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Original Article

Tamoxifen treatment adherence assessment by women with breast cancer

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ABSTRACT

Justification and objectives: oral antineoplastic therapy has advantages compared to other therapies for the treatment of cancer, as it is administered at home, in a simple and fast way. However, this therapy increases patients' responsibility for their treatment, and compliance is critical to its effectiveness. Few studies are evident regarding pharmacotherapeutic follow-up in oral antineoplastic therapy. In this context, this study seeks to assess adherence to tamoxifen treatment in women with breast cancer, before and after pharmacotherapeutic follow-up. **Methods:** this is a randomized, quantitative clinical study. Data collection was carried out for six months. Random randomization was divided into a control group and a follow-up group, with the follow-up subdivided into before and after follow-up. The follow-up group received individual pharmaceutical interventions monthly. Adherence was assessed by The Brief Medication Questionnaire, Brazilian version and drug-related problems as to necessity, effectiveness, and safety. **Results:** after pharmaceutical follow-p, a difference was observed between the follow-up group and the control group regarding physical activity (p=0.043), treatment adherence (p=0.006), reduction of side effects (p=0.003) and associated diseases (p=0.002). The most frequent drug-related problems were safety and adherence, for which 54 pharmaceutical interventions were performed. The side effects described by patients mainly affected the genital system and gastrointestinal tract. **Conclusion:** it was evident that pharmacotherapeutic follow-up effectively contributed to adherence to treatment with tamoxifen and the pharmaceutical interventions performed contributed to prevention and reduction of drug-related problems.

Descriptors: Medication Adherence; Antineoplastic Agents, Hormonal; Pharmaceutical Services; Breast Neoplasms; Oncology.

INTRODUCTION

Cancer is a public health problem, with high incidence and morbidity and mortality, requiring care and consequences for patients and families. Among women, breast cancer is the most prevalent in Brazil and in the world, with the exception of cases of non-melanoma skin cancer. Between 2018 and 2019, an estimated 56.33 new cases per 100 thousand women, in the South Region it rises to 73.07 per 100 thousand women.[1]

Breast cancer treatment varies according to the stage of the disease, its biological, clinical and sociodemographic characteristics. Treatment modalities include local treatment such as surgery and radiation therapy, and systemic treatment with chemotherapy, hormone therapy and biological therapy.[2] Oral hormone therapy comprises an important part of treatment associated with increased long-term survival and reduced risk of recurrence and mortality.[2,3] Among the hormonal drugs used in breast cancer, tamoxifen (TMX), a selective estrogen receptor modulator, is the most used.[3,4]

The use of oral antineoplastic therapy has advantages such as not requiring venous access, treatment at home or at work without compromising patients' usual routine, with simple and quick administration.[5] On the other hand, this therapy increases patients' responsibility for treatment and adherence becomes essential for its effectiveness. A systematic review identified adherence between 41 to 88% of TMX users and treatment discontinuation between 15 to 20% in the first year of use and 31 to 60% after five years.[3] In this context, there is a need for pharmaceutical guidance and follow-up. The pharmacist, due to his or her strategic position, between the physician and the patient, can contribute to patient compliance and well-being, by detecting, preventing and solving drug-related problems (DRP) and other patient health conditions.[5,6]

Few studies have been identified that address the practice of follow-up or pharmaceutical care for patients with breast cancer using oral hormonal therapy. This study aimed to assess adherence to treatment with TMX in women with breast cancer before and after pharmacotherapeutic follow-up.

METHODS

The research followed an outline of a randomized clinical study conducted with women diagnosed with breast cancer using TMX. They were randomized into two groups: control and follow-up. The research was carried out in an oncology clinic located next to a hospital in a city in the state of Rio Grande do Sul, Brazil.

The study sample consisted of women over the age of 18, diagnosed with breast cancer, using TMX, registered and seen at the oncology clinic, who lived in the city of the study and

agreed to participate in the research. Women were identified from the access to the database/medical record of the referred hospital, in March 2016, and after that, a telephone contact was made to invite the participation of this research. All women who met the aforementioned inclusion criteria were included and those with an outdated phone or address were excluded. In addition, the number of participants to compose the sample was obtained for convenience, subject to the assessment capacity of a single investigator. He collected data and performed interventions as a way of reducing possible variations observed.

The research was carried out between June and November 2016. 40 women using TMX were identified in the clinic's database, of which 21 were included in the study. Data collection at the oncology clinic, in a private room, through a follow-up form consisting of sociodemographic variables, health conditions, information on pharmacotherapy and an instrument for assessing treatment adherence.

Sociodemographic variables were age, education, marital status, and occupational activity. Education level was classified as *low* for those with incomplete elementary school, complete elementary school and incomplete high school and *high* for complete high school, incomplete higher education or complete higher education. Health conditions assessed the presence of associated diseases, physical activity, use of prescription and self-medication, use of self-reported medicinal plants and DRPs. In relation to the practice of physical exercises, those who reported practicing at least three times a week were considered practitioners. Medicinal plants were considered users who reported using infusion/decoction or macerated with plants daily. DRPs were classified as necessity, effectiveness, and safety, according to the Granada Consensus.[7]

Participants were randomized randomly into control group (CG) and follow-up group (FG). For analysis purposes, FG was divided into two subgroups: before follow-up (FG1) and after follow-up (FG2). FG was followed up monthly and individual pharmaceutical interventions were proposed to improve patients' pharmacotherapy, while CG was exempt from interventions. Pharmacotherapy assessment was performed at the initial assessment and after six months, being categorized into CG1 in the initial assessment and CG2 in the final assessment. For randomization purposes, the results regarding treatment adherence were used through The Brief Medication Questionnaire (BMQ), Brazilian version. This questionnaire was applied on the first day of service, and was divided between the two adherent and non-adherent groups into CG and FG.

BMQ is a self-report method used to identify barriers to adherence in terms of regimen, beliefs and recall in relation to pharmacological treatment from patients' perspective. This

method classifies individuals into four categories in relation to treatment adherence, according to the number of positive responses in any of the domains. These categories are high adherence (no positive response); likely high adherence (a positive response); likely low adherence (two positive responses); and low adherence (three or more positive responses) in any domain.[8] For purposes of the study, it was stratified into high adherence and likely high adherence as adherents, and likely low adherence and low adherence as non-adherent. The investigation of side effects to the medication was based on patients' self-report.

The data obtained were compiled in tables using the Statistical Package for the Social Sciences (SPSS), version 18.0. Simple descriptive analysis resources were used. For the quantitative variables, measures of central tendency (mean) and dispersion (standard deviation) were used, and for the qualitative variables, relative and absolute frequency. The normality of the variables was verified by the Kolmogorov-Smirnov test. To verify the association between two or more qualitative variables, Fisher's exact hypothesis test was used, and for quantitative variables, the Mann-Whitney test was used to compare means for nonparametric and independent samples. For all tests, $p < 0.05$ was considered statistically significant.

The study followed all ethical principles involving research with human beings. The Research Ethics Committee approved the study, under Opinion 016287/2016 and CAAE (*Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration) 53902916.1.0000.5322.

RESULTS

Twenty-one women participated in the study, 11 in FG and 10 in CG. The mean age of the participants was 49.38 ± 8.1 years. The variables that describe the sociodemographic profile of CG and FG1 participants are described in Table 1. There was a higher frequency of people under 60 years of age. A higher percentage of study participants (57.14%) had low education both in CG and FG, with a statistical difference between these groups in this variable (p=0.024). The same statistical relationship was not observed regarding the marital status of patients in both groups, among whom more than half were married (66.66%). In relation to the occupational activity of the participants, 15 (71.42%) declared themselves housewives or retired and 6 (28.57%) were employed.

Table 1. Sociodemographic profile of patients using TMX from a hospital in the state of Rio Grande do Sul, 2016

	FG		CG		p**
	AD	N.AD	AD	N.AD n(%)	

		n(%)	n(%)	n(%)		
Age	Up to 60 years old	4(66.7)	5(100)	6(100)	3(75)	0.538
	Older than 60 years	2(33.3)	0 (0.0)	0(0.0)	1(25)	
Marital status	Wih a companion	4(66.7)	3(60.0)	2(33.3)	0(0.0)	0.056
	Without a companion	2(33.3)	2(40.0)	4(66.7)	4(100)	
Education level	Low	2(33.3)	0(0.0)	4(66.7)	3(75)	0.024*
	High	4(66.7)	5(100)	2(33.3)	1(25)	
Professional activity	Employed	2(33.3)	3(60.0)	2(33.3)	0(0)	0.221
	Unemployed	4(66)	2(40.0)	4(66.7)	4(100)	

AD - adherent; N.AD - non-adherent; CG - control group; FG – follow-up group; * p <0.05, Fischer's exact test; **Between CG and FG.

As for the discovery of breast cancer, 13 patients (61.9%) reported that they discovered the disease through self-examination; five women (23.8%) reported that it was due to clinical examination; two patients (9.5%) answered that it was by another type of exam; in addition to those mentioned, a patient (4.8%) informed that it was through the Family Health Strategy (FHS).

The clinical profile of the women participating in the study is shown in Table 2. There was an improvement in treatment adherence (p=0.006) in FG when compared to CG at the end of the follow-up, in FG adherence increased from 54.5% to 90.9%, while in CG it remained at 40%. In addition, there was a statistically significant difference in the practice of physical activity (p=0.043) in reporting side effects (p=0.003) and in terms of presenting other comorbidities besides cancer (p=0.002) between FG and CG.

Table 2. Assessment of groups and between groups before and after follow-up regarding characteristics related to treatment, 2016

		FG			CG			
		FG1	**FG2**	**p***	**CG1**	**CG2**	**p***	**p****
		n(%)	**n(%)**		**n(%)**	**n(%)**		
Treatment adherence	Yes	6(54.5)	10(90.9)	0.455	4(40.0)	4(40.0)	-	0.006
	No	5(45.5)	1(9.1)		6(60.0)	6(60.0)		
Use of medications	One	1(9.1)	2(18.2)	0.182	0(0.0)	4(40.0)	-	0.286
	> 1	10(9.1)	9(81.8)		10(100)	6(60.0)		
Physical activity practice	Yes	7(63.6)	8(72.7)	0.088	3(30.0)	3(30.0)	-	0.043
	No	4(36.4)	3(27.3)		7(70.0)	7(70.0)		

Use of plants	Yes	9(81.8)	4(36.4)	0.382	9(90.0)	7(70.0)	0.003	0.090
	No	2(18.2)	7(63.6)		1(10.0)	3(30.0)		
Side effects	Yes	2(18.2)	1(9.1)	0.182	2(20.0)	2(20.0)	-	0.003
	No	9(81.8)	10(90.9)		8(80.0)	8(80.0)		
Associated diseases	Yes	2(18.2)	4(36.4)	0.197	5(50.0)	5(50.0)	-	0.002
	No	9(81.8)	7(63.6)		5(50.0)	5(50.0)		

SF: start of follow-up; EF: end of follow-up; II: initial interview; FI: final interview; *Analysis between before and after follow-up; Fischer's exact; **Analysis between FG and CG; Fischer's exact.

Table 3 shows patients stratified regarding adherence and non-adherence to treatment, regardless of FG and CG. There was no difference regarding the mean number of drugs in use (p=729), reports of side effects (p=0.952) and time of use of TMX (p=0.691).

Table 3. Assessment of patients regarding adherence to treatment with TMX and its association with the number of medications, number of side effects and time of use of TMX, 2016

	Adherent	**Non-adherent**	**p***
	M±SD	**M±SD**	
Number of drugs in use	2.3±1.2	4.6±4.3	0.729
Number of self-reported side effects	2.9±1.6	3.6±2.7	0.952
Time of use of TMX	1.6±1.1	1.8±1.2	0.691

M = mean; SD = standard deviation; TMX = tamoxifen; *Mann-Whitney.

Regarding DRPs, there was a predominance of those classified as safety, related to side effects to medications (Table 4). The data show that in nine cases, patients were referred to the physician; in three patients, drug interaction with TMX was identified; three reported side effects; 11 cases were given pharmaceutical guidelines; and 11 patients were instructed on the risk of self-medication. Only five guidelines were not accepted by patients.

Among the side effects reported by the participants during the follow-up, it was found that the most frequent were those that affected the genital system (44 - 40.0%), followed by the gastrointestinal tract (19 - 17.3%), nervous system (17 - 15.5%), integumentary system (14 - 12.7%), urinary system (13 - 11.8%) and cardiac system (3 - 2.7%).

During the study period, 54 pharmaceutical interventions were performed, as well as interventions of non-pharmacological measures for the resolution and prevention of DRPs. Among these, those related to the practice of physical activities, healthy eating and the rational consumption of medicinal plants stand out. These interventions took place in verbal and written

form, with the delivery of an information pamphlet on the use and storage of medications. Medical referrals were made in writing and reinforced by telephone contact, when necessary.

Table 4. Identified DRPs and pharmaceutical interventions performed in FG. n=11, 2016

DRP	Problem	Conduct	N	Outcome
SAFETY DRP	Vaginal discharge	Referral to physician	3	Medical prescription and improvement
	Headache	Referral to physician	4	Medical prescription and improvement
	Interaction with food and nausea	Guidance to administer two hours after breakfast	3	Reduced risk of potential drug interactions and decreased motion sickness
	Care with medication storage	Pharmaceutical education on the storage, administration and care of TMX and other medications in use	11	Improved storage
	Heart failure by Herceptin® (Trastuzumab)	Referral to physician for management	1	Herceptin suspension and patient improvement
EFFECTIVENESS DRP	Interaction of Ondansetron with TMX	Metoclopramide replacement	2	Reduced risk of potential drug interaction
	Health problem from not taking the medication correctly	Pharmaceutical guidance on the correct use of TMX	11	Reported taking medication every day at the correct time
		Fasting TMX in the morning	7	Reduction of the risk of potential drug interaction
NECESSITY DRP	Use of painkillers	Guidance on self-medication	12	Decreased use of medication and minimized the possibility of MI

DRP: drug-related problem; TMX: tamoxifen.

DISCUSSION

It is evident from the results of the present study that the performance of pharmaceutical care promoted an improvement in adherence to drug treatment with oral antineoplastic agents, since in FG, adherence increased significantly when compared to CG. The pharmacist's performance also helped in adherence to non-drug treatment, as in the practice of physical activity.

With regard to the profile of the participants, most are in the age group below 60 years, this finding is in line with the literature.[9,10] Low education level was also a frequent characteristic, education is an important sociodemographic condition in the proposition pharmaceutical guidelines, as lower levels of education may be associated with a lack of knowledge about methods of prevention and early detection of breast cancer. Moreover, the level of education impacts access to basic health services and treatment, since patients with higher schooling tend to describe symptoms better, making their journey through the health system easier.[11]

Concerning marital situation, most of the study participants were married or in a stable relationship, it is noteworthy that the partner has an important role in the woman's life, supporting in coping with the disease from diagnosis to the end of treatment. In addition, married women generally take over the role of home caregiver, carrying out preventive exams and health care.[11]

Regular practice of physical activity showed a significant difference between FG and CG, which demonstrated that pharmaceutical interventions also helped to promote non-pharmacological treatments. Regular practice of physical activity is important during the treatment of women with breast cancer. A meta-analysis showed that physical activity in post-diagnosis significantly reduced the risk of death for all causes and deaths related to breast cancer.[12]

Cancer patients are potential candidates to discontinue the use of oral antineoplastic agents, especially women in advanced stage of breast cancer, as treatment requires changes in behavior and in living standards.[4] In this context, it is emphasized that adherence to treatment does not it is related only to access, but it is influenced by several personal, social and structural factors of patients.[13] As well as it depends on the bond between patients and health professionals, guidelines and actions that improve patients' quality of life. The present study demonstrated that the pharmacotherapeutic follow-up, and the approximation between patient and pharmacist, improved adherence to pharmacotherapy, and consequently improves the expected therapeutic result.

With regard to the rate of adherence of the studied patients, it is similar to the findings of a systematic review in which adherence varied from 41 to 88% among patients using oral hormone therapy.[3] In Japan, a study identified that 85% of women were adherent to treatment.[14] In Brazil, 45% of respondents at Arthur de Siqueira Cavalcanti State Institute of Hematology (HEMORIO) were adherent to treatment.[5] While in a highly complex hospital in oncology in Muriaé, MG it was found that 85.2 % were adherent.[4] Differences in percentages between studies may be related to the methods of determining adherence used such as reviewing records in dispensing databases, reviewing medical records, or applying questionnaires to patients.[8] In this study, a validated questionnaire, the BMQ method, was used, which may justify the difference between study results.

Moreover, a systematic review noted that discontinuation in the first year is around 15 to 20% and this figure rises to 31 to 60% at the end of five years.[3] Association between treatment time and reduced adherence was also observed in a study carried out in New Zealand with 1,230 women. In the assessment after one year of treatment with TMX ,90% were adherent, with two years, 84%, at three years, 81%, at four years, 76%, and at five years, only 50%.[15] These findings in nursing literature demonstrate that the longer the treatment time the greater the risk of patients giving up treatment.[15] It may also be associated with the severity of the disease, presence of other associated diseases and even side effects, producing different responses to treatment.[6] No association was observed between treatment time and adherence. However, it appears that the mean time of use was greater than one year and these patients were not followed up until the end of treatment, which makes this analysis difficult and presents itself as a limitation.

Among the factors associated with non-adherence, a research carried out in New Zealand showed that the occurrence of side effects and low tolerability with therapy.[15] In Brazil, forgetfulness was found to be the main reason among 27 participants.[16] The authors also show that other factors such as lack of information about the disease and lack of understanding about how to use the drugs were remedied with intervention. In the present study, it was evidenced that pharmaceutical interventions improved adherence to treatment, since participants reported the need for more information about the disease and medications, and that side effects and forgetfulness were the main causes non-adherence, which sought to remedy with guidance and resolution of DRPs.

In this study, 95% of the participants reported occurrence of side effects. In a research carried out with postmenopausal women revealed vasomotor, gynecological, or other side effects among 48% of women who received TMX.[17] Recurring effects in these women may

also be related to chemotherapy treatment, performed prior to treatment with TMX. Therefore, some reported side effects are probably the remaining effects of chemotherapy and also the drugs used concomitantly with chemotherapy and cannot be associated exclusively with the use of TMX.[17]

In a study conducted in New York, it was identified that 67% of patients using hormone therapy reported side effects.[18] The authors also show that although the side effects are bothersome, discussions with patients about them remain below ideal, with this, highlight the need for health professionals to address this issue with their patients in order to improve quality of life and medication adherence.

During follow-up, it was possible to reduce DRPs through pharmaceutical interventions, especially those related to side drug effects (safety DRPs). FG participants received guidance about these reactions, inherent to the mechanism of action of TMX, and were instructed to seek out the oncologist in specific cases. Non-pharmacological measures such as guidance of oral and topical hydration to help improve the dryness of the skin; regular consultation with the gynecologist to assess abnormal discharge; regular practice of physical exercises to help reduce the frequency of hot flashes and improve the emotional state; healthy eating to control weight and improve immunity were pharmaceutical guidelines performed and may have collaborated to reduce the frequency of this type of DRPs. Also, they may have contributed to the reduction of side effects observed at the end of the follow-up.

Pharmaceutical interventions to reduce and prevent DRPs have been shown to be effective in different settings and have contributed to safety of drug therapy and, consequently, of patients. A review of this topic pointed out that pharmaceutical interventions help to control side effects.[19] As a study conducted in France that sought five educational objectives (gaining knowledge, improving communication skills, managing anxiety, managing side effects and improving adherence) identified that educational programs help patients to adhere to and live with the effects of endocrine therapy.[20] It was observed that the use of medicinal plants as a complementary treatment was frequent, but there was no difference between the groups. This shows that this practice continued after pharmaceutical interventions, especially because it is a traditional practice, about which the existence of contraindications or side effects with plants is unknown.[21] In California, a cohort of 685 women with breast cancer found that 87% used alternative and complementary treatment therapies.[22]

Therefore, there is a need for guidance, especially in patients who use oral chemotherapy. It should be noted that the use of medicinal plants with TMX treatment may involve interactions between the drug and the plants, especially those with flavonoids and an

estrogenic effect, which may increase the synergistic cytotoxicity with TMX.[23] The need for new actions with this population is highlighted in order to provide guidance on the potential risks and that they need to inform the physician or pharmacist about this practice during the use of oral chemotherapy. In addition to plants, it is also important to provide guidance on the use of medications by self-medication, this practice can compromise the safety and efficacy of oral therapy, due to potential drug interactions and consequently side effects.

The effectiveness of the pharmacist's performance for the drug user is described in the literature. A meta-analysis on pharmaceutical care found that the pharmaceutical intervention reduced mortality among the patients followed.[24] A research carried out in Norway has shown that adherence to hormone therapy is influenced by the attention paid by the health professional, the information received by patients and the influence of the medication on the disease, which reinforces the need for pharmaceutical interventions.[25]

Considering the complexity of cancer treatment, at the same time its ease with the alternative of oral administration of treatment, the role of the pharmacist is essential in the treatment of cancer. In this sense, pharmaceutical assessment of the medical prescription and the way patients use medications can corroborate the optimization of the expected results. Changes in the usage process can be made from the detection of DRPs.[7]

This study has as limitations the number of participants and follow-up time determined according to the researcher's ability to perform as well as the lack of assessment of biochemical parameters that could bring other relevant information. However, it demonstrates positive results from the pharmacist's clinical performance to cancer patients. This reinforces the conduct of new research to elucidate factors associated with adherence and which interfere with the effectiveness of pharmacotherapy as well as the implementation of pharmacotherapeutic follow-up in oncology services to ensure safety and efficacy to the prescribed treatment.

It was evidenced that pharmacotherapeutic follow-up carried out by a pharmaceutical professional contributed effectively to adherence to treatment with TMX. It was identified that pharmaceutical interventions can prevent, prevent or reduce problems associated with pharmacotherapy. Thus, the clinical pharmacist through pharmacotherapeutic follow-up can improve the safety and effectiveness of drug treatment.

Cancer treatment is complex because it involves emotional, social, cultural aspects and specific treatment conditions. Pharmacotherapeutic follow-up is a fundamental intervention strategy. Follow-up constitutes a space for forming a bond between patient and pharmacist, thereby facilitating the clarification of doubts about treatment and illness. Follow-up also seeks

to reduce side effects and injuries resulting from cancer treatment, with a view to ensuring therapeutic success and improving the quality of life of cancer patients.

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Authors' contribution:

Caroline Oliveira and Roberta Cattaneo Horn contributed to the conception and design of the research project, data collection, data analysis and interpretation and writing of the article.

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