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ORIGINAL ARTICLE

Adherence and quality of life in women with breast cancer being treated with oral hormone therapy

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Abstract

Purpose To evaluate adherence to oral hormone therapy (HT) and which factors impact in incomplete adherence and quality of life.

Methods This was a cross-sectional study. Setting: Women's Hospital Prof. Dr. José Aristodemo Pinotti. Participants: women with breast cancer under treatment with oral HT. Main outcome measures: interview and performed an adherence questionnaire (Morisky–Green) and two questionnaires of quality of life (EORTC-QLQ30/BR23). The interviews were done once in a 5-month period.

Results Fifty-eight women were interviewed: 42 under treatment with tamoxifen (TX) and 16 under treatment with aromatase inhibitor (AI). Twenty-six women (44%) showed high adherence to the treatment, 31 (54%) medium adherence, and 1 (2%) low adherence. Statistical analysis showed a relation between incomplete adherence and systemic therapy side effects as well as higher stages of disease, with no difference between the two drugs. When treatments were compared, this study showed treatment with AI presented less breast symptoms and better role functioning. Quality of life score was high, compared to the reference value.

Conclusions A low percentage of women with breast cancer were highly adherent to HT treatment. Low/medium adherence was associated with higher stages of disease and systemic side effects. Quality of life had high scores, with better role function and less breast symptoms in women being treated with an AI.

Keywords Adherence · Tamoxifen · Aromatase inhibitor · Quality of life · Breast cancer

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Introduction

After diagnosing a breast tumor, the prognosis is important to conduct appropriate treatments. Many variables concerning morphological and histopathological features are taken into consideration. When the tumor is positive for hormone receptor (estrogen and/or progesterone), an endocrine therapy is suggested, either as an adjuvant to chemotherapy and/or surgery or as a neoadjuvant treatment prior to surgery. Treatment with oral hormone therapy (HT) can take 5 to 10 years, one pill a day, every day [1]. The two most common action mechanisms are estrogen receptor modulation (e.g., tamoxifen) and aromatase inhibitor (AI) (e.g., anastrozole) [2, 3]. As these drugs modulate the concentration of estrogen that reaches the tumor cell, it also affects healthy cells, leading to the most common side effects: hot flushes and other symptoms similar to the ones experienced during menopause, called the genitourinary

syndrome of menopause (GSM) [4]. Some symptoms are more specific to each drug such as gastrointestinal and thrombosis for tamoxifen and musculoskeletal for anastrozole [2, 5].

An oral treatment is considered convenient and with less adverse events related to administration route. The oral treatment for cancer has been evolving for the last two decades and can be less expensive since it does not involve hospitalization for its administration [6, 7]. However, it is important that the woman is properly informed about both benefits and risks and encouraged to follow the treatment correctly to ensure a successful therapy [8–10]. Studies vary in methods to evaluate adherence as well as in percentage of adherence but agree that the adherence rate is not optimal and is influenced by level of information provided, patient, provider, and treatment-related factors [11–13]. Women with hormone receptor-positive breast cancer who take this type of medication have increased survival rates and have less side effects than the those who have treatment with chemotherapy. Nevertheless, these side effects can prevent compliance to the treatment, since they can influence quality of life [1, 14, 15]. Validated questions concerning medication taking can be implemented, helping the medical team to detect problems with adherence and find solutions, from suggesting a reminder system to resolving serious side effects [12].

The general objective of this study was to evaluate adherence to oral HT and which factors impact in incomplete adherence and quality of life, comparing both treatments.

Methods

Settings and criteria

This is a cross-sectional study with breast cancer patients under treatment with tamoxifen or AI who were selected when receiving the medication from a pharmacy at the Women's Hospital Prof. Dr. José Aristodemo Pinotti, University of Campinas, Brazil. Inclusion criteria were as follows: they agree to participate, are over 18 years old, and will be treated with tamoxifen or AI during the study, be followed at the hospital, and be available to participate in the interview in person. Exclusion criterion was not being legally capable.

The study was explained by a pharmacist researcher, and the women signed a consent form, approved by an ethical committee. Data was collected from June to October 2016, when the researcher was at the distribution pharmacy.

Variables

Independent variable was treatment with oral HT in women with breast cancer. Dependent variables were adherence and quality of life. Adherence is measured by using a validated Morisky–Green 4-item questionnaire [16]. Quality of life is the individual perception of how the current life context is according to their expectation [16].

Questionnaires

The interview was based on the Pharmacists' Workup of Drug Therapy (PWDT) method [17], adapted to the context, in which the researcher asked the woman about her overall health. Then, the woman answered the Morisky–Green questionnaire with four questions:

1. Do you ever forget to take your medicine?
2. Are you careless at times about taking your medicine?
3. When you feel better do you sometimes stop taking your medicine?
4. Sometimes if you feel worse when you take your medicine, do you stop taking it?

Answers "no" add one point and answers "yes," zero point; high adherence, "no" to all questions; medium adherence, "yes" to one or two questions; and low adherence, three or four "yeses" [18].

The European Organization on the Research and Treatment of Cancer Quality of Life Questionnaire 3.0 (EORTC-QLQ C30) with 30 general questions about overall quality of life and the EORTC Breast Cancer Module questionnaire (QLQ BR23) with 23 additional questions assessing disease symptoms, side effects, body image, sexual functioning, and future perspective were used to evaluate quality of life. They were translated to Portuguese and validated [19].

Statistical analysis

Adherence statistical analysis was conducted by exploratory analysis through mean, standard deviation, minimum, maximum, frequency, and percentage. The relation of adherence to the other variables was verified through Fisher's exact test, chi-squared, or Mann–Whitney tests. Significance level was at 5% [20, 21]. Scoring of the quality of life questionnaires was performed according to the EORTC manual and transformed to 0–100 scale. Quality of life was evaluated comparing the two treatments, using the linear regression Mann–Whitney test, with variables adjusted for duration of treatment [20, 22, 23]. SAS 9.4 for Windows was used for all analyses. A chi-squared test was used to analyze the relationship of incomplete adherence and stage of disease, neo/adjuvant treatment, age, duration of treatment, schooling years, number of concomitant drugs, and quality of life.

Table 1 Demographic data divided by treatment

Characteristic	Tamoxifen ($n = 42$)	Aromatase inhibitor ($n = 16$)	p value
Age	59 ± 12	56 ± 11	0.5028*
Schooling (years)			
≤ 4	5 (12%)	0	
5–8	17 (40%)	8 (50%)	
9–11	7 (17%)	1 (6%)	
≥ 12	13 (31%)	7 (44%)	
Duration of treatment (months)	25 ± 15	17 ± 25	*0.0122**
Number of concomitant drugs	1 ± 2	1 ± 2	
Stage (n)			
0	1	0	
I	16	2	
II	14	6	
III/IV	11	8	
Adjuvant treatment n (%)	40 (95%)	13 (81%)	
Neoadjuvant treatment n (%)	2 (5%)	3 (19%)	

* Mann-Whitney, 5% significance

Results

This study included 58 women: 42 treated with tamoxifen and 16 with AI. Twenty-six (44%) women showed high adherence, 31 (54%) medium adherence, and 1 (2%) low adherence. Demographic data divided by treatment is presented in Table 1. There was no difference in the demographic characteristics between groups besides duration of treatment. The treatment was longer in the tamoxifen group ($p = 0.0122$), but distribution of months was very broad, with women receiving the drug for the first time at the time of the interview and women in the last months of their treatment.

Women with low/medium adherence had more systemic side effects than women with high adherence ($p = 0.0346$). Half of women in stage I of disease had high adherence and 42% of women with stage III/IV had low/medium adherence ($p = 0.0229$). There was no significant difference in adherence levels between tamoxifen and AI groups ($p = 0.4759$). This was also observed when comparing neoadjuvant and adjuvant treatment groups ($p = 1$) (Table 2).

There was no difference between quality of life in the two treatment groups, except the role function that showed better scores in the AI group ($p = 0.0206$) and breast symptoms that was less shown in the women under treatment with AI ($p = 0.0481$) (Table 3).

Discussion

Results showed that less than half of women were highly adherent to the treatment with oral HT. Low/medium adherence were associated with stage of disease and higher scores of side effects. Treatment with AI presented less breast symptoms and better role functioning than treatment with tamoxifen.

Adherence is key for a successful HT, which is proven to increase survival rates and reduce recurrence and mortality [24, 25]. Also, it is important to study treatment adherence in HT and the factors related, as this is a treatment modality that is administered for a long period of time. More than half of women in this study had low/medium adherence, mostly defined by forgetting to take the medication. Most of them reported forgetting once or twice a year, or not taking it at about the same time every day, either due to schedule changes or forgetfulness. Only one woman wanted to stop taking her medication for not feeling well (dizziness and vaginal discharge with tamoxifen). Studies vary in methods to measure adherence and rate it. Clinical trials show that 72–92% of women are compliant in their treatment for the prescribed duration. However, these women are closely monitored and encouraged to take their medication properly [25, 26]. In clinical settings, this number can be as low as 50% [27].

Other than treatment duration, there was no difference in the demographic characteristics, later used for adjustments on other statistical tests. Statistical analysis was performed to evaluate which factors could influence on non-adherence to the treatment, showing an association with systemic side effects. These include dry mouth, different taste, eye irritation, hair loss, feeling ill or unwell, hot flushes, and headache. Hot flushes are common to both treatments and the most reported symptom. For tamoxifen, dry mouth, eye irritation, and loss of hair are among the other complaints, which is consistent with the most common side effects predicted in clinical studies [2]. For AI, there was no other complaint that stands out, other than musculoskeletal pain, which was self-reported during the interview.

Table 2 Comparison of adherence ($n = 32$) of both treatments and age, duration of treatment, schooling, number of concomitant drugs and quality of life domains

Variable ($\chi \pm$ SD)	Low/medium adherence ($n = 32$)	High adherence ($n = 26$)	p value
Type of treatment			0.4759
Tamoxifen	25 (59.5%)	17 (40.5%)	
Aromatases inhibitor	7 (43.7%)	9 (56.3%)	
Age	57.8 ± 12.9	58.1 ± 10.6	0.6557
Duration of treatment	26.6 ± 18.9	18.7 ± 17.5	0.0660
Schooling	8.3 ± 4.2	8.8 ± 3.7	0.6117
Concomitant drugs	1.3 ± 1.9	1.5 ± 2.1	0.8313
Quality of life			
Global health status	70.7 ± 28.5	83.4 ± 18.7	0.0909
Body image	61.2 ± 40.2	75.1 ± 33.5	0.3137
Sexual function	29.3 ± 32.2	36.6 ± 33.0	0.4451
Sexual enjoyment	72.9 ± 34.9	78.6 ± 28.0	0.8013
Future perspectives	39.6 ± 39.2	43.6 ± 46.8	0.7979
Systemic side effects	30.7 ± 22.0	19.4 ± 16.5	*0.0346*
Breast symptoms	22.9 ± 24.6	22.3 ± 25.5	0.8237
Arm symptoms	34.4 ± 29.1	24.8 ± 28.5	0.1456
Upset by hair loss	66.7 ± 37.3	33.3 ± 47.1	0.1874
Treatment n (%)			
Adjuvant	29 (90.6%)	24 (92.3%)	1.0000
Neoadjuvant	3 (9.4%)	2 (7.7%)	
Stage of disease			
I	6 (16%)	13 (50%)	
II	13 (42%)	7 (27%)	*0.0229*
III–IV	13 (42%)	6 (23%)	

$\chi \pm SD$ average ± standard deviation; p value calculated through Mann-Whitney, 5% significance

In this study, women with higher stages of disease had low/medium adherence, similar to a Japanese study [28]. Hershman et al. found an association of higher mortality risk in women with less adherence [29]. This study also found a connection between low adherence and side effects, but there is no consensus on this matter. Some say that if women receive more information on the expected side effects and have support from the follow-up team, their adherence is higher than those who do not have access to information or to medical team [28, 30].

In the general quality of life questionnaire, tamoxifen showed significantly lower scores than AI for the role function domain, in which women felt that their daily activities were hindered by the treatment. However, both values were considerably higher (≥ 7 points) than the reference for EORTC [31]. Values of global health status were higher than reference values. For BR23, this was also true for values of sexual function and sexual enjoyment in this population. Nevertheless, these are still lower than values for the other domains, highlighting a well-known problem that most breast cancer patients have. Some studies aims to reduce symptoms through non-hormonal therapies [32], even in different stages of the disease. Averages found in this study for all domains are slightly different from the reference values, which might be explained by the slightly higher age of the population studied and other environmental factors. Lower values than the reference were found in the domains of body image and future perspective for the tamoxifen group. Higher values were found in the symptom domains, especially for "upset by hair loss" in the tamoxifen group, with an indicative p value. Future perspective values were higher for the AI group with an indicative p value [31].

To our knowledge, this is one of the first studies that compared adherence in two types of HT: tamoxifen and AI, including all stages of disease and without age limit. Limitations of this study include a difference between the total of interviewed women in each group, since the number of women using tamoxifen at the setting is three times larger than the ones treated with AI. In addition, this being a cross-sectional study, there is no follow-up of women. Future prospective studies with a larger group of women are necessary to confirm the associations found in this study. The small number of patients is also a limitation. The sample was not calculated for this study, because it is an innovative pilot study.

Table 3 Quality of life and adverse events comparison between tamoxifen and aromatase inhibitor in women with breast cancer

Quality of life ($\chi \pm$ SD)	Tamoxifen	Aromatase inhibitor	Total	*p* value
EORTC-QLQC30				
Physical functioning	78.7 ± 21.4	80.4 ± 19.2	79.3 ± 20.6	0.8715
Role functioning	77.4 ± 31.8	94.8 ± 16.9	82.2 ± 29.4	*0.0206*
Emotional functioning	57.0 ± 35.3	64.6 ± 33.3	59.1 ± 34.6	0.5058
Cognitive functioning	64.3 ± 34.8	80.2 ± 29.3	68.7 ± 33.9	0.1225
Social functioning	82.9 ± 29.1	85.4 ± 29.7	83.6 ± 29.0	0.2533
Financial difficulties	37.3 ± 44.3	25.0 ± 41.3	33.9 ± 43.5	0.3279
Global health status	75.4 ± 27.0	78.9 ± 20.2	76.4 ± 25.2	0.8720
Fatigue	22.5 ± 28.4	20.9 ± 27.8	22.1 ± 28.0	0.6564
Nausea and vomiting	10.7 ± 22.0	4.2 ± 12.9	8.9 ± 20.0	0.1684
Pain	43.7 ± 40.6	44.8 ± 38.8	44.0 ± 39.8	0.8413
Dyspnea	11.1 ± 25.2	0.0 ± 0.0	8.1 ± 21.9	N/A
Insomnia	30.2 ± 38.3	37.5 ± 43.7	32.2 ± 40.0	0.5162
Appetite loss	17.5 ± 33.9	12.5 ± 29.5	16.1 ± 32.6	0.3950
Constipation	23.0 ± 40.6	8.4 ± 14.9	19.0 ± 35.9	0.2423
Diarrhea	5.6 ± 16.3	4.2 ± 11.4	5.2 ± 15.1	0.7985
EORTC-QLQ-BR23				
Body image	63.9 ± 36.9	76.6 ± 39.5	67.4 ± 37.7	0.2343
Sexual function	32.6 ± 32.4	32.3 ± 33.6	32.6 ± 32.5	0.8660
Sexual enjoyment	84.1 ± 20.0	55.6 ± 44.1	75.6 ± 31.5	0.0829
Future perspective	35.7 ± 39.2	56.3 ± 46.7	41.4 ± 42.0	0.0559
Systemic side effects	27.2 ± 20.9	21.4 ± 18.8	25.6 ± 20.3	0.2259
Breast symptoms	25.3 ± 26.2	15.6 ± 19.7	22.7 ± 24.8	*0.0481*
Arm symptoms	30.7 ± 28.6	28.6 ± 31.0	30.1 ± 29.0	0.5543
Upset by hair loss	73.3 ± 34.4	8.3 ± 16.7	54.8 ± 42.6	0.0835

p value calculated though linear regression, taking into account time of tretament, 5% significance

$\chi \pm SD$ average ± standard deviation, *EORTC-QLQC30* European Organization on the Research and Treatment of Cancer–Quality of Life Questionnaire), *EORTC QLQ-BR23* European Organization on the Research and Treatment of Cancer Breast Cancer Module

Results showed a low percentage of women with breast cancer were highly adherent to the treatment with oral HT. Non-adherence was associated with higher stages of disease and systemic therapy side effects, with no difference between the two drugs. Overall quality of life had high scores, with better role function and less breast symptoms in women being treated with an AI.

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Compliance with ethical standards

Ethical standards This study was approved by the Ethics Committee of the Faculty of Medical Sciences (CAAE: 54977116.0.0000.5404).

Conflict of interest The authors declare that they have no conflict of interest.

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