322. https://doi.org/10.1007/s00520-019-05144-x

Viswanathan, M., Golin, C. E., Jones, C. D., Jones, C. D., Blalock, S. J., Wines, R. C. M., Coker-Schwimmer, E. J. L., Rosen, D. L., Sista, P., & Lohr, K. N. (2012). Interventions to Improve Adherence to Self-administered Medications for Chronic Diseases in the United States A Systematic Review. *Annals of Internal Medicine,* 157(11), 785–795.

Wagstaff, A. J., Ibbotson, T., Goa, K. L., Muggia, F. M., York, N., York, N., & Papamichael, D. (2003). A Review of its Pharmacology and Therapeutic Efficacy in the Management of Advanced Breast Cancer. *Drugs*, 63(2), 217–236.

Walko, C. M., Lindley, C., Hill, C., & Carolina, N. (2005). Capecitabine : A Review. *Clinical Therapeutics*, 27(1), 23–44.

Wick, J. A., & Elswick, B. M. (2018). Impact of Pharmacist Delivered Education on Early Parent Awareness and Perceptions Regarding Human Papillomavirus (HPV) Vaccination in the Community Pharmacy Setting in West Virginia. *INNOVATIONS in Pharmacy*, 9(3), 8. https://doi.org/10.24926/iip.v9i3.1396

Wood, L. (2012). A review on adherence management in patients on oral cancer therapies. *European Journal of Oncology Nursing,* 16(4), 432–438. https://doi.org/10.1016/j.ejon.2011.10.002

World Health Organization. (2003). Adherence to long-term therapies: Evidence for action. World Health Organization.

Zullig, L. L., Affairs, V., Peterson, E. D., Bosworth, H. B., Affairs, V., Internal, G., Carolina, N., & Sciences, B. (2015). Ingredients of Successful Interventions to Improve Medication Adherence. *JAMA*, 310(24), 2611–2612. https://doi.org/10.1001/jama.2013.281078.8