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Interference of the tamoxifen dispensing system in the adherence to pharmacotherapy of women with breast cancer

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Abstract

Objectives: To evaluate the medication adherence of women with breast cancer undergoing treatment with tamoxifen, before and after the change in the frequency of medication dispensing from monthly to quarterly, to elucidate the influence of this factor on adherence to therapy. **Methods:** A prospective, quantitative, cross-sectional, interview-type field study was carried out from the collection of data from women with breast cancer, on hormone therapy with tamoxifen, treated at an oncology hospital in the State of Paraná, Brazil. At first, a questionnaire of sociodemographic and clinical data was applied to characterize the patient in the sample and, also, the adherence to refills and medications scale (ARMS) instrument to assess adherence to treatment. The ARMS questionnaire was applied a second time, after changing the medication from monthly to quarterly dispensing. **Results:** Thirty patients is an interviewed, with a mean age of 54 years and most of them (80%) were in the initial stage at diagnosis. In the first interview, 66% had already undergone chemotherapy and radiotherapy, 86% had a record of tumors in the family and the average time of treatment with tamoxifen was 22 months. The mean adherence score obtained by ARMS in the first interview was 13.2 ± 1.52 (12 to 48 points) and 13.3 ± 1.73 in the second interview. **Conclusions:** There was no significant difference in the adherence score to tamoxifen treatment before and after changes in the frequency of dispensing.

Keywords: adherence, ARMS, breast cancer, tamoxifen.

Interferência do sistema de dispensação de tamoxifeno na adesão à farmacoterapia de mulheres com câncer de mama

Resumo

Objetivos: Avaliar a adesão medicamentosa de mulheres com câncer de mama em tratamento com tamoxifeno, antes e após a mudança na periodicidade da dispensação do medicamento de mensal para trimestral, para elucidar a influência desse fator na adesão à terapia. **Métodos:** Realizou-se um estudo de campo, do tipo entrevista, prospectivo, quantitativo e transversal a partir da coleta de dados de mulheres com câncer de mama em terapia hormonal com tamoxifeno, atendidas em um hospital oncológico no Estado do Paraná, Brasil. Num primeiro momento, foram aplicados um questionário de dados sociodemográficos e clínicos para caracterizar a paciente na amostra e, também, o instrumento adherence to refills and medications scale (ARMS) para avaliar a adesão ao tratamento. O questionário ARMS foi aplicado uma segunda vez, após alteração da dispensação mensal para trimestral do medicamento. **Resultados:** Foram entrevistadas 30 pacientes, com idade média de 54 anos e, em sua maioria (80%) estadiamento inicial ao diagnóstico. Na primeira entrevista, 66% já haviam realizado quimioterapia e radioterapia, 86% apresentavam registro de tumores na família e o tempo médio de tratamento com o tamoxifeno era de 22 meses. O score de adesão médio obtido por ARMS na primeira entrevista foi de 13,2 ± 1,52 (12 a 48 pontos) e de 13,3 ± 1,73 na segunda entrevista. **Conclusões:** Não houve diferença significativa no score de adesão ao tratamento com tamoxifeno antes e após alteração na periodicidade de dispensação.

Palavras-chave: adesão, ARMS, câncer de mama, tamoxifeno.

Introduction

Breast cancer is the main malignant neoplasm diagnosed among women in developed and developing countries, representing nearly 23% of the cases in women and 14% of the deaths due to cancer in 2012[1]. In developed countries such as the United States, Canada, United Kingdom, Netherlands, Norway and Denmark, the incidence has increased each year; however, mortality has been decreasing due to early detection by means of mammography and adequate treatment[2].

Some factors are related to development of the disease, such as old age (commonly after 50 years old), early menarche, late

menopause, late age for first pregnancy or nulliparity, hormone replacement therapy, prolonged use of oral contraceptives, exposure to high ionizing radiation doses, obesity, hypercaloric diets, not breastfeeding, smoking, exposure to environmental toxins and miscarriages. A family history of breast cancer and some genetic mutations in tumor suppressor genes, such as Breast-Related Cancer Antigens 1 and 2 (BRCA 1 and 2) and p53, result in increased risks for breast cancer[3-6].

Approximately two-thirds of the breast neoplasms express the Estrogen Receptor (ER) α protein. ER+ tumors are dependent on ER and its cognate ligand, estrogen, for their development, survival and progression. There are three main endocrine therapy drugs that differ by their mechanism of action and that are used the treatment and/or prevention of ER+ breast cancer. These medications were designed to block ER function and signaling[7].

Among them, Selective Estrogen Receptor Modulators (SERMs) are competitive estrogen inhibitors binding to the ER and have mixed agonist or antagonist activity, depending on the target tissue.

Tamoxifen, which has an important antagonistic effect on breast tissue in breast cancer, is a SERM used in the treatment of all ER+ breast cancer stages in pre- and post-menopausal women and in hormonal treatment for male breast cancer[8]. Among women with ER+ breast cancer, it reduces the relapse and death risks when administered as adjunctive therapy in early-stage disease, and may provide palliation in patients with metastatic disease[7].

This medication is available in oral presentation and some authors discuss the advantages of this administration route for the patients, such as convenience, elimination of the need for venous access, daily impact and the possibility of a better quality of life, with a greater sense of control over their treatment and less interference. However, some disadvantages are highlighted, such as variation in absorption, management of side effects, cost of the medications and low patient adherence to the therapy[9,10].

The World Health Organization (WHO) defines adherence to pharmacological treatments as the degree to which a patient taking a medication corresponds to and agrees with what was advised by physicians or other health professionals[10].

Medication adherence is a complex aspect that involves several factors related to the following: the patient (gender, age, marital status, schooling, socioeconomic level, life habits, cultural aspects), the disease (treatment time, absence of late symptoms and consequences), the treatment (costs, adverse effects, scheme complexity), the institution (health policy, access to the service, waiting and service time) and the relationship between the patient and health team. This latter is relevant for adherence to the treatment because patients that are satisfied with the team and with the treatment adhere better to the guidelines, with trust in the team as a determining factor for adherence[11].

Low adherence represents a global problem, as it can affect therapeutic results and increase health system costs. It can be portrayed as difficulty initiating treatment, early suspension, omissions or forgetfulness, missing appointments, self-medication, lack of change in lifestyle or in the habits necessary for proper treatment[12].

Among the ways to indirectly measure adherence is the application of structured questionnaires, which are based on direct questions about pharmacotherapy and which verify the patient's attitude towards medication use (forgetfulness, attitude towards adverse effects, improvement in the clinical condition). The advantages of this method include the following: low cost, short application time, quantitative characteristic and application ease in a large number of patients. However, the patient can manipulate this information and give the false impression of satisfactory adherence, which is oftentimes the case, as many patients feel embarrassed when reporting that they do not adhere to the treatment[13].

To improve adherence, pharmacists can identify barriers that hinder it, assist in their resolution and prevent the emergence of others, using strategies adapted to each patient's individual needs, thus contributing for them to better understand the treatment[14]. Such actions are part of pharmaceutical care, which is the set of practices carried out by pharmacists aimed at rational pharmacotherapy and at obtaining defined and measurable results, targeted at improving the patient's quality of life[15].

In this context, the objective of this study was to evaluate the medication adherence of women with breast cancer undergoing treatment with tamoxifen, before and after changing the medication dispensing frequency from monthly to quarterly, in order to verify the influence of this process and, timely, that of other possible factors in adherence to the therapy.

Methods

This research is a field study of the interview type, prospective, quantitative and cross-sectional, based on the collection of data from women with breast cancer on hormone therapy with tamoxifen, treated at a high-complexity philanthropic hospital specialized in Oncology, a reference in cancer treatments in southern Brazil. The project was submitted to and approved by the Research Ethics Committee of the Paraná League Against Cancer (CAAE 90538218.7.0000.0098).

The sample consisted of 30 patients randomly selected during the first three months of the research, who were interviewed when they attended the outpatient pharmacy to fetch tamoxifen according to the schedule of the hormone therapy sector (Stage 1), and who met the inclusion criteria. This study included women diagnosed with breast cancer, aged at least 18 years old and undergoing treatment for at least 3 months under the following High-Complexity Procedure Authorization (*Autorização de Procedimento de Alta Complexidade*, APAC) codes: 304050113, 304050040, 304050121; and who agreed to participate in the study by signing the Free and Informed Consent Form (FICF). Patients who had initiated their treatment less than 3 months ago were excluded from the study, as well as those who were already in the process of quarterly tamoxifen dispensing for more than 3 months and/or those who did not agree to participate. The calculated sample was 250 patients; however, at the time the interviews began, only 56 patients were not yet in the quarterly dispensing scheme and, of these, only 30 patients participated in both stages of this research.

The study was divided into two stages, which were carried out by a research pharmacist. Stage 1 consisted of the first interview, carried out in the 2nd half of 2018, with the patient the first time she fetched enough tamoxifen for 3 months of treatment at the outpatient pharmacy, according to the schedule of the hormone therapy sector. At that moment, diverse information was collected to characterize the variables (sociodemographic and clinical characteristics) through a form developed for the study, and the Adherence to Refills and Medications Scale (ARMS)[16] instrument (Figure 1) was applied to assess adherence to the pharmacological treatment (the word "tamoxifen" was abbreviated as TMX in the Figure).

Figure 1. ARMS questionnaire

Questions	Never	Sometimes	Often	Ever
1 - Do you miss scheduled appointments?	1	2	3	4
2 - Forget to take TMX?	1	2	3	4
3 - Do you decide not to take TMX?	1	2	3	4
4 - Forget to go to the pharmacy to get the TMX?	1	2	3	4
5 - Let the TMX end?	1	2	3	4
6 - Do you stop taking TMX because you are going to a doctor's appointment?	1	2	3	4
7 - Do you stop taking TMX when you feel better?	1	2	3	4
8 - Do you stop taking TMX when you feel bad or sick?	1	2	3	4
9 - Do you take someone else's TMX?	1	2	3	4
10 - Do you stop taking TMX when you are more careless about yourself?	1	2	3	4
11 - Do you change the dose of TMX to suit your needs?	1	2	3	4
12 - Do you plan ahead and pick up TMX at the pharmacy before they run out at home?	4	3	2	1

Ninety days after the first interview, the second research stage (Stage 2) was carried out within the first half of 2019 through the second interview, at the time of the second quarterly tamoxifen dispensing instance at the outpatient pharmacy or through a telephone call. In this phase, the instrument to analyze pharmacotherapy adherence was reapplied.

ARMS is an instrument to assess adherence developed for patients with chronic medical conditions. This questionnaire contains questions related to the patient's concern about buying medications or fetching them at a health service and to forgetting to administer doses; it showed good performance in patients with low schooling levels and was validated in a Portuguese language version to assess adherence to the treatment with oral antineoplastic agents. This validation was made in a survey of 123 patients at the same researched institution[17], Patients who present better adherence to drug therapy score twelve, whereas those with worse adherence score forty-eight[16].

After data collection, a statistical analysis was performed using Microsoft Excel in order to compare the patients' adherence to the treatment before and after the start of the quarterly tamoxifen distribution scheme. *Pearson*'s correlation coefficient and the *Wilcoxon* test were used to verify the correlation between the variables.

In order to enable better understanding of the study stages, a flowchart was prepared (Figure 2).

In the first stage, 30 patients using tamoxifen were interviewed from July to December 2018. The mean age of the patients interviewed was 54 years old (minimum of 38 and maximum of 77), most of whom were married (60%) and 76.7% declared themselves as white-skinned. 80% reported earning up to two minimum wages and 86.7% studied up to Elementary or High School.

As for the clinical characteristics, half of the women were diagnosed when they were 49 years old or less (50%), whereas 80% were in the initial stage and 66.7% had already undergone combined chemotherapy and radiotherapy at the time of the interview. In addition to that, 56.7% reported having some comorbidity and 86.7% had some family history of cancer. The complete data on sociodemographic and clinical characteristics are presented in Table 1.

In relation to the treatment, the mean adherence score obtained by ARMS in the first interview was 13.2 ± 1.52, and 13.3 ± 1.73 in the second interview, as shown in Table 2.

Figure 2. Research Flowchart

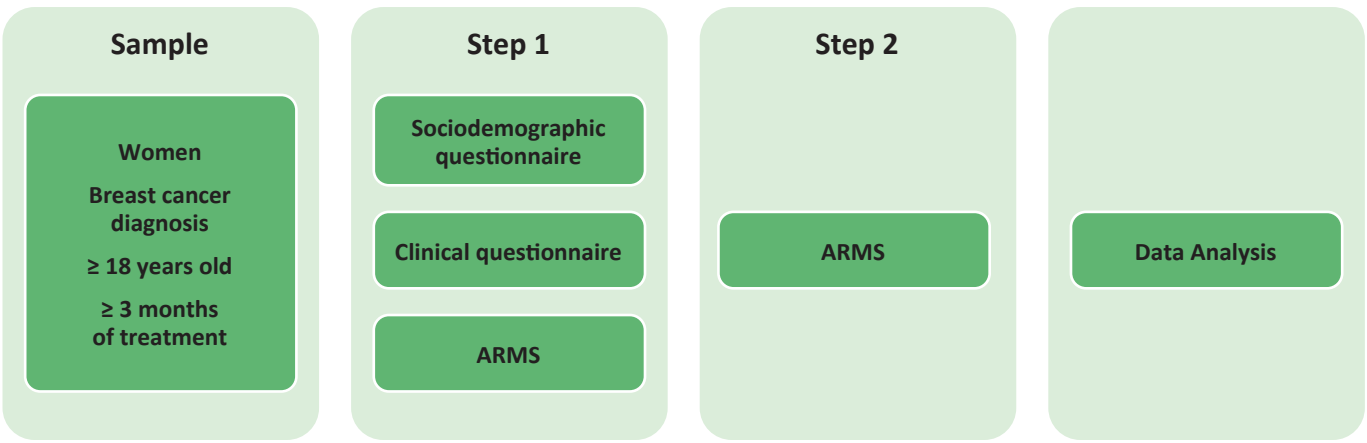

Table 1. Sociodemographic and clinical characteristics of the patients

Variables	n (%)
Age (years old, mean ± SD)	**54.0 ± 9.7**
Schooling	
Elementary School	12 (40.0)
High School	14 (46.7)
Higher Education	4 (13.3)
Marital status	
Single	6 (20.0)
Married	18 (60.0)
Divorced	1 (3.3)
Widowed	5 (16.7)
Self-declared race/skin color	
White	23 (76.7)
Black	2 (6.6)
Others	5 (16.7)
Family income (minimum wages)	
<2	24 (80.0)
3-4	6 (20.0)
>5	0 (0.0)
Age at Diagnosis (years old)	
≤49	15 (50.0)
From >50 to ≤69	14 (46.7)
≥70	1 (3.3)
Staging at diagnosis[1]	
Baseline	24 (80.0)
Advanced	6 (20.0)
Treatments underwent until the first interview	
Chemotherapy (CTx)	1 (3.3)
Radiotherapy (RTx)	9 (30.0)
CTx + RTx	20 (66.7)
Comorbidities	
Yes	17 (56.7)
No	13 (43.3)
Family History of Cancer	
Yes	26 (86.7)
No	4 (13.3)
Treatment time with tamoxifen (Months, mean ± SD)	22.4 ± 13.0

[1]Estadiamento segundo a Classificação dos Tumores Malignos (TNM) (inicial – estadiamentos 0, I e II; e avançado – estadiamentos III e IV).

When applying the *Pearson*'s correlation coefficient and the Wilcoxon tests to verify the correlation between the variables, it was not possible to verify any relevant association between the variables and adherence to the treatment.

Discussion

The mean scores resulting from applying the ARMS questionnaire in this study are similar to those found in another survey carried out at the same institution[17], in which 123 patients using oral antineoplastic agents were evaluated and a mean value of 13.2 was obtained using the same method. These scores are also lower than those found in a Polish study[18], where patients using antihypertensive drugs for at least 6 months obtained a mean score of 19.7 and than in the study by Kipralani *et al.* (2008)[16], which developed and evaluated the ARMS scale and obtained a mean score of 16.3.

There is still some concern with the group of patients in the current study, as adherence problems can seriously compromise therapeutic success and be associated with higher rates of comorbidities, mortality and hospitalizations[10]. Therefore, it is crucial to identify patients with adherence failures and barriers to following pharmacological therapy as recommended by the health team in an attempt to minimize such risks.

The pharmacist-patient interaction is a relevant factor in this context, as it is through this communication that it is possible to obtain diverse information about individual factors that may hinder adherence, which favors specific interventions for each patient[19].

The interviews with the patients are an indirect method of assessing adherence. Among the strategies to improve adherence to the treatment that can be implemented and/or suggested in this process we can mention the following: individual interventions, medication use reminders, information about pharmacotherapy, counseling, self-monitoring, family participation in the treatment and continuous monitoring (face-to-face or by phone)[11]. However, in order to obtain reliable information and make a decision about which method to apply, during the consultation it is important to establish an adequate relationship of trust between the professional and the patient and there should be no judgments on the part of the professional[11].

In the institution where this study was carried out, before initiating the treatment with oral antineoplastic, the patients attend a pharmaceutical consultation in which they are guided about the importance of their treatment, how to use and dose the medication, risks of non-adherence, possible adverse effects and drug interactions; at this moment, the patient also has the

Table 2. Adherence Measuring Questionnaire (ARMS)

Questions	Mean ± SD Stage 1	Mean ± SD Stage 2
1 - Do you miss scheduled appointments?	1.2 ± 0.407	1.28 ± 0.678
2 - Do you forget to take TMX?	1.47 ± 0.507	1.4 ± 0.5
3 - Do you decide not to take TMX?	1.2 ± 0.407	1.16 ± 0.374
4 - Do you forget to go to the pharmacy to fetch TMX?	1.1 ± 0.305	1.12 ± 0.332
5 - Do you let TMX run out?	1.0 ± 0	1.0 ± 0.0
6 - Do you stop taking TMX because you go to an appointment with a physician?	1.07 ± 0.254	1.16 ± 0.374
7 - Do you stop taking TMX when you feel better?	1.03 ± 0.183	1.04 ± 0.2
8 - Do you stop taking TMX when you feel bad or sick?	1.03 ± 0.183	1.04 ± 0.2
9 - Do you take someone else's TMX?	1.0 ± 0	1.04 ± 0.2
10 - Do you stop taking TMX when you are more careless with yourself?	1.0 ± 0	1.08 ± 0.277
11 - Do you change the TMX dose to meet your needs?	1.03 ± 0.183	1.0 ± 0.0
12 - Do you plan ahead and fetch TMX at the pharmacy before it runs out at your home?	1.1 ± 0.548	1.0 ± 0.0
ARMS score	13.2 ± 1.52	13.3 ± 1.73

opportunity to ask questions and clarify doubts. In this way, when identifying barriers to adequate adherence to the therapy, pharmacists can indicate strategies and provide the patients with tools that can help with adherence, such as a medication table with dosages and personalized guidelines. This initial guidance can be related to the low mean scores found in the ARMS method, as pharmaceutical monitoring can be an important tool to improve adherence to the pharmacological treatment[20].

In relation to the pharmacological therapy itself, the complexity of dosage, treatment duration, previous histories of therapeutic failure and presence of adverse effects are related to lower adherence rates[10,19]. According to a literature review that evaluated 76 articles with the objective of verifying adherence in relation to the daily administration frequency, it was noticed that simpler treatments with fewer daily administrations were associated with better results in adherence[21]. Given that the treatment in study consists of a single daily dose, this fact can also be related to a low score in the ARMS questionnaire. However, as already discussed, it is a long-term treatment (between 5 and 10 years depending on the patient's disease and conditions) and with undesirable adverse effects inherent to it, such as hot flashes, menstrual abnormalities, uterine cancer and thromboembolic events[8].

The World Health Organization (2003) mentions that in developing countries there are many socioeconomic problems that are barriers to adherence to the treatment of diseases, including poverty, illiteracy, low schooling, unemployment, high costs of public transportation and distance from health centers, and which may exert a greater influence on adherence than sociodemographic variables such as age, gender and marital status[10]. In this sense, changing the tamoxifen dispensing periodicity can contribute advantages to the patients and their adherence to the therapy, as this change aims at reducing hospital visits and, consequently, saving costs and time to get to the institution, as some patients live far from the hospital.

In the current study it was not possible to find a correlation between the schooling, age, race and income variables; however, a number of studies show that patients with lower income and schooling levels are associated with lower adherence, as well as young and black-skinned patients have low adherence to the treatment[10,12,13].

Another factor related to adherence is the cost of the medications. A study showed that patients with health insurance, but who had co-participation in the cost of the medications, had up to 11% more non-adherence to drug treatment[22]. In the current study, the patients have free access to tamoxifen through the Unified Health System, which may have exerted a positive influence on adherence to the treatment among these patients.

The following stand out among the limitations observed in this study: the reduced sample, justified by the fact that part of the patients were already on the quarterly tamoxifen dispensing scheme when the interviews began, which precluded their participation in the research; the fact that the second stage was carried out through a telephone call with some patients may have interfered with the answers they gave; the difficulty contacting some participants in the second interview and those who were excluded from the study for not having answered the questionnaire in the second stage; and the fact that the interviews were conducted by only one researcher.

Conclusion

In this study it was concluded that the change in the tamoxifen dispensing periodicity from monthly to quarterly did not affect adherence to the treatment of women with breast cancer in the short-term. However, an adherence study evaluating this change in the medium- and long-term is suggested, as the treatment with tamoxifen can vary from 5 to 10 years and treatment time can be a limiting factor in adherence.

The contributions of this study may be related to the relevance of pharmaceutical consultations, which allows instructing the patient regarding the treatment, dosage and importance of adherence. However, studies that can qualify and quantify the influence of pharmaceutical guidance on adherence to the pharmacological treatment may offer better understanding and bring about greater discussions about the pharmacists' role in adherence to pharmacological treatments.

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Collaborators

JMS, AO: Conception and design or data analysis and interpretation. JMS, AO: Writing of the article or relevant critical review of the intellectual content.

Declaration of conflict of interest

The authors declare that there are no conflicts of interest in relation to this article.

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