

Patient Adherence to Oral Anticancer Agents

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Research Article

Keywords: Adherence, Cancer, Modified Morisky Scale, Modified Medication Adherence Scale-6, Oral anticancer drugs

Posted Date: April 8th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1417121/v1>

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Abstract

Purpose: The aim of the study was to measure the adherence to oral anticancer treatments in cancer patients using the Modified Morisky Scale (Modified Medication Adherence Scale-6, MMAS-6) which has been shown to be valid and reliable in Turkish.

Methods: This study was an observational, single-center study involving 300 cancer patients using various oral anticancer agents admitted to our outpatient clinic. Motivation and knowledge scores were calculated according to the MMAS-6.

Results: 71.3% of the patients had high motivation level, 28.7% had low motivation level, 68.7% had high knowledge level and 31.3% of the patients had low level of knowledge. The motivation and knowledge levels of the population under 65 years of age were found to be significantly higher than the geriatric population (≥ 65 years old) ($p < 0.003$ and $p < 0.001$, respectively). It was observed that the patients with higher education levels had significantly higher motivation and knowledge levels ($p < 0.0001$ for both). There was no correlation between the motivation and knowledge levels of the patients with gender, marital status, living status and stage of the disease ($p > 0.05$). In addition, the duration of drug use > 12 months and the cyclical use of drugs were also found to be significantly associated with increased motivation and knowledge levels.

Conclusion: Identifying adherence and related factors, informing patients in detail about the efficacy and toxicity of treatments are the simplest and most basic methods. Particular attention should be paid to patients aged > 65 years, patients with a low level of education and patients in the earlier stages of their treatments.

Introduction

Intravenous cytotoxic therapies have been the main treatment option in cancer care for many years but the use of oral anticancer drugs has increased, especially in recent decades. With better understanding of new signal transduction pathways, genetic, genomic and molecular alterations in cancer, molecular-based therapies, mostly in oral form, have been developed. An estimated 25–30% of the oncology drug pipeline in 2008 contained oral agents, most of which were targeted therapies. Approximately 40% of all oral anticancer medications (OAMs) were approved within the last seven years [1]. The number of patients using oral treatment options is increasing with oral chemotherapeutics, hormonal therapy agents and targeted-therapies.

This provides an advantage in terms of both patient comfort and cost. During the 2019 Coronavirus disease (COVID-19) pandemic, guidelines such as the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) recommended reducing hospitalizations as much as possible during a time when oral agents were chosen for treatment [2, 3].

In addition to these advantages of oral treatment agents, there are problems with patient compliance and persistence with oral treatment that directly affect the success of treatment. This results in patients not effectively benefiting from the valuable treatment options.

Adherence, defined as the extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency [4]. It has long been an important issue for patients with other chronic diseases such as diabetes, hypertension, heart disease, asthma, and acquired immune deficiency syndrome (AIDS) [5–10]. The cost of non-compliance to therapy in patients with chronic diseases is estimated at \$300 billion per year in the United States health care system [11]. Numerous studies have shown that good adherence to therapy is associated with a reduction in health care costs [12]. Techniques used to measure adherence are inadequate [13]. Various methods have been studied in cancer patients, but there is no consensus on a “gold standard” for measuring adherence [14]. However, in the era of molecularly targeted drugs, some studies show treatment resistance and failure even with minor deviations from full compliance, as demonstrated in chronic myeloid leukemia (CML) [15].

In this study, we aimed to measure cancer patients’ adherence to oral anticancer drugs using the Modified Morisky Scale (Modified Medication Adherence Scale-6, MMAS-6), which has been shown to be valid and reliable in Turkish [16].

Methods

Study population

We conducted a single-centre observational study to investigate treatment adherence and factors influencing this adherence in 300 patients receiving various oral anticancer drugs such as oral chemotherapeutic agents (capecitabine, vinorelbine, temozolomide, etoposide) oral tyrosine kinase inhibitors (sorafenib, ribociclib, regorafenib, pazopanib, axitinib, sunitinib, imatinib, erlotinib, alectinib, everolimus) and oral hormone therapies (tamoxifen, letrozole, anastrozole, enzalutamide, exemestane, bicalutamide, abiraterone).

Study tool

The records of patients using OAMs were examined, and the amount of medication remaining was reviewed in face-to-face interviews. A short, easy-to-use, reliable 6-item self-report questionnaire, called MMAS-6, validated in Turkish, was used to assess patients’ adherence to treatment. The questions were answered with “yes” or “no”. When scoring the questionnaire, for questions 2 and 5, “yes” is 1 point, “no” is 0 points; for the other questions, “yes” is 0 points, “no” is 1 point. If the total score of questions 1,2 and 6 is “0” or “1”, it means low motivation level, > 1 means high motivation level. If the total score from questions 3, 4 and 5 is “0” or “1”, it indicates a low level of knowledge; >1 indicates a high level of knowledge (Table 1). Participants whose treatment was discontinued were asked about the reasons for discontinuing treatment (side effects, according to the program, lack of efficacy) and who discontinued treatment (patient, physician, family, and others).

Table 1
Modified Morisky Scale (MMS)/ Modified Medication Adherence Scale-6 (MMAS-6)

Modified Morisky Scale (MMS)/ Modified Medication Adherence Scale-6 (MMAS-6)		
Question	Motivation	Knowledge
1. Do you ever forget to take your medication?	Yes (0) NO (1)	
2. Are you careless at times about taking your medicine?	Yes (0) NO (1)	
3. When you feel better, do you sometimes stop taking your medicine?		Yes (0) NO (1)
4. Sometimes if you feel worse when you take your medicine, do you stop taking it?		Yes (0) NO (1)
5. Do you know the longterm benefit of taking your medicine as told to you by your doctor or pharmacist?		Yes (0) NO (1)
6. Sometimes do you forget to refill your prescription medicine on time?	Yes (0) NO (1)	
Total Score	0–1 = Low Motivation 2–3 = High Motivation	0–1 = Low Knowledge 2–3 = High Knowledge
* Ask the patient each question and circle the corresponding “yes” or “no” response. Circle the answer to each question and add the score for the motivation column and add the score for the knowledge column.		

Patients who had used OAMs for at least 6 months were included in the study. OAMs were also analyzed by duration of drug use (6–12 months vs. >12 months) and treatment regimen (continuous vs. cyclical).

Interviews were conducted in the outpatient clinic, taking into account the rules of pandemic isolation and social distance from patients who had registered for follow-up or the treatment process. Patients older than 18 years, in whom clinical observation showed normal intelligence, who had no brain metastases, and who were not in the terminal phase of the disease were included in the study..

Statistical Analysis

The “Statistical Package for Social Science (SPSS) 23.0” programme was used for all analyses. Descriptive statistical analysis was performed to identify the items included in the questionnaire. In performing the analyses, we presented continuous numeric variables with normal distribution as mean ± standard deviation (SD). For the description of categorical data, the values without normal distribution were used as median, minimum, maximum, and percentages. The chi-square test or Fisher’s exact test

was used to compare these data in different groups. A two-tailed p value less than 0.05 was considered statistically significant in the results of the comparison between groups.

Ethical Considerations

The study protocol was approved by the Ethics Committee of the Medical Faculty of Karadeniz Technical University (Ref No: 24237859-229 Date: 13.03.2020). The oral statement of the patients who agreed to answer complete the questionnaire was accepted as consent.

Results

A total of 300 cancer patients taking oral anticancer drugs were enrolled in the study. The demographic characteristics of the participants are shown in Table 2. Of all participants, 203 (67.7%) were female and 97 (32.3%) were male. The mean age of the patients was 58 years and the majority (70.7%) of the patients were 65 years or younger; 91.3% of patients were married and almost all patients (99.3%) lived with their family. Among the patients who participated in our survey, 53.3% were diagnosed with breast cancer, 21% with GIS tumors, 9% with prostate cancer and 5.7% with lung cancer. In addition, 48% of patients were at the metastatic stage, and 52% were at the non-metastatic stage. The Eastern Cooperative Oncology Group Performance Score (ECOG-PS) was 0–1 in 69% of patients; 31% had ECOG-PS 2–3.

Table 2
Socio-demographic characteristics of the 300 cancer patients enrolled in the study.

Socio-demographic Characteristics	Frequency (n)	Percents (%)
Sex		
Female	203	67.7
Male	97	32.3
Age (years)		
≤65	212	70.7
> 65	88	29.3
Marital Status		
Married	274	91.3
Never-Married	8	2.7
Widow	16	5.3
Divorced	2	0.7
Living Status		
Living with family	298	99.3
Living alone	2	0.7
Educational Background		
Illiterate	38	12.7
Primary school	131	43.7
High school	11	3.7
University	120	40.0
ECOG-PS		
0–1	207	69.0
2–3	93	31.0
Cancer types		

Others* included malignant melanoma, renal cell carcinoma, sarcoma, head and neck cancers, gastrointestinal stromal tumor, bladder cancer, endometrium cancer and ovarian cancer.

Others** included vinorelbine, anastrozole, enzalutamide, sorafenib, ribociclib, exemestane, regorafenib, pazopanib, axitinib, etoposide, temozolomide, abiraterone, sunitinib, imatinib, erlotinib and alectinib.

Socio-demographic Characteristics	Frequency (n)	Percents (%)
Breast	160	53.3
Gastrointesitinal system	63	21.0
Prostat	27	9.0
Lung	17	5.7
Oral anticancer agents		
Letrozole	83	27.0
Capecitabine	66	22.0
Tamoxifen	60	20.0
Bicalutamide	15	5.0
Others**	76	26.0
Stages		
Non-metastatic	156	52.0
Metastatic	144	48.0
Others* included malignant melanoma, renal cell carcinoma, sarcoma, head and neck cancers, gastrointestinal stromal tumor, bladder cancer, endometrium cancer and ovarian cancer.		
Others** included vinorelbine, anastrozole, enzalutamide, sorafenib, ribociclib, exemestane, regorafenib, pazopanib, axitinib, etoposide, temozolomide, abiraterone, sunitinib, imatinib, erlotinib and alectinib.		

The 20 types of oral anticancer drugs were used by patients. In order of frequency, 27% took letrozole, 22% capecitabine, 20% tamoxifen, 5% bicalutamide, and 3.3% oral vinorelbine. It was found that 40% of patients took oral anticancer drugs for 6–12 months and 60% of them for longer than 12 months. While 36.7% of patients took the drugs cyclically, 63.3% took them continuously. 66.3% of patients continued oral anticancer treatment, and the remaining patients discontinued it. Of the patients who were previously treated and not receiving treatment at the time of the survey, 50.5% were discontinued according to the planned treatment, 42.5% were discontinued due to lack of efficacy, and only 6.9% were discontinued due to side effects. Only one patient discontinued treatment at his own request. (Table 3).

Table 3
Questionnaire on discontinuation of the treatment

	N (%)
Reasons for discontinuation* n = 101	
Side effects	7 (6,9)
Lack of efficacy	43 (42,5)
Scheduled	51 (50,5)
Other	0 (0)
Initiative for discontinuation n = 101	
Patient	1 (0,99)
Physician	100 (99,01)
Partner/family	0 (0)
Other	0 (0)

Motivation and knowledge scores were calculated according to the MMAS-6. The classification of patient characteristics according to their level of motivation and knowledge is shown in Table 2. 71.3% of patients had high motivation level, 28.7% had low motivation level, and 68.7% had high knowledge level, 31.3% of patients had low knowledge level.

The motivation and knowledge levels of the population younger than 65 years were significantly higher than those of the geriatric population (≥ 65 years) ($p < 0.003$ and $p < 0.001$, respectively). There was no correlation between patients' motivation and knowledge level with gender, marital status, and living status with family ($p > 0.05$). It was found that the patients with higher education level had significantly higher motivation and knowledge level ($p < 0.0001$ and $p < 0.0001$, respectively). There was no statistical significance between disease stage and motivation and knowledge level ($p > 0.05$). On the contrary, patients with high ECOG-PS had low motivation and knowledge level (ECOG-PS:0–1 vs 2–3, $p < 0.0001$ and $p < 0.0001$, respectively). Considering the duration of patients' drug use, high motivation and knowledge scores were found in patients who used OAM for more than 12 months (6–12 months vs > 12 months, $p = 0.029$ and $p = 0.021$, respectively) (Table 4).

Table 4

Classification of patients' characteristics according to their motivation and knowledge levels according to the MMAS-6

	Motivation Level		P	Knowledge Level		P
	Low ≤ 1	High > 1		Low ≤ 1	High > 1	
Sex						
Female	63 (31%)	140 (69%)	> 0.05	68(33.5%)	135 (66.5%)	> 0.05
Male	23 (23.7%)	76.3(73.2%)		26(26.8%)	71 (73.2%)	
Age (years)						
≤ 65	50 (23.6%)	162 (76.4%)	<0,001*	54(25.5%)	158 (74.5%)	<0,001*
> 65	36 (40.9%)	52(59.1%)		40(45.5%)	48 (54.5%)	
Marital Status						
Married	78 (28.5%)	196(71.5%)	> 0.05	85 (31%)	189(69%)	> 0.05
Never-Married	0 (0.0%)	8 (100%)		0 (0.0%)	8 (100%)	
Widow	7 (43.8%)	9 (56.3%)		7(43.8%)	9(56.3%)	
Divorced	1 (50%)	1 (50%)		2(100%)	0 (0.0%)	
Educational Background						
Illiterate	20 (52.6%)	18(47.4%)	< 0,001*	22(57.9%)	16(42.1%)	< 0,001*
Primary school	61 (46.6%)	70 (53.4%)		67(51.1%)	64(48.9%)	
Middle School	2 (18.2%)	9 (81.8%)		2 (18.2%)	9 (81.8%)	
High school and Univeristy	3 (2.5%)	117 (97.5%)		3 (2.5%)	117 (97.5%)	
Living Status						
Living with family	86 (28.9%)	212 (71.1%)	> 0.05	94(31.5%)	204(68.5%)	> 0.05
Living alone	0 (0%)	2 (100%)		0 (0%)	2 (100%)	

* Statistically significant at $p < 0.05$

	Motivation Level		P	Knowledge Level		P
	Low ≤ 1	High > 1		Low ≤ 1	High > 1	
Stages						
Metastatic	41(28.5%)	103(71.5%)	> 0.05	47(32.6%)	97(67.4%)	> 0.05
Non-metastatic	45(28.8%)	111(71.3%)		47(30.1%)	109 (69.9%)	
ECOG-PS						
0–1	6 (2.9%)	201 (97.1%)	< 0,001*	8 (3.9%)	199 (96.1%)	< 0,001*
2–3	80 (86.0%)	13 (14.0%)		86(92.5%)	7 (7.5%)	
Duration of Oral Anticancer Agents						
6–12 months	26 (21.7%)	94 (78.3%)	< 0,001*	28(23.3%)	92(76.7%)	< 0,001*
> 12 months	60 (33.3%)	120 (66.7%)		66(36.7%)	114(63.3%)	
Method of Application						
Cyclic	5 (4.5%)	105 (95.5%)	< 0,001*	7 (6.4%)	103 (93.6%)	< 0,001*
Continuous	81(42.6%)	109(57.4%)		87(45.8%)	103 (54.2%)	
* Statistically significant at p < 0.05						

It was found that motivation and knowledge levels were significantly higher in those who took OAMs cyclically than in those who took their medications daily (cyclically vs. continuously, p < 0.0001 and p < 0.0001, respectively). When the patients' diagnoses and medications were examined, the "p value" could not be calculated because the groups were heterogeneously distributed. However, the patients with breast cancer, who accounted for more than half of our patients, had 63.1% high motivation level and 60.6% high knowledge level. Approximately 70% of the patients were taking letrozole, capecitabine, and tamoxifen. Of these medications, patients taking capecitabine had a very high level of motivation (93.9%) and knowledge (90.0%) (Table 5).

Table 5

Classification of patients' common cancer types and oral anticancer agents according to their motivation and knowledge levels according to the Modified Morisky Scale

	Motivation Level		Knowledge Level	
	Low \leq 1	High $>$ 1	Low \leq 1	High $>$ 1
Cancer Types				
Breast	36.9%	63.1%	39.4%	60.6%
Gastrointesitinal system	4.8%	95.2%	7.9%	92.1%
Prostat	70.4%	29.6%	74.1%	25.9%
Lung	11.8%	88.2%	17.6%	82.4%
Oral anticancer agents				
Letrozole	44.6%	55.4%	45.8%	54.2%
Capecitabine	6.1%	93.9%	9.1%	90.9%
Tamoxifen	20.0%	80.0%	25.0%	75.0%
Bicalutamide	86.7%	13.3%	86.7%	13.3%

Discussion

Cancer is a deadly disease and effective treatment is very important. Because of the long duration of treatment and the toxicity of treatments, we are dealing with the problem of adherence and treatment compliance. Low adherence to oral chemotherapeutic agents has been associated with poor treatment outcomes, increased toxicity, and higher healthcare costs. Studies have shown that cancer patients are 16% less likely to adhere to oral chemotherapy than patients receiving infusion therapy under physician supervision [17]. Given the importance of the direct impact of adherence on treatment efficacy and treatment resistance, we wanted to investigate adherence to oral anticancer drugs among cancer patients in our clinic.

The average adherence to oral therapy in our study was high with high motivation and knowledge. Patient-related factors that may influence adherence include cognitive impairment, comorbidities, gender, psychopathology, and other medications taken. We excluded patients with cognitive impairment from the study. When gender was examined, no correlation was found between patient motivation and knowledge level and gender in this study. In the literature, some studies have shown that treatment adherence was better in women than in men, an inconsistent pattern [18, 19] and two studies [20, 21] showed that female gender was associated with unfavourable outcomes in treatment adherence and self-care in diabetes and cardiac rehabilitation. In our study, the motivation and knowledge level of the young population was significantly higher than that of the geriatric population (\geq 65 years), and statistically significant. In a

study by Barron et al of 2816 patients who continued tamoxifen treatment, patients aged 35–44 years and older than 75 years were more likely to discontinue tamoxifen compared with a reference group of women aged 45–54 years [22].

As expected, we found that the motivation and knowledge level of patients with higher educational level were significantly higher ($p < 0.0001$ for both). However, in some studies, there was no association between adherence and education level [23, 24]. In addition, social support may be important for adherence. However, in our study, there was no association between living status with family and marital status with motivation and knowledge level [25]. However, in our study, more than 90% of patients lived with their family and were married.

ECOG- PS status is a very important parameter in the cancer treatment process, especially in selecting optimal therapies and determining prognosis. It has been shown that patients with poor performance status (PS) have an increased risk of chemotherapy toxicity and poor treatment outcomes compared to patients with better performance status [26]. In this study, it was found that motivation and knowledge levels were statistically significantly lower in patients with a high ECOG-PS score.

Another issue is the relationship between duration of treatment and adherence. Adherence to long-term therapy for chronic diseases averages 50% in industrialised countries [27]. When the duration of patients' medication use was examined in our study, it was found that both motivation and knowledge levels were high among patients who had been taking oral anticancer medications for more than 12 months. This was in contrast to what was reported in the literature regarding the duration of tamoxifen use. In the study by Barron et al, the cumulative discontinuation rate of tamoxifen within 1 year of starting treatment was 22.1%. After a follow-up period of 3.5 years, the cumulative discontinuation rate increased to 35.2%. Age and history of antidepressant use were among the predictors of observed persistence [22]. However, in a study examining treatment adherence and duration of medication use in schizophrenia patients, patients who had been on medication for 1–5 years were compared with those who had been on medication for less than 1 year, and adherence was found to be lower in those who had been on medication for a short time [28]. In a study of 7525 patients measuring treatment adherence with antidepressants, the discontinuation rate in the first 4 months was 54% [29]. These data are similar to our findings, which may indicate that the critical period for treatment adherence is the early phase of therapy. The daily or cyclical nature of treatment was also examined in the study, as it may influence treatment adherence. It was found that motivation and knowledge levels were significantly higher in those who took oral anticancer medications cyclically than in those who took their medications daily. Adherence to cyclical treatments may have increased as patients perceived the importance of individualised follow-up of their own treatments.

In addition to the MMAS-6 questions, patients were also asked about reasons for treatment discontinuation. Most treatments were discontinued after the scheduled program or due to lack of efficacy, only 6.9% of patients discontinued treatment due to side effects, and only one patient discontinued treatment at his own request. It is very important that patients are informed in detail about

the efficacy of the treatment and possible toxicities when adhering to the treatment. In this study, all but one patient discontinued treatment on the advice of physicians.

Subgroup analysis according to patients' diagnoses and medications could not be performed because of the heterogeneity of the groups. However, patients with breast cancer, who accounted for more than half of our patients, were highly motivated and had a high level of knowledge. The most commonly used drugs in this study were letrozole, capecitabine, and tamoxifen. Patients taking capecitabine had very high levels of motivation and knowledge. However, these data could not be statistically analyzed because of the heterogeneity of the groups. This was one of the limitations of our study.

There is no "gold standard" method for assessing adherence and compliance. The MMAS-6 has been used in many studies, including those with cancer patients. After some inadequacies were identified in this scale, 2 additional questions were added and the Morisky Medication Adherence Scale-8 (MMAS-8) was developed. However, we used this scale because MMAS-6 has Turkish validation. This was another limitation of our study. In addition, our study was conducted during the pandemic period and when the number of patients reached 300, the study was terminated. Since it was a pandemic, only the patients who could come to the hospital could be included in the study.

Conclusion

Low treatment adherence is associated with poor treatment outcomes and also has economic consequences. Therefore, efforts should be made to increase adherence and compliance. Identifying adherence and related factors, informing patients in detail about the efficacy and toxicity of treatments at baseline are the simplest and most basic methods, managing toxicities in continuation of treatment will increase adherence to treatment. Special attention should be paid to patients aged > 65 years, patients with low educational level, and patients in earlier stages of their treatments, and closer follow-up should be performed. Efforts are being made to develop various solutions. Methods recommended and developed include reminders (pill diaries, pill boxes, blister packs...), cell phones and alarms, electronic battery bottles, computerized pill boxes for home use. These methods should be offered to patients who have problems with adherence and compliance.

Declarations

Author contribution SNK and AY conceptualized the project and drafted the manuscript. All authors reviewed, edited, and approved the final manuscript.

Availability of data Not applicable.

Code availability Not applicable.

Acknowledgements Not applicable.

Funding Not applicable.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committee of Karadeniz Technical University (Ref No: 24237859-229 Date: 13.03.2020).

Consent to participate The oral statement of the patients who agreed to answer complete the questionnaire was accepted as consent.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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