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Original research paper

Exploring adherence in patients with advanced breast cancer: focus on CDK4/6 inhibitors

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ABSTRACT

Treatment adherence is crucial for optimal outcomes in advanced breast cancer, but can be challenging due to various factors, *i.e.* patients' attitudes and behavior upon diagnosis, and complex therapies with high adverse effect rates. Our aim was to explore the adherence to oral anticancer medications (OAM) in women with advanced breast cancer, focusing on cyclin-dependent kinase 4 and 6 inhibitors (CDKI), and identify factors associated with the adherence. We conducted a cross-sectional study at the University Hospital Centre Zagreb, Croatia, involving women with stage IV advanced breast cancer receiving OAM. Data collection included a questionnaire assessing socio-demographic and clinical information, Beck Depression Inventory-II for depressive symptoms, Medication Adherence Report Scale (MARS-5) for adherence to OAM, and Beliefs about Medicines Questionnaire. Plasma concentrations of CDKI were confirmed by LC-MS/MS in three randomly selected participants. A total of 89 women were included. The most prescribed OAMs were anti-estrogen (71.3 %) and CDKI (60.9 %). MARS-5 scores (mean: 24.1 ± 1.6) correlated with CDKI plasma concentrations. Forgetfulness was the primary reason for non-adherence (25.9 %). Women receiving CDKI ($p = 0.018$), without depressive symptomatology ($p = 0.043$), and with more positive beliefs about medicines were more adherent ($p < 0.05$). This study enhances understanding of medication adherence in advanced breast cancer and identifies influential factors.

Keywords: advanced breast cancer, oral anticancer therapy, CDK 4/6 inhibitors, adherence, depressive symptoms, beliefs about medicines

INTRODUCTION

In the past decade, there has been a significant increase in the availability and use of oral anticancer medications (OAMs), especially for breast cancer (1). The use of OAMs

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improves the patient's quality of life by reducing hospital stays and provides a greater sense of control over treatment while guaranteeing the treatment efficacy (2).

Although OAMs are more convenient for patients and provide the opportunity for treatment at home, sufficient patient education, safe medication handling, timely prescription filling, monitoring of adverse effects, adherence, and persistence have become major challenges in routine oncological practice (3, 4). It has been emphasized that medication adherence is a key precondition of the evidence-based therapies' effectiveness, but also one of the major obstacles in treating chronic diseases, cancer not being an exemption (5). Although the ease of taking medicine at home might be expected to improve patients' adherence, there are also concerns that some patients' management of their disease and medicines get worse when not supervised or monitored by healthcare professionals (1). Therefore, the reliability and applicability of direct (*i.e.* quantifying drug concentration levels in serum) and indirect methods (*i.e.* patient self-reported adherence measured by validated scales) for measuring adherence have been widely discussed (6, 7).

The patient is considered non-adherent if doses are missed, extra doses are taken or doses are taken in the wrong quantity or at the wrong time (8). Non-adherence is associated with disease progression, lower quality of life, and premature death, thus it is vital for patients with cancer to adhere to OAMs therapy (9). Prior studies of OAM adherence have found wide variability of adherence rates from 16 to 100 % (8, 10–12).

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths in women worldwide (13). As many breast cancer OAMs are used for up to a decade, long-term adherence becomes a critical aspect of continued breast cancer clinical care (1). However, literature data shows that adherence to long-term oral therapy for breast cancer is suboptimal and continues to decrease over time (12, 14–19).

Hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer is responsible for approximately 65 % of all metastatic breast tumours with endocrine therapy (ET) as a preferred option for treatment (20). However, studies have shown that after four years only 50 % of women with early breast cancer, adhere to their ET doses as prescribed (15), while higher adherence rates were observed in metastatic disease (20). Adjuvant therapy, prescribed for early breast cancer, is usually administered for five to ten years, whereas in the case of metastatic breast cancer, the duration of treatment is not easily defined and typically continues until disease progression or if unacceptable toxicity occurs. Many adjuvant studies reported that up to half of breast cancer survivors discontinue ET before completing the recommended treatment course (19, 21, 22). According to literature data, non-adherence to ET was associated with extremes of age (≤ 45 and ≥ 85 years), higher out-of-pocket costs per prescription, higher comorbidity index, and severity of adverse effects (15, 23, 24).

Since their first approval by the Food and Drug Administration (FDA) in February 2015, the introduction of cyclin-dependent kinase 4 and 6 inhibitors (CDKI) in combination with ET has made a big impact on the treatment of HR+, HER2- metastatic breast cancer and has become the new 'standard of care' first-line treatment showing significant improvement in patient progression-free survival and overall survival (25, 26). Given that it is a new therapy recently introduced in clinical practice, there is limited published real-world data, and to the best of our knowledge only one study describing adherence to treatment with palbociclib (27). Further investigation is required to identify factors associated with (non)adherence to CDKI.

So far, studies of adherence to breast cancer treatment have mainly focused on early--stage patients. However, the reported results may not generalize to patients with metastatic/advanced breast cancer (28).

Therefore, we conducted an observational, cross-sectional study aiming to explore adherence in patients with advanced breast cancer and to determine the factors associated with non-adherence, particularly the association with patients' beliefs about medicines and depressive symptoms. Our study aimed to explore adherence in patients with advanced breast cancer no matter which OAM they were prescribed, but in our analysis, we focus on the newer therapy with limited previously published data, CDKI therapies. In addition to measuring adherence with a validated scale, we also employed our previously developed LC-MS/MS method for determining plasma concentrations of CDKI in three selected patients (29). This served as a verification for the indirect self-reported adherence measurement, as well as a piloting of our novel analytical method for the purposes of CDKI direct adherence monitoring.

EXPERIMENTAL

This cross-sectional study was conducted at the Department of Oncology, University Hospital Centre Zagreb, Croatia, the largest hospital in Croatia and the teaching hospital of the University of Zagreb. Eligible patients visiting the oncologist were asked to participate in the study. Patients signed informed consent forms before completing the questionnaire. The investigator read the questions to the patients who were not able to fill out the questionnaire by themselves due to their health conditions. The study was approved by the Ethics Committee of the University of Zagreb Faculty of Pharmacy and Biochemistry, and the Ethics Committee of the University Hospital Centre Zagreb. The study was conducted in accordance with the Declaration of Helsinki. Data were collected from October 2021 to February 2022.

Study population

Women aged 18 years or older with advanced breast cancer (stage IV) who were treated with OAM were eligible for the study. Non-inclusion criteria were cancer stage 0-III and patients with cognitive impairment.

Instruments

The questionnaire consists of five parts, encompassing socio-demographic and clinical data, the Medication Adherence Report Scale (MARS-5), the Beliefs about Medicines Questionnaire (BMQ), and the Beck Depression Inventory-II (BDI-II).

Socio-demographic data included information about age, level of education (finished primary, secondary, or tertiary education), partner status (0 = not in a relationship, 1 = in a relationship), household status (0 = living alone, 1 = living with other people), work status (employed, unemployed, on sick leave, students, working in the household without payment, retired), monthly household income, body mass index (BMI), smoking (not at all, sometimes, every day) and alcohol consumption (1 = never to 9 = every day).

The part of the questionnaire on clinical data was utilised to gather information on various factors, including age at which the cancer was diagnosed, disease duration, cancer

stage, treatment received and type of surgical procedure (if applicable), current therapy for breast cancer, and its adverse effects. In addition, the questionnaire captured data on the total number of medications used, use of antidepressants three months prior to study enrolment, benzodiazepine use in the previous week, and history of adverse reactions to any medication.

Medication adherence report scale (MARS-5)

The Medication Adherence Report Scale (MARS-5) (34) was used for assessing adherence to cancer therapy. MARS-5 is a self-reported instrument with five items that describe the range of non-adherent behaviour. Each item is rated on a five-point Likert scale ranging from "Always" to "Never". Total scores range from 5 to 25 points, higher scores indicate better adherence.

Beliefs about Medicines Questionnaire (BMQ)

We employed both Specific and General Beliefs about Medicines Questionnaire (BMQ-Specific, and BMQ-General, respectively). BMQ-Specific consists of two subscales, a (1) Necessity (five items) and a (2) Concerns scale (six items). They measure patients' beliefs about the necessity of using OAM and patients' concerns about OAM.

BMQ-General used four subscales: (1) Overuse (three items), (2) Harm (five items), (3) Benefit (four items), and (4) Sensitivity (five items). They assess the following concepts: (1) beliefs about the extent to which medicines are overused in society, (2) concerns about the potentially harmful effects of medicines, (3) beliefs about the general benefits of medicines, and (4) perceptions of personal susceptibility to the effects of medicines. Answers to positive statements (Benefit and Necessity subscales) are scored on a five-point Likert scale (where 1 = strongly disagree, 2 = disagree, 3 = uncertain, 4 = agree and 5 = strongly agree) with scores ranging from 3 to 25, higher scores indicate stronger beliefs about the particular concepts (31, 32). Answers to negative statements (Concerns, Overuse, Sensitivity, and Harm subscales) were assigned points in the opposite direction, and the assessment "strongly agree" was assigned 1 point, to the assessment "strongly disagree" which was assigned 5 points. This modification was necessary to keep patients' beliefs direction. Based on whether participants scored above or below the scale midpoint for BMQ scales, they were categorised as having positive or negative attitudes towards a particular concept (33). Both MARS-5 and BMQ questionnaires were adapted to the Croatian language in accordance with 'Principles of good practice for the translation and cultural adaptation process for patient-reported outcome measures' (34) and their use was approved by Horne.

The Cronbach's alpha (α) indicated that all scale measures were internally consistent in the study sample with high values of α (BMQ-specific, concern) = 0.763, α (BMQ-specific, necessity) = 0.885, α (BMQ-general, benefit) = 0.806, α (BMQ-general, sensitivity) = 0.871 and low values of α (MARS) = 0.587, α (BMQ-general, overuse) = 0.668, and α (BMQ-general, harm) = 0.692.

Beck Depression Inventory-II (BDI-II)

BDI-II is a self-reported instrument for indicating the presence and degree of depressive symptoms consistent with the Diagnostic and Statistical Manual of Mental Disorders,

Fourth Edition (DSM-IV). It consists of 21 items evaluating 21 symptoms of depression, each item is rated on a four-point scale, total score ranging from 0 to 63 and higher scores mean higher severity of symptoms (35). BDI-II in the Croatian language was provided by Naklada Slap. According to Croatian standardization, the cut-off score for depressive symptomatology is 12 points. Cronbach's alpha reliability for BDI-II in this study was 0.941.

Quantitative determination of CDK4/6 inhibitors' plasma concentrations

This study also aimed to pilot a novel method for quantification of CDKI in patient plasma. We used CDKI concentration measurements as a verification technique for determining adherence. For that purpose, blood samples were collected from three randomly selected participants of the study who were prescribed CDKI.

Blood samples were collected in tubes containing K2 EDTA anticoagulant. Plasma, obtained by centrifugation, was stored at –80 °C. Before the analysis, the samples (50 μL) were deproteinised with acetonitrile (200 μL), evaporated (200 μL), and redissolved in 65 % methanol (50 μL). The analyses were performed on a Phenomenex Kinetex biphenyl column (150 × 4.6 mm, 2.6 μm) with the mobile phase consisting of water and acetonitrile containing 0.1 % formic acid in gradient elution. The patient samples were analysed using Agilent 1290 Infinity II UHPLC system coupled to a QTOF mass spectrometer, with the following mass transitions monitored for quantification: m/z 435.27 → 322.14 for ribociclib, 507.28 → 393.16 for abemaciclib, and 448.25 → 380.18 for palbociclib, as previously described (29).

Concentrations were measured at several time points after CDKI dose administration during the steady state. Minimal and maximal concentration (C_{min}, C_{max}), time to achieving C_{max} (T_{max}), as well as the area under the concentration-time curve ($AUC_{0\text{-}24\ h}$) were assessed from the obtained data using the PK solver Excel extension (linear trapezoidal model for non-compartmental analysis of plasma data after extravascular input).

Statistical analysis

All statistical analyses were run in IBM SPSS (version 22.0, Armonk, NY, 2013). First, we examined descriptive statistics including frequencies, means, medians, IQR, standard deviations, normality of distributions (Kolmogorov-Smirnov test), and reliabilities. Categorical variables were presented as absolute and relative numbers (percentages). Student's *t*-test for normally distributed data and Mann-Whitney test for data deviating from normal distribution were used to test differences between two groups, and ANOVA was used to compare more than two groups, with a post hoc LSD test. Categorical data were analysed using the Chi-square test. Statistical significance was set at $p < 0.05$. Missing data were not included in the statistical analysis.

RESULTS AND DISCUSSION

Sociodemographic and clinical characteristics of the participants

During the study period, a total of 89 participants were recruited. The mean age was 58.7 ± 13.6 years (age range 33–87 years) and all participants were females. The mean age

when diagnosed with breast cancer was 51.0 ± 13.8 years (age range 24–87 years) and the median duration of breast cancer since diagnosis was 6 (IQR 2.6–11.4) years (age range 0.5–25 years). Out of the participants, only 21 (23.6 %) confirmed that they had been diagnosed with stage IV breast cancer. A majority 57 (64 %) were unaware of the stage of their breast cancer, while others reported the incorrect stage.

Most of the participants previously received breast cancer treatment including chemotherapy 74 (83.1 %), surgical treatment 68 (76.4 %), radiation therapy 58 (65.2 %), or ET 50 (56.2 %). The most frequent previous breast cancer surgical treatments included mastectomy 43 (48.3 %) and axillary lymph node dissection 42 (47.2 %). A total of 53 (60.9 %) patients received a combination of CDKI and ET whereas 34 (39.1 %) patients received other OAMs not including CDKI. The most frequent combination of CDKI and ET was palbociclib and fulvestrant 13 (14.9 %), followed by ribociclib and letrozole 12 (13.8 %), ribociclib and fulvestrant 9 (10.3 %). Other medications used in breast cancer treatment without CDKI included: capecitabine 5 (5.6 %), ibandronic acid 4 (4.5 %) and letrozole 3 (3.4 %), followed by zoledronic acid 2 (2.3 %), olaparib 2 (2.3 %), anastrozole 2 (2.3 %), tamoxifen 2 (2.3 %) and combination of fulvestrant and alpelisib 2 (2.3 %).

The median number of all medications used was 5 (IQR 3-6). Antidepressants were prescribed to 10 (11.2 %) participants at least three months prior to study enrolment and 24 (27.9 %) were using benzodiazepines in the last week. The most common adverse effects during the current breast cancer treatment included hair loss 32 (36.4 %) and bone and/or joint pain 30 (34.1 %). Less than half of the participants 37 (41.6 %) experienced adverse effects previously. Detailed sociodemographic and clinical characteristics of the participants are presented in Table I and the current breast cancer treatment of the participants in Table II.

Table I. Sociodemographic and clinical characteristics of study participants

Characteristic	Number of patients (%)
Age, years, mean ± SD[a] (min – max)	58.7 ± 13.6 (33–87)
Level of education (%)	
Primary school	6 (6.7)
Secondary school	50 (56.2)
University, Academy	29 (32.6)
Postgraduate education (Specialist degree, Master's degree, Doctorate)	4 (4.5)
Partner status (marital or extra-marital) (%)	
Without partner	26 (29.2)
With partner	63 (70.8)
Living in the household alone or with somebody (%)	
Alone	16 (18.0)
With somebody	73 (82.0)

Number of persons in the household, median[a] (IQR)	2 (IQR 2–4)
Employment status (%)	
Employed	23 (25.8)
Unemployed	8 (9.0)
Sick leave	12 (13.5)
Run the household, work in/around the house	3 (3.4)
Retired	43 (48.3)
Number of days on sick leave due to breast cancer in the last 6 months (%)	
0 days	8 (9.0)
1–3 days	2 (2.2)
Up to 2 weeks	2 (2.2)
More than 1 month	22 (24.7)
Retired/ unemployed	55 (61.8)
Number of days spent in hospital due to breast cancer in the last 6 months (%)	
0 days	63 (70.8)
1–3 days	9 (10.1)
More than 3 days	17 (19.1)
Monthly income of the household[b] (%)	
Up to 524.68 €	14 (17.3)
Up to 1049.37 €	29 (35.8)
Up to 1574.05 €	18 (22.2)
Up to 2098.73 €	7 (8.6)
More than 2098.73 €	13 (16.0)
Smoking (%)	
Current smokers	13 (14.6)
Alcohol intake in the last year** (%)	
Less than once a month	62 (69.7)
Less than once a week	15 (19.1)
At least once per week 1–2 days a week	10 (11.3)
Age when diagnosed with breast cancer, years, mean ± SD[a]	51.0 ± 13.8
Breast cancer duration, years, median (IQR)[a]	6 (IQR 2.6–11.4)
Breast cancer stage, as reported by participants (%)	
Reported to have breast cancer stage I, II, or III	11 (12.4)
Reported to have breast cancer stage IV	21 (23.6)
Did not know the answer	57 (64.0)

Previous breast cancer treatment[c] (%)	
No previous treatment	2 (2.2)
Surgical treatment	68 (76.4)
Chemotherapy	74 (83.1)
Radiation therapy	58 (65.2)
Biological therapy	12 (13.5)
Endocrine therapy	50 (56.2)
Don't know	1 (1.1)
Other treatment	5 (5.6)
Type of previous breast cancer surgical treatment[c] (%)	
No previous surgical treatment	18 (20.2)
Lumpectomy	18 (20.2)
Mastectomy	43 (48.3)
Bilateral mastectomy	7 (7.9)
Axillary lymph node dissection	42 (47.2)
Other treatment	19 (21.3)
Total number of medications used, median (IQR)	5 (IQR 3–6)
Use of antidepressants 3 months prior to study enrollment (%)	
No	79 (88.8)
Yes	10 (11.2)
Use of benzodiazepines in the last week[b] (%)	
No	62 (72.1)
Yes	24 (27.9)
Previous adverse effects (%)	
No	52 (58.4)
Yes	37 (41.6)

[a] normally distributed interval variables are shown as mean ± SD, and non-normally distributed as median (IQR); [b] missing values: monthly income of the household (n = 8), alcohol intake in the last year (n = 2), use of benzodiazepines in the last week (n = 3); [c] possible multiple answers

Medication adherence measured by the MARS-5 scale

Our study found a high adherence rate among metastatic breast cancer patients, with the average MARS-5 score being 24.1 ± 1.6, which could serve as a benchmark for optimal adherence in this patient population and encourage efforts to improve medication adherence in patients with advanced breast cancer. A total of 60 (67.4 %) women reported never missing the dose and were categorised in the high adherence group with maximum MARS-5 scores. We believe that the patient-oncologist relationship and frequent follow-up (usually every four weeks) may be important contributors to adherence in our sample. Both factors are recognised as a strength of the health centre where the study was conducted.

Table II. Current breast cancer treatment in participants of the study

Anticancer therapy[a]	Number of patients (%)
CDK 4/6 inhibitor	53 (60.9)
Other anticancer therapy	34 (39.1)
Type of CDK 4/6 inhibitor used in treatment of breast cancer (%)	
Ribociclib	25 (28.7)
Palbociclib	21 (21.3)
Abemaciclib	7 (8.1)
Prescribed combinations including CDK4/6 inhibitors[a]	
Letrozole + ribociclib	12 (13.8)
Anastrozole + ribociclib	3 (3.4)
Fulvestrant + ribociclib	9 (10.3)
Letrozole + palbociclib	5 (5.7)
Anastrozole + palbociclib	2 (2.3)
Fulvestrant + palbociclib	13 (14.9)
Letrozole + abemaciclib	4 (4.6)
Anastrozole + abemaciclib	2 (2.3)
Fulvestrant + abemaciclib	1 (1.1)
Exemestan + ribociclib/palbociclib/abemaciclib	2 (2.3)
Other	34 (39.1)
Other oral anticancer treatment[b]	
Capecitabine	5 (5.6)
Ibandronic acid	4 (4.5)
Letrozole	3 (3.4)
Zoledronic acid	2 (2.3)
Olaparib	2 (2.3)
Anastrozole	2 (2.3)
Tamoxifen	2 (2.3)
Combination of fulvestrant and alpelisib	2 (2.3)
Adverse effects experienced during the current breast cancer treatment	
Bone pain and/or joint pain	30 (34.1)
Hair loss	32 (36.4)
Stomatitis	8 (9.1)
Nausea	20 (22.7)
Diarrhoea	20 (22.7)
Vomiting	7 (8)
Constipation (obstipation)	7 (8)
Other	29 (33)

[a] Missing data: Anticancer therapy ($n = 2$), Prescribed combinations including CDK4/6 inhibitors ($n = 2$), Other oral anticancer treatment ($n = 1$); [b] the less frequently prescribed other OAMs ($n = 1$; 1.1 %) were: exemestane, vinorelbine, combinations of fulvestrant and vigabatrin, letrozole and trastuzumab, fulvestrant and neratinib, exemestane and goserelin, neratinib and capecitabine, vinorelbine and neratinib, tamoxifen and goserelin, letrozole and ibandronic acid, letrozole and goserelin, anastrozole, trastuzumab, pertuzumab and zoledronic acid.

This observation is also supported by previous findings from a review of systematic reviews, which identified that effective healthcare provider-patient communication and relationship is one of the multifactorial determinants of good adherence, *i.e.* quality, duration, and frequency of interaction between the patient and the doctor (41).

The primary cause of non-adherence observed in our study was forgetfulness (nonintentional non-adherence), with 23 (25.9 %) participants reporting that they sometimes 7 (7.9 %) or rarely 16 (18 %) forgot to take their therapy. Moreover, 19 (21.3 %) participants sometimes or rarely missed their dose. These findings are consistent with prior research conducted among women with breast cancer (13, 42–43). Although studies indicate that patients consider both unintentional and intentional dimensions of non-adherence to therapeutic regimens, more evidence points towards interventions supporting non-intentional non-adherence. This is supported by findings in other patient groups, such as those with asthma and hypertension, where the strength of the patient's routine or habit for taking their medication has been shown to predict unintentional non-adherence (44, 45). In addition, a cross-sectional survey conducted among over 24,000 adults with chronic illnesses such as hypertension, diabetes mellitus, and hyperlipidaemia, revealed alarming results: 62 % of the participants forgot to take their medications, and 37 % ran out of their medications within a year (46).

Considering our findings, we believe that strategies to improve unintentional adherence should be implemented in our sample, despite the high reported adherence. Bandiera *et al.* demonstrated that omitting even a single dose of palbociclib can impact clinical outcomes, such as the occurrence of adverse drug reactions (27). Some patients try to compensate for missed doses by taking an additional dose at the end of the cycle, which shortens the off phase, decreases recovery time, and consequently, increases the risk of severe neutropenia during the next cycle.

Patients characteristics according to adherence level

Characteristics of patients according to their levels of adherence are shown in Table III. In our sample, a statistically significant difference in adherence was found only between patients who received the combination of CDKI with ET and patients who received other OAMs ($p = 0.018$), suggesting patients on CDKI therapy were more adherent. Significantly higher adherence in patients taking CDKI could be explained by patients' awareness that they are prescribed newer, high-cost drugs for which they need approval from the Hospital Drug Committee. In Croatia, the Hospital Drug Committee is responsible for reviewing and approving the use of certain medications, including high-cost or specific drugs. To be eligible for reimbursement of CDKI, patients must meet certain criteria, including having a confirmed diagnosis of HR+, HER2- advanced or metastatic breast cancer, and having previously received ET. Patients must also have evidence of disease progression after prior treatment with ET. Patients included in our study got approval from the Hospital Drug Committee for prescribed CDKI and the cost of CDKI was reimbursed by the Croatian Institute for Health Insurance. This may not be the case in other countries and could have an influence on adherence. For example, in the United States, the cost of CDKIs for the patient is very high, with prices ranging from around $10,000 to $15,000 per month of treatment. While some patients may be able to access these medications through insurance coverage or patient assistance programs, others may need to pursue treatment due to cost concerns (47).

Table III. Characteristics of patients according to their levels of adherence

Characteristic	The number of patients with higher adherence (60/89) MARS-5 score = 25	The number of patients with lower adherence (20/89) MARS-5 score 20–24	*p*
Age, years, mean ± SD	60.1 ± 13.3	56.0 ± 13.1	0.196
Level of education (%)			
Primary or secondary school	46.1 %	16.9 %	0.128
University or postgraduate education	21.3 %	15.7 %	
Partner status (marital or extra-marital) (%)			
Without partner			
With partner	16.9 %	12.4 %	0.209
	50.6 %	20.2 %	
Living in the household alone or with somebody (%)			
Alone	9 %	9 %	0.101
With somebody	58.4 %	23.6 %	
Monthly income (%)			
Up to 787,02 €	22.2 %	13.6 %	0.803
787,02–1574,05 €	27.2 %	12.3 %	
More than 1574,05 €	17.3 %	7.4 %	
Breast cancer duration, years, mean ± SD	7.4 ± 5.7	7.5 ± 5.9	0.933
Total number of medications used, mean ± SD	5.3 ± 3.2	4.3 ± 2.9	0.144
Current breast cancer treatment (%)	51.7 %	16.9 %	0.018
CDKI + ET	15.7 %	15.7 %	
Other			
Adverse effects experienced during the current breast cancer treatment (%)	14.8 %	6.8 %	0.885
	52.3 %	26.1 %	
No adverse effects			
One and/or more adverse effects			
Previous adverse effects (%)	41.6 %	16.9 %	0.372
No	25.8 %	15.7 %	
Yes			

[a] *p*-values obtained using Student's *t*-test, Mann Whitney test, or Chi-square test, as appropriate; CDKI – cyclin-dependent kinase 4 and 6 inhibitors, ET – endocrine therapy

Similarly, in some countries without universal healthcare coverage or national health insurance programs, patients may need to pay out-of-pocket for the cost of CDKI and this could be a risk for their lower adherence. Previous studies revealed that lack of drug insurance coverage and high patient out-of-pocket expenses can reduce adherence to prescribed medications in the way they stop filling prescriptions, delay prescriptions, or take less frequent and smaller doses to make them last longer (48–51). Factors beyond cost alone may influence adherence rates. For example, adverse effects associated with different treatment approaches could also contribute to the differences observed. While our study did not directly investigate the impact of adverse effects on adherence, it is plausible that CDKI treatments are associated with a more favourable adverse effect profile compared to alternative therapies. Real-world safety data on CDKI provided by Husinka *et al.* demonstrated that over 60 % of the study population did not experience an adverse drug event, potentially contributing to patients' persistence with the therapy (52). Additionally, Marra *et al.* found that patients receiving CDKI, despite experiencing alopecia, exhibited prolonged treatment durations and maintained a very good quality of life (53).

Beliefs about medicines and association with adherence to oral anticancer treatment

The analysis of data collected *via* BMQ revealed that all means of scale scores were above the scale midpoints, indicating positive patients' beliefs about their anticancer

Table IV. Patient beliefs about medicines according to their levels of adherence

BMQ		Participants' scores (scale midpoint)	Percentage above (↑) or below (↓) the scale midpoint[a]	The number of patients with higher adherence participants scores (MARS-5 score = 25)	The number of patients with lower adherence participants scores (MARS-5 score 20–24)	*p*
BMQ-General	Harm, mean ± SD (scale range 5–25)	17.3 ± 3.2 (midpoint 15)	↑ 13.3 %	17.7 ± 3.4	16.5 ± 2.8	0.109
	Overuse, mean ± SD (scale range 3–15)	9.6 ± 2.5 (midpoint 9)	↑ 11.1 %	10.1 ± 2.5	8.8 ± 2.3	0.024
	Benefit, mean ± SD (scale range 4–20)	18.2 ± 4.4 (midpoint 12)	↑ 33.3 %	17.0 ± 2.1	16.2 ± 2.7	0.138
	Sensitivity, mean ± SD (scale range 5–25)	16.8 ± 2.3 (midpoint 15)	↑ 22.7 %	18.9 ± 4.5	16.9 ± 3.8	0.043
BMQ-Specific	Necessity, mean ± SD (scale range 5–25)	19.9 ± 3.5 (midpoint 15)	↑ 33.3 %	20.2 ± 3.4	19.3 ± 3.8	0.317
	Concerns, mean ± SD (scale range 6–30)	19.5 ± 5.0 (midpoint 18)	↑ 11.1 %	20.3 ± 4.5	17.9 ± 5.7	0.036

[a] Scores above the midpoint represent positive attitudes towards medications and scores below the midpoint represent negative attitudes; *p*-values obtained using Student's *t*-test

therapy as well as about medications in general (Table IV). The highest scores were obtained on the BMQ-Specific Necessity scale (mean 19.9 ± 3.5) and on the BMQ-General Benefit scale (mean 18.2 ± 4.4) both being 33.3 % above the scale's midpoint. Patients also had strong perceptions of personal non-susceptibility to the effects of medicines (mean 16.8 ± 2.3; 22.7 % above the scale's midpoint). A statistically significant difference in the strength of patient beliefs about medicines according to their levels of adherence was found between the high-adherent group and lower-adherent group for BMQ-General, Overuse scale ($p = 0.024$) and Sensitivity scale ($p = 0.043$), and BMQ-Specific, Concerns scale ($p = 0.036$).

Our analysis confirmed that the higher-adherent group had stronger beliefs that medications were not being overused, considered themselves less sensitive to medicines, and had fewer concerns about their current antitumor therapy. These findings suggest that addressing patients' beliefs about medicines could be an important strategy for improving adherence to OAM.

Depressive symptoms and association with adherence to oral anticancer treatment

The incidence of depressive symptoms in the participants of this study was pretty high, with 37 (41.6 %) participants scoring 12 or more, which is according to Croatian standardization the cut-off score for mild depression. Patients' depressive symptoms according to their levels of adherence are shown in Fig. 1.

The data reveals that within the group of lower adherent patients, there was a significantly higher prevalence of patients exhibiting depressive symptomatology (17 (19.1 %) with depressive symptoms) compared to those without depressive symptoms (12 (13.5 %) with no depressive symptoms) ($p = 0.043$). Conversely, within the high adherence group, a higher percentage of patients were found to have no depressive symptoms (40 (44.9 %) with

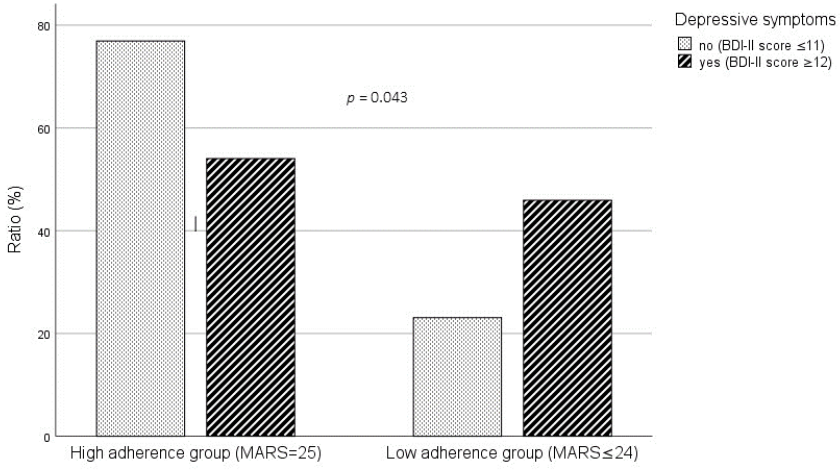

Fig. 1. Patient depressive symptoms according to their levels of adherence.

no depressive symptoms) compared to those with depressive symptoms (20 (22.5 %) with depressive symptoms).

Our findings that depressive symptoms were associated with lower adherence to treatment among breast cancer patients are consistent with previous research in other populations with chronic diseases (54, 55). This highlights the importance of recognizing and addressing depressive symptoms in breast cancer patients. In our sample, 37 (41.6 %) women had depressive symptoms, which is alike findings from other studies (35.6–48 %) (56–58).

Non-adherence due to depression can have a negative impact on treatment outcomes, including increased risk of recurrence and mortality in breast cancer patients (59). In fact, elevated depressive symptoms have been shown to reduce the five-year survival rate of cancer patients. A meta-analysis has suggested that identifying and managing depressive symptoms in cancer patients can improve long-term adherence to adjuvant therapy, leading to better treatment outcomes (55). Additionally, patients who have received more psychotherapy consultations tend to have higher adherence rates than those who have received fewer consultations (60).

Our findings highlight the importance of involving psychiatrists and/or psychologists in the care of patients with breast cancer, as such involvement may positively impact patients' overall well-being and improve medication adherence, ultimately leading to better treatment outcomes.

Direct adherence monitoring of CDK4/6 inhibitors by LC-MS/MS

Self-reported methods for assessing medication adherence are known to overestimate adherence, particularly for expensive medications such as CDKI, where patients may not be honest about missing doses for fear of losing reimbursement approval. Therefore, it is important to develop objective methods for measuring adherence, especially for these medications. Our research team recently developed a novel method for determining the concentration of abemaciclib, palbociclib, and ribociclib in the patients' plasma, and we tested it for the first time in this sample (29). The determined drug concentrations of two patients taking ribociclib and one patient taking palbociclib are shown on time-concentration diagrams (Fig. 2). Patients were administered standard doses of CDKIs, specifically 600 mg of ribociclib or 125 mg of palbociclib once daily for 21 consecutive days, followed by a 7-day period without therapy. Pharmacokinetic data illustrative of patient adherence (C_{min}, C_{max}, T_{max}, $AUC_{0\text{-}24\,h}$) are presented in Table V.

The obtained results show that all three patients' plasma concentrations were within the expected ranges as reported in the literature (36–40). These patients were in the high--adherence group (scored 25 on the MARS scale) which is in accordance with the results obtained by the LC-MS/MS method. Although self-reported adherence scales are frequently used in clinical practice due to their ease of use, their reliability is sometimes questioned because of potential bias. Therefore, developing and implementing direct measurement of drug concentrations in the blood is of importance and represents a more objective approach for validating adherence measurements, particularly in patients whose adherence is uncertain. The results of this pilot study suggest that the developed method for determining CDKI concentrations could be useful in clinical practice. We plan to further evaluate this approach by testing it on a larger sample of patients.

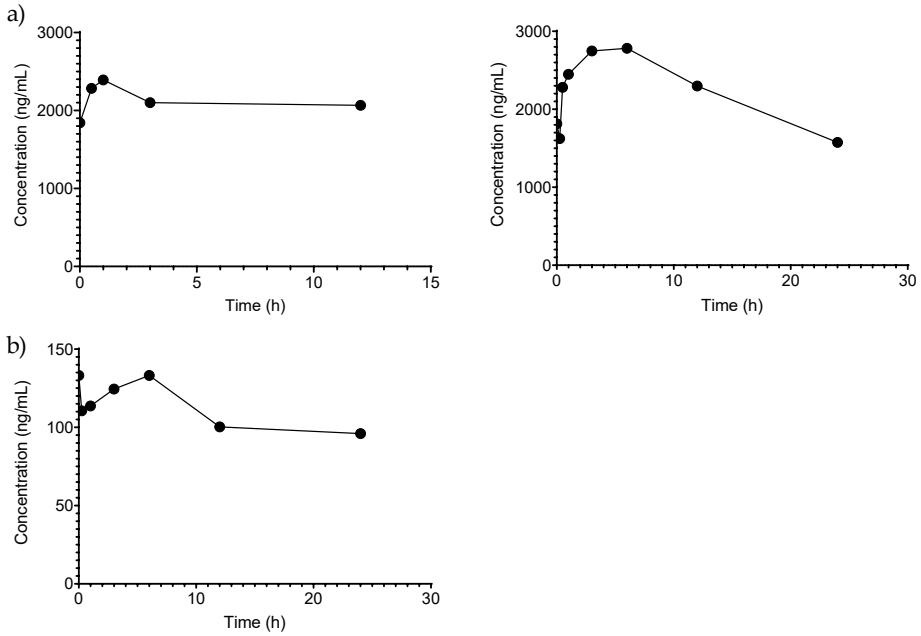

Fig. 2. Time-concentration diagrams for: a) two patients on ribociclib, and b) one on palbociclib.

Table V. Pharmacokinetic parameters for three randomly selected patients on CDKI

Pharmacokinetic parameter	Patient 1 (RIB)	Patient 2 (RIB)	Patient 3 (PAL)
C_{min} (ng mL^{-1})	1842.4	1575.7	96.0
C_{max} (ng mL^{-1})	2392.0	2782.2	133.2
T_{max} (h)	1	6	6
$AUC_{0\text{-}24\,h}$ (ng h mL^{-1})	49954.6	54075.0	2601.1

CDKI – cyclin-dependent kinase 4 and 6 inhibitors, RIB – ribociclib, PAL – palbociclib

Limitation

The present study has certain limitations. As a cross-sectional study, it does not allow for the establishment of any causal relationships. This study was conducted at a single centre, which is the largest clinic in Croatia serving patients mainly from Zagreb, but also from other regions of the country. Hence, the findings may not be generalizable to the entire population of patients with advanced breast cancer in Croatia. Additionally, the sample size of the study was relatively small, which may affect the generalizability and statistical power of the results.

While our questionnaire was comprehensive, covering aspects such as adherence, depressive symptoms, patients' beliefs about medicines, as well as sociodemographic and clinical data, we made a deliberate choice to focus solely on oral antitumor therapy, aiming to alleviate participant burden and minimize the time required for questionnaire completion. The exclusion of overall therapy data limits the holistic perspective of the patients' treatment landscape. It is essential for subsequent research to encompass a more comprehensive range of therapeutic information, including but not limited to overall treatment regimens, associated side effects, and concurrent comorbidities.

CONCLUSIONS

It is noteworthy that our study population, who were severely ill and especially those receiving new, expensive drugs, such as CDKI, demonstrated high levels of adherence. These results suggest that patients are responsible and committed to adhering to treatment when they receive the best therapy available. The high level of adherence observed in our sample is encouraging, but occasional forgetfulness remains a concern, and strategies for improving unintentional non-adherence should be implemented. Additionally, we showed that depressive symptoms and beliefs about medicine were associated with adherence in our sample, and addressing these issues may also improve adherence in patients with advanced breast cancer. Finally, it is of great importance to have reliable direct measurements of the level of adherence and this study demonstrated the use of a novel LC-MS/MS method for measuring CKDI in patients' plasma.

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Authors' contributions. – Conceptualization, M.O.H. and M.S.; methodology, M.O.H., M.S., T.S., M.B. (Martina Bago); formal analysis (statistical), M.O.H. and M.B. (Matea Baković); formal analysis (drug concentrations), L.T. and M.S.; data curation, L.B., M.K., T.S., N.D.P.; writing, original draft preparation, M.O.H., M.B. (Martina Bago), M.B. (Matea Baković); writing, review and editing, M.S. and L.T.; supervision, M.S., M.O.H.; funding acquisition, M.S. All authors read, critically reviewed, corrected and approved the final version of the manuscript.

Institutional review board statement. – Ethical approval for this study was obtained from the Ethics Committee of the University Hospital Centre Zagreb (class number 8.1-/171-2, reference number 02/21-JG, approval date: 20/8/2019) and the Ethics Committee of the University of Zagreb Faculty of Pharmacy and Biochemistry (class number 643-02/21-03/01, reference number: 251-62-03-21-50, approval date 13/12/2021). Participating subjects were free to decline participation any time during the study. Data were collected and stored under specific codes with an assurance of anonymity and data confidentiality. All methods were carried out in accordance with relevant project guidelines and regulations. The study was conducted in accordance with the Declaration of Helsinki.

Informed consent statement. – Informed consent was obtained from all subjects involved in the study.

Availability of data and materials. – The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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