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CHARACTERIZATION OF BREAST CANCER SURVIVORS REGARDING ADVERSE EFFECTS AND LIFESTYLE DURING HORMONE THERAPY WITH TAMOXIFEN

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ABSTRACT

Objective: to carry out a study with women diagnosed with breast cancer and under hormone therapy with Tamoxifen (TAM) and to represent the adverse effects and the lifestyle of the patients, as well as their sociodemographic and therapeutic characteristics in a public oncology hospital of Brazil. **Materials and Method**: exploratory, descriptive and quantitative study whose population was composed of women (n = 20) under hormonal treatment. For evaluation, a questionnaire to obtain socio-demographic, therapeutic, anthropometric, lifestyle and adverse effects data was applied and the Excel and BioStat 5.0 programs were used to analyze the results. **Results**: Brown women between 40 and 45 years old, self-employed and commercial, income from 1 to 3 minimum wages, married and in stable union, in the pre and post-menopause, with grade II ductal carcinoma, submitted to chemotherapy and radiotherapy, in treatment with TAM for 2 to 3 years, make up the profile of patients. Gynecological and vasomotor complications comprise the adverse effects that are the most troublesome such ashot flushes, irritation, itching and vaginal bleeding followed by mood changes, body weight gain, gastrointestinal intolerance, visual disturbances and to a lesser extent memory lapses, depression, lipid changes, hepatic and endometrial. Sedentary lifestyle favored overweight and obesity. **Conclusion:** patients undergoing hormonal treatment with tamoxifen had adverse effects suggestive of estrogen deficiency with possible exacerbation due to the use of the drug, with negative variables for overweight and obesity. They should be warned about the possible adverse effects of anticancer treatments so that other therapeutic options can be considered based on the profile and clinical history of the patients.

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INTRODUCTION

Breast cancer is currently the neoplasm that most affects and changes the health of women in Brazil and worldwide [1–3]. Hormonal therapies that use antiestrogens to decrease relapses and increase life expectancy are still of great relevance and are used successfully for increasingly long periods ranging from 5 to 10 years [4]. Tamoxifen (TAM) is an antiestrogen and selective estrogen receptor modulator. It works by blocking estrogen receptors, decreasing the proliferation of cancer cells. It was introduced in hormonal therapy to treat ER (+) positive breast cancer in 1978s. It is considered a pioneering drug, and breast cancer patients have been benefiting from its therapeutic effects for more than 50 years, increasing survival and decreasing breast cancer mortality [5].

Clinical studies conducted with women using TAM have shown evidence of adverse effects related to thromboembolism [6], endometrial carcinoma [7], uterine sarcoma in humans and animals [8,9], ocular toxicity and retinopathy [10–13], hepatotoxicity in humans and animals [14,15], hepatocarcinogenicity in rats [16] and lipid changes with hypertriglyceridemia and acute pancreatitis [17–19]. Women who use TAM for many years may experience changes in the metabolism and distribution of body fat. Age, menopausal status, weight gain with an increase in the Body Mass Index (BMI), and changes in lipid levels that are common due to the decline in ovarian and estrogenic function, are factors that add to the profile of women with continued use of this drug [20–22]. Although TAM therapy is safe and therapeutic benefits are decisive for anticancer use, adverse effects must be carefully studied and reported and require monitoring by pharmacovigilance agencies in order to improve treatment adherence

and quality of life for survivors of cancer [23]. Thus, we present a study conducted with women undergoing hormone therapy with TAM and its sociodemographic and therapeutic characteristics, adverse effects and lifestyle during outpatient treatment at a public oncology reference hospital in the Brazilian Unified Health System.

MATERIALS AND METHODS

Study participants: An exploratory, descriptive and quantitative study was carried out with female patients who had been diagnosed with breast cancer and were undergoing outpatient treatment at the Oncology Service of the Hospital Ophir Loyola located in Belém do Pará, Brazil. The patients had undergone chemotherapy, radiotherapy and mastectomy and were candidates for treatment with tamoxifen citrate (20 mg/day), based on immunohistochemistry tests for estrogen and progesterone positive receptors according to the clinical protocol established at the hospital. The process of recruiting patients was based on an active search and spontaneous demand based on the analysis of medical records, the Hospital Information system and the authorization service for highly complex procedures for medicines of the specialized component of the Ministry of Health. The interviews and other procedures were performed in the mastology sector. After the first part of the selection process, inclusion and exclusion criteria were applied: women diagnosed with breast cancer, non-diabetic, without serious heart problems, without systemic diseases, co-infections, serious visual changes and who were using tamoxifen citrate under medical prescription were included in the research. Candidates who did not fit this profile were excluded.

Application of the questionnaire: After authorization and signing of the Free and Informed Consent Form, the candidates were invited to fill out the survey questionnaire with questions about personal data, lifestyle (type of diet, physical exercise, smoking and drinking), comorbidities, history of other medications used and adverse effects occurring while using tamoxifen. Anthropometric measurements (weight, height, waist circumference) were obtained using instruments such as a digital scale (OMRON®), tape measure and metric height scale. To collect data on the adverse effects of tamoxifen, an adapted questionnaire was adopted on monitoring and recording of self-reported adverse effects by patients with daily administration of tamoxifen citrate related to the frequency and severity of the adverse effect (common occurrence reaction, uncommon, rare and very rare) according to the manufacturer's original package insert. Adverse effects that were not included in the manufacturer's package insert were also recorded. Questions about the use of tamoxifen citrate included: name of the drug under medical prescription, dose, start and duration of treatment, route of administration, place of access to the drug and if the patient had any complaints related to the medication (yes or no). If the patient answered yes, the list of adverse effects already known was given and for each of them the answer option: yes (occurred) and no (did not occur).

Statistical analysis: The results were processed using Excel and Biostat 5.0 software. The frequency of distribution was used for absolute and relative values and percentages.

Ethical analysis: The information collected from patients during the research was based on the principles of bioethics, present in Resolution 466/2012 of the National Health Council, which provides for research involving human beings. All patients included in the study, or their guardians, were informed about the objectives and development of the research in order to authorize data collection and subsequent signing of the Free and Informed Consent Form. The research received ethical approval, numbers 1.897.057 (CEP-ICS-UFPA / PA) and 7.915.051 (CEP Hospital Ophir Loyola / PA).

RESULT AND DISCUSSION

The characteristics of the patients participating in the research who underwent hormonal treatment with TAM are listed in Table 1. Half of them had a risk age of 40 to 45 years (50%, n = 10). According to the National Cancer Institute, the risk of breast cancer manifesting itself is higher from the age of 40, especially estrogen-dependent types. As for color, 75% (n = 15) declared themselves brown. Sixty percent (n = 12) had completed high school. Self-employed and employed professionals accounted for the majority of occupations (75%, n = 15) and 35% were housewives (n = 7). Regarding family income, 75% (n = 15) reported a monthly income of 1 to 3 minimum wages, which contributed to their treatment, food, and housing expenses. These data, when compared to a study of women with breast cancer in Brazil and users of the Unified Health System, highlighted that black and brown women have a high incidence of breast cancer, given the socioeconomic, cultural and social conditions related to self-examination, access to mammography and late diagnosis [24]. Given the socioeconomic situation, the fact of earning a living as a self-employed trader or freelancer generates a stress factor, since the daily struggle for sales and the exhausting workload compromise the quality of life and the time available for rest. The marital status of the patientsis a positive factor, with more than half (55%, n = 11) claiming to be married or living in a stable union, reinforcing the importance of the partner in treatment compliance and psychological support and in the woman's self-esteem, since the participation of the spouse in consultations, medical examinations and domestic activities is essential for the treatment and the hopes for recovery. A study by Cecílio *et al*., (2013) [25] of male companions of women with breast cancer in Divinópolis (MG) in Brazil confirmed that the life expectancy of female companions was associated with fears, uncertainties and hopes about the improvement of health felt by their companions.

Table 1. Characteristicsofthepatientsparticipating in the study (N=20)

Characteristics	N	%
Age (years)		
35 a 39	2	10
40 a 45	10	50
45 a 50	8	40
Breed		
White	3	15
Black	2	10
Brown	15	75
Indigenous	-	-
Marital status		
Single	9	45
Married / stablerelationship	11	55
Widow	-	-
Divorced	-	-
Education		
Illiterate	-	-
ElementarySchool	4	20
High school	12	60
Universityeducation	4	20
Occupation		
From home	4	20
Commercial / Autonomous	7	35
Teacher	2	10
Administrator	3	15
Housekeeper	1	5
Others	3	15
Family income		
<1 minimumwage	3	15
1a 3 minimumwage	15	75
> 3 minimumwage	2	10
Menopause status		
Pre-menopause	8	40
Postmenopause	12	60
Tumor type		
Ductal G-II	18	90
Ductal G-III	2	10
Tamoxifen treatment time (years)		
1 a 2		
2 a 3	7	35
3 a 5	10	50
	3	15

The physiological state of the respondentes varied, with 60% (n = 12) of postmenopausal women and 40% (n = 8) in the pre-menopause. However chemotherapy and radiotherapy themselves can lead to a decrease in ovarian function. According to Dohou *et al*., (2017) [26], young patients over 43 years of age with breast cancer and undergoing chemotherapy are at increased risk of chemotherapy-induced early menopause. As for the type of tumor diagnosed, grade II ductal carcinoma (90%, n = 18) was the most commonly found and only two patients received a diagnosis of grade III. According to the American Cancer Society it is the most common type diagnosed and affects the cells of the breast ducts. Studies show that if this type of cancer were diagnosed in the initial phase (I) and not in phase (II), the prognosis would be better, but socioeconomic conditions, inadequate access to mammography and the lack of information due to the majority having a low education and income, hinder the chances of an early diagnosis and a good prognosis [24]. As for hormone therapy with TAM, all patients interviewed used the drug both before and after menopause, as its therapeutic indication is for low-risk breast cancer [27]. It is known that TAM reduces the recurrence of breast cancer, however a study by Lorizio *et al*., (2012) [28] highlighted that despite its beneficial effects, the use of TAM may be limited due to its adverse effects, and confirmed the participation of endoxifene, the active metabolite of the drug, in the induction of these effects. Because it has a complex action and acts in an antagonistic manner towards the estrogen receptor in the breast cell, it can act as a partial agonist, inhibiting bone demineralization in postmenopausal women, thus strengthening its protective effect.

Table 2. Adverse effects self-reported by the patients participating in the study during hormonal treatment with TAM at the oncology hospital (Brazil). (N = 20)

Adverse effect	N	%
Complaints of adverse effects		
Yes	20	100
No	-	
Hot flushes / heatwaves		
Yes	18	90
No	02	10
Vaginal changes		
(Itching, discharge, bleeding)		
Yes	18	90
No	2	10
Irritability		
Yes	14	70
No	6	30
Forget fulness / Memory lapse		
Yes	5	25
No	15	75
Weight gain		
Yes	12	60
No	8	40
Gastrointestinal intolerance (feeling sick / vomiting)		
Yes	11	55
No	9	45
Depression		
Yes	5	25
No	15	75
Eye changes (itchy eyes / visual embarrassment)		
Yes	13	65
No	7	35
Changes in cholesterol and triglyceride levels		
Yes	4	20
No	16	80
Liver changes		
Yes	4	20
No	16	80
Endometrial changes		
Yes	4	20
No	16	80
Headache / dizziness		
Yes	8	40
No	12	60
Cramps		
Yes	12	60
No	8	40

Among the respondents 100% reported having complaints and/or discomfort when taking the medication, even over different durations of treatment (1 to 2 years, 2 to 3 years and 3 to 5 years), unlike the findings of Love *et al*., (2015) [29], who compared placebos (without use of TAM) with the use of TAM for 3, 6 and 12 months. Hot flushes bothered 90% (n = 18) of our patients, followed by vaginal changes, including itching, discharge and vaginal bleeding. Data in the literature provide evidence that the undesirable effects related to gynecological and vasomotor complications produced by TAM can be confused with those already known in the female climacteric, and appear most frequently in the ranking of undesirable effects during treatment with TAM according to Day *et al*., (1999) [30] and Mouritis *et al*., (2001) [31]. Honna *et al*., (2015) [32] showed that women after menopause and above 60 years old suffer the negative consequences of the reduction in estrogen, which regulates both the breasts and uterus and other organs, reinforcing the importance of the hormone. Vasomotor symptoms such as hot flushes and night heat are due to hormonal block, as estrogen participates in hypothalamic thermoregulation. Table 2 shows the adverse effects self-reported by the patients.

Irritability or mood change was reported by 70% (n = 14) of patients, who mentioned having episodes of lack of patience and irritation regardless of the treatment time after a year or more, which contrasts with the findings of Love *et al*., (2015) [29], who reported that these effects occur from 3 months of treatment onwards. Irritability was increased in most patients, but depression was only mentioned by 25% (n = 5), although this adverse effect is important as it can compromise quality of life and follow-up treatment [33]. Weight gain was another adverse effect reported by 60% (n = 12) of the patients. Lima *et al*. (2017) [34] found that changes in body weight during chemotherapy and hormonal treatment negatively influence the prognosis, survival and quality of life of women with breast cancer. The weight of women undergoing endocrine therapy often increases by 1 to 2 kg, whereas those undergoing chemotherapy gain 3 to 7 kg. As they are usually menopausal women, this condition is unfavorable given the usual increase in weight in this life stage. Gastrointestinal intolerance such as nausea and vomiting were very pronounced (55%, n = 11), which can be attributed to the pharmacodynamics of TAM.
Visual changes occurred in 65% (n = 13) of patients, with reports of itchy eyes, excessive tearing and blurred vision. Kashiwagi, (2010) [35] made reference to anticancer treatments and the risk of eye disorders. Despite being uncommon reactions, changes can occur in the location of the anterior segment (eyelid, conjunctiva, cornea), retina, optic nerve and lacrimal duct. TAM and docetaxel, both used by patients, are drugs that can lead to tear disorders. Irreversible changes can occur during treatment if they are not detected early, although the option of stopping treatment or not should be evaluated in patients with an unfavorable history together with the ophthalmologist [36]. As for the occurrence of cramps and discomfort in the legs, these were mentioned by 60% (n = 12) of the patients.

Other less frequent effects corroborate reports of symptoms during long-term treatment with TAM presented by Love *et al*., (2015) [29] and Jordan VC, (2003) [5]. Headache associated with dizziness was reported by 40% (n = 8) of patients. Memory lapses with forgetfulness episodes including related to taking the medication were reported by 25% (n = 5); depression was reported by 25% (n = 5) of the patients who used antidepressants; changes in cholesterol levels with hypertriglyceridemia were confirmed by 20% (n = 4) patients who had their lipid profile tested and were taking medications such as statins and fibrates; changes of a hepatic nature such as in transaminases and suspected hepatic steatosis were reported by only 20% (n = 4) of them; endometrial changes such as uterine polyps were also reported by 20% (n = 4) of the patients interviewed. Previous studies on the adverse effects of TAM have also reported loss of memory and cognition [37,38]; lipid changes and hypertriglyceridemia [18,39,40]; thromboembolism in menopausal women [41]; pancreatitis at 4 years of treatment [42]; hepatic changes due to TAM [43]; and mood disorders, depression and altered cognition in endocrine and chemotherapy therapies [44]. Thus, TAM is associated with a series of adverse effects and its use depends on

whether patients with a menopause profile, undergoing breast cancer treatment and who develop symptoms of estrogen deficiency have a therapeutic indication for hormonal treatment that is associated with a long treatment time with menopausal discomfort [45]. To assess the patients' lifestyle we used several factors as a reference: when asked about their diet, 14 (70%) patients claimed to eat healthily with fruits and vegetables on their daily menu; 100% of them confirmed that they did not smoke, however 7 (35%) stated that they consumed alcoholic beverages even during the use of TAM; 6 (30%) reported performing regular physical activities recommended by the doctor such as walking and light exercises versus 14 (70%) who did not do any type of physical activity, being very sedentary; the abdominal circumference, via which central obesity is assessed, was high, above 80 cm in 100% of the patients; 16 (80%) of them were overweight and obese, as demonstrated by a BMI above 25 kg/m^2 (Figure 1).

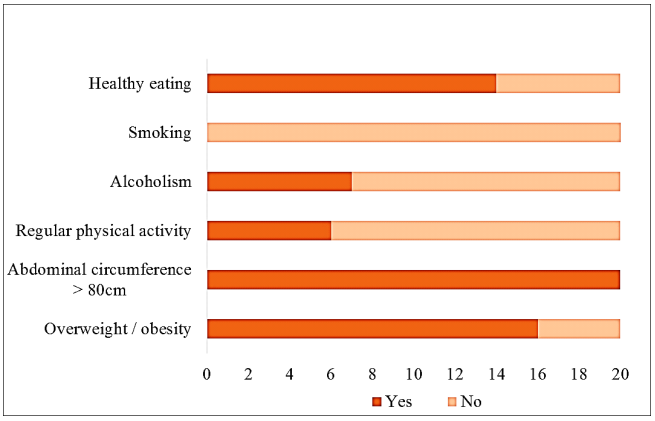

Figure 1. Distribution of the sample regarding the variables related to the lifestyle of patients undergoing TAM treatment at the oncology hospital (Brazil)

Our lifestyle results reveal a negative effect on survival and quality of life for anthropometric parameters such as a high BMI and waist circumference. Lima *et al.*, (2017) [34] pointed to the importance of good nutrition and reduced body weight. An imbalanced food intake is an important modifiable risk factor and contributes to the nutritional profile and risk of obesity in women with breast cancer. Although 70% of our patients claimed to have a healthy diet during chemotherapy and the use of TAM, the majority revealed that they were overweight and obese and did not do physical activity or did not have a regular physical activity program. Patients undergoing chemotherapy and hormonal treatment may experience changes in body weight and are liable to metabolic complications such as glycemic and lipid changes, which may have a negative impact on treatment. In a study of pre-menopausal women Hojan *et al*., (2013) [46] highlighted that aerobic exercise reduced the percentage of body fat mass and improved the quality of life, reinforcing the importance of physical activity in reducing adverse effects of endocrine therapy with TAM, in addition to improving mood and the expectation of treatment success; however physical activity programs should be specifically designed for such patients. Regarding alcohol intake and tobacco use, despite little or no use by patients, these factors precede a reorientation due to the negative interaction with the treatment in question. Due to the importance of quality of life in anticancer treatment, more investigations are needed to clarify the results of this research.

CONCLUSION

Most of the women in our sample were brown, aged between 40 and 45 years old, self-employed or employed, with a low income, married or in a stable union, in pre- or post-menopause, diagnosed with grade II ductal carcinoma, and treated with chemotherapy, radiotherapy and mastectomy, followed by TAM in hormone therapy for 2 to 3 years. Gynecological and vasomotor complications such as hot flushes, irritation, itching and vaginal bleeding followed by mood changes, body weight gain, gastrointestinal intolerance, visual disturbances and to a lesser extent memory lapses, depression, and lipid, liver, and endometrial changes, among others, were the most reported adverse effects that bother patients during hormonal treatment. A sedentary lifestyle with little or no physical activity favors overweight and obesity. Even with a healthy diet, modifiable risk factors still compromise patients' well-being. Although these results have some methodological limitations, we have described a profile of women with breast cancer that does not differ much from that reported by other studies referenced in this research. Many of the adverse effects of hormone therapy with TAM are exacerbated by the estrogenic deficiency present in the studied age group, but we cannot say by what mechanisms they arise. Because our sample comprised patients who were exposed to chemotherapy and later to TAM, we cannot rule out the possibility that the adverse effects of TAM are exclusive, since cytotoxic agents are also responsible for some of the reported effects. Women undergoing breast cancer treatment should be warned about the possible adverse effects of different anticancer treatments, while paying attention to individual characteristics and being able to choose therapeutic options that best suit their profile, strengthening treatment adherence and therapeutic expectations.

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