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RESEARCH ARTICLE

Hormone therapy adherence in breast cancer: Predictive factors in Uruguay

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ABSTRACT

Background/Aim: Adjuvant hormone therapy (HT) significantly improves survival in patients with hormone receptor-positive breast cancer, yet adherence to this therapy is critical and tends to decrease over time. This study aims to identify risk factors for suboptimal adherence to adjuvant HT among patients treated at the Hospital de Clínicas and the Hospital Departamental de Soriano, Uruguay, to inform future strategies to improve adherence.

Materials and Methods: A retrospective, cross-sectional study was conducted, including 96 breast cancer patients in stages I-III treated with HT for at least three years. Adherence was assessed using the Morisky-Green questionnaire. Statistical analysis was employed to estimate the odds ratios (OR) for non-adherence, with a significance threshold of α0.05.

Results: Out of the 96 patients included, 22.9% demonstrated suboptimal adherence to hormone therapy. Analysis revealed that the use of tamoxifen (adjusted OR of 4.86, $p<0.05$) and living with others were significant predictors of non-adherence. The aggressiveness of the treatment did not show a statistically significant correlation with adherence. Additionally, the analysis highlighted that sociodemographic characteristics, such as marital status and employment situation, did not directly influence adherence, underscoring the complexity of factors contributing to treatment adherence. Intriguingly, the analysis showed a trend towards greater adherence among postmenopausal patients and those with a history of combined treatment of tamoxifen and aromatase inhibitors, though these results warrant further exploration.

Conclusion: Suboptimal adherence to adjuvant HT in breast cancer patients is significantly influenced by the type of hormone therapy prescribed and the patient's social environment. It is necessary to develop personalized interventions that address these factors to improve adherence.

Keywords: Adjuvant hormonal therapy; Breast cancer; Medication adherence; Risk Factors; Tamoxifen; Aromatase inhibitors.

Introduction

It is widely recognized that adjuvant treatment with aromatase inhibitors or tamoxifen for 5 years in estrogen receptor (ER) and/or progesterone receptor (PR) positive breast cancer (BC) increases disease-free survival (DFS) and overall survival (OS)[1]. Currently, adherence to hormone therapy (HT) for BC in routine clinical practice is a subject of growing international interest and poses an increasing challenge in clinical care, to which must be added the impact in economic terms[2,3]. On average, only 74% of BC patients continue with adjuvant HT for 5 to 10 years[4,5], and adherence tends to decrease over time[6]. A systematic review showed that lack of adherence to treatment negatively impacts both DFS and OS in patients with early ER/PR positive BC. These findings underscore the importance of improving follow-up and focusing on treatment adherence to optimize health outcomes in this population[7].

Previously, our group assessed adherence to HT in patients treated in the Breast Unit in real life, showing a reduction of between 20 and 30% over five years[8,9]. These results clearly indicate that adherence to HT is suboptimal among patients diagnosed with early BC treated at the Breast Unit of the Hospital de Clínicas, despite the fact that this treatment is provided free of charge, is easy to administer, and is generally well tolerated.

Several studies have evaluated the effectiveness of interventions to improve adherence to HT treatment, but the results have been mostly unsatisfactory[10,11]. Two relevant systematic reviews[12,13], which examined a total of seven different interventions, concluded that none had significantly impacted adherence to HT. These interventions included strategies such as patient education (present in all interventions), reminders (in three interventions), and problem-solving (in one intervention).

One possible explanation for the failure of these interventions is that they were not individualized and therefore did not adapt to the individual needs of each patient. This highlights the importance of identifying patients who present risk factors for poor adherence, thus enabling timely interventions to maintain and improve it.

Many factors can influence treatment adherence. Some are related to the treatment itself, for example, its duration or certain adverse effects; factors linked to the patient, such as age, comorbidities, a lack of understanding of the importance of continuous treatment, as well as their psychological profile, socio-economic factors, and those related to the health system, among others[5,14,15]. It should be considered that these characteristics may differ from one country to another.

It's important to remember that adherence to treatment is the most significant modifiable factor impacting the efficacy outcomes of medical treatment. To improve the quality of care for users and provide the best possible attention, it's essential to evaluate the factors that can influence adherence to HT in routine clinical practice in our setting, hence the importance we place on the present study.

Within this context, our primary objective is to identify risk factors for suboptimal adherence to adjuvant HT in BC patients treated at the Breast Unit of the Oncology Service at the

Hospital de Clínicas and the Oncology Service of the Soriano Departmental Hospital in Uruguay, underlining our commitment to addressing this crucial aspect of patient care.

Materials and methods

This is a retrospective, cross-sectional, descriptive study, including patients over 18 years old diagnosed and treated for BC stages I-III ER/PR positive at the Breast Unit of the Hospital de Clínicas and the Oncology Service of the Soriano Departmental Hospital, during the period from January 1, 2018, to December 31, 2022, who have received HT treatment for at least 3 years.

Demographic, occupational (considering the patients' occupation class), and tumor variables that could have influenced both treatment adherence and its discontinuation were investigated.

Patients were asked to anonymously complete a structured questionnaire at the end of the medical consultation. The questionnaire includes items related to sociodemographic characteristics: age, marital status, number of children, origin, education level, and type of work.

To assess adherence, the Morisky-Green treatment adherence questionnaire was used, which evaluates compliance directly with the patient, and its use is validated for chronic diseases. It consists of 4 questions with dichotomous answers: yes/no, assessing the patient's behavior regarding treatment compliance.

1. Do you ever forget to take your medication for your condition? Yes/No.
2. Do you take your medication at the prescribed times? Yes/No.
3. When you feel well, do you stop taking the medication? Yes/No.
4. If you ever feel bad, do you stop taking it? Yes/No.

A patient is considered to comply with the treatment if they answer the four questions correctly, i.e., No/Yes/No/No[16].

This questionnaire has a high correlation with data obtained from electronic devices or medication dispensing records and its use is recommended in routine clinical practice.

Data regarding the diagnosis date, type of surgery, systemic treatment (chemotherapy and HT), and radiation received will be collected through a thorough examination of medical records, maintaining patient anonymity. To analyze the data, an Excel database was used, where each patient was assigned an identification number.

All patients signed an informed consent form, through which they agreed to participate in the study and to answer the questions posed in the questionnaire to be seen later, also authorizing the use of the information that emerged from it in this research.

Patients who were unable to take the medication on their own (as is the case, for example, with dementia) were excluded.

Study variables

Included were:

Variables related to the patient: age at diagnosis and current age; marital status; number of children; occupation; origin (Montevideo or the interior of the country, rural area) and living situation.

Variables related to the tumor: date of diagnosis; stage according to the TNM classification; HER2 status.

Variables related to the treatment: type of surgery, whether chemotherapy, trastuzumab, radiation therapy was received, and type of adjuvant HT (tamoxifen vs. aromatase inhibitors).

The anonymity of the patients was maintained for the analysis and reporting of these data.

Statistical analysis

The quantitative variable "number of children" is described using its measures of central tendency and dispersion. Qualitative variables (age group, origin, living situation, educational level, occupation, marital status, stage, and number of medications) are presented using their absolute frequencies and relative percentages.

Odds ratios (OR) were estimated for non-adherence to treatment in simple and multiple models.

In all cases, a significance threshold of α=0.05 was considered.

The analyses were performed using R software version 4.0.4.

The study population was divided into two groups: adherent patients (those who correctly answer all four questions in the questionnaire) and non-adherent patients (those who do not correctly answer all four questions in the questionnaire).

Ethical considerations

The proposed study was conducted following international ethical standards for biomedical research: "MERCOSUR Standards on the Regulation of Clinical Studies" and the "Declaration of Helsinki," along with the research regulations approved by the National Ethics Committee in 2019.

Results

A total of 96 patients were included, and their sociodemographic characteristics are detailed in Table 1. The median age at the time of diagnosis was 61.35 (SD 10.35), and the median age at the time of survey completion was 67.27 (SD 9.80). The majority lived with others (71.9%, n = 69). Fifty-eight point three percent of participants (n = 56) were married, and 61.9% (n = 60) had secondary or higher education. Regarding employment status, 44.4% (n = 43) were retired, and 43.8% (n = 42) were employed; the remaining data are shown in Table 1.

Table 1: Epidemiological and demographic characteristics of the patients included in the study (n= 96).

Variables	N	%	Mean (SD)
Age category at diagnosis, years			
≤ 45	7	7.3	
46-60	35	36.4	
61-70	37	38.5	
> 70	17	17.7	

Variables	N	%	Mean (SD)
Marital status			
Married or living with a partner	56	58.3	
Divorced	20	20.8	
Widowed	16	16.7	
Single	4	4.2	
No data	1	1	
Number of children			2.50 (1.28)
0	5	5.2	
1 or 2	54	56.2	
> 2	37	38.5	
Educational level			
Completed primary education	15	15.6	
Incomplete secondary education	22	22.9	
Completed secondary education	50	52	
Tertiary education	9	9.4	
Occupation			
Homemaker	11	11.4	
Retired or pensioner	43	44.8	
Employed	42	43.7	
Living situation			
Lives alone	27	28.1	
Lives with partner	52	54.2	
Lives with children	43	44.8	
Lives with parents	15	15.6	

The majority of patients were postmenopausal at the time of diagnosis (83.3%, n = 80). The distribution by stage was as follows: Stage I 27% (n = 26); Stage II 53.1% (n = 51); Stage III 19.8% (n = 19). Regarding HER2 status, 82.3% (n = 79) were HER2 negative.

Table 2: Surgical and adjuvant treatment received (n= 96).

Variables	N	%
Type of breast surgery		
Mastectomy	42	43.8
Conservative surgery	54	56.2

Variables	N	%
Type of axillary surgery		
Sentinel lymph node biopsy	71	75.5
Axillary lymph node dissection	23	24.5
No data	2	2
Time elapsed since diagnosis		
≤2 years	10	10.4
3-4 years	38	39.6
≥5 years	48	50
Received adjuvant radiotherapy	77	81.1
Received adjuvant chemotherapy	58	60.4
Received adjuvant trastuzumab	17	17.7
Menopausal status at the start of HT		
Premenopausal	16	16.7
Postmenopausal	80	83.3
Type of HT		
Received HT with tamoxifen	13	13.5
Received HT with aromatase inhibitors	15	15.6
Received HT with tamoxifen + aromatase inhibitors	68	70.8
Current type of HT		
Aromatase Inhibitors	83	86.5
Tamoxifen	13	13.5

The treatments administered are shown in Table 2. Breast-conserving surgery was more common than mastectomy, and approximately half of the patients had received adjuvant chemotherapy. The majority of participants were taking aromatase inhibitors (86.5%), and among them, 83.1% (n = 69) had previously received tamoxifen.

Upon examining the Morisky-Green questionnaire, it was observed that 22.9% (n = 22) were non-adherent to treatment.

Among the patients who exhibited poor adherence to treatment, 72.7% (n = 16) reported forgetting to take the medication, and 31.8% reported intentionally interrupting the treatment when they felt well or unwell (4 and 3 patients respectively).

The potential predictors for non-adherence to treatment identified in the uni and multivariate analysis are shown in Table 3.

Table 3: Uni- and multivariate analysis of factors predicting non-adherence to HT treatment.

	OR (Odds Ratio) Crude	P-Value	OR Adjusted	p-Value
Age at diagnosis				
≤ 45	1			
46-60	0.13	<0.05		
61-70	0.02	<0.05		
> 70	1.8	NS (Not Significant)		
Current Age	1.02	NS		
Marital Status				
Married/partnered	1			
Divorced	1.31	NS		
Single	1.74	NS		
Widowed	5.22	<0.05		
Number of Children	1.11	NS		
Occupation				
Homemaker	1			
Employed/self-employed	2.35	NS		
Retired	4.33	NS		
Lives Alone				
No	1		1	
Yes	0.09	<0.05	0.09	<0.05
Lives with Partner				
No	1			
Yes	2.81	NS		
Lives with Children				
No	1			
Yes	2.72	<0.05		
Lives with Parents				
No	1			
Yes	1.27	NS		
Stage				

	OR (Odds Ratio) Crude	P-Value	OR Adjusted	p-Value
I	1			
II	2.51	NS		
III	0.65	NS		
Her2				
Negative	1			
Positive	0.17	NS		
Type of Breast Surgery				
Conservative surgery	1			
Mastectomy	1.76	NS		
Type of Axillary Surgery				
Sentinel lymph node biopsy	1			
Axillary lymph node dissection	0.61	NS		
Received Chemotherapy				
No	1			
Yes	0.93	NS		
Received Radiotherapy				
No	1			
Yes	0.35	NS		
Type of HT				
Aromatase Inhibitors	1		1	
Tamoxifen	5.29	<0.05	4.86	<0.05
Time Since Diagnosis				
≤2 years	1			
3 or 4 years	1.21	NS		
≥5 years	0.33	NS		

Only the type of hormone therapy (tamoxifen) and living with a companion were significant predictors for non-adherence in the multivariate analysis.

Patients living with their children showed a higher tendency toward non-adherence; however, this was only evident in the simple model.

Although it was observed that patients who underwent more aggressive axillary surgery (Axillary lymph node dissection) and those who received treatment with chemotherapy and radiotherapy were more adherent, this was not significant.

Compared to the reference group aged <=45 years, patients aged 46 to 70 years had lower odds of non-adherence to treatment in the simple model.

The time since diagnosis was not associated with treatment adherence.

Discussion

The lack of compliance with long-term pharmacological treatments for chronic diseases is a well-recognized challenge in various populations[17-22]. The efficacy of adjuvant HT in early BC is indisputable[1], improving DFS and OS. Recently, clinical guidelines have recommended extending therapy up to 10 years for women at increased risk of recurrence[23-26]. However, the lack of adherence to this treatment compromises its success. On average, only 74% of BC patients adhere to HT treatment for 5-10 years, with a decrease in adherence rates over time[4,5], recent guidelines recommending extended therapy for up to 10 years for some women at increased risk of recurrence.

It has been established that non-adherence to HT carries a higher risk of recurrence, a reduction in survival, as well as an increase in medical costs and a decrease in quality of life due to disease progression[27-29]. Previous research by our team demonstrated that, in the Breast Unit, adherence to HT decreased by 20 to 30% over a five-year period[8,9].

This issue has serious implications for healthcare systems and medical professionals, as well as a significant economic impact[2,3]. Adherence to treatment emerges as the most significant modifiable factor influencing outcomes. Recognizing this, it is crucial to optimize the quality of care and provide the best possible attention to patients, leading us to evaluate outcomes in daily clinical practice. This need underscores the relevance of the study we present. In response to this scenario, we have designed a study with the specific purpose of identifying risk factors for suboptimal adherence to adjuvant HT treatment in patients with early BC.

Certainly, here's the revised text with square brackets:

Our study demonstrated an adherence rate of 22.9%, which is comparable to what has been reported nationally[8,9] and in international studies. For instance, Davies S and Voutsadakis IA found a non-adherence rate of 21.2% at 3 years[2]. Similarly, in Sweden, an academic study from 2012 revealed that 69% of patients continued treatment 3 years after initiation[31], while in the United States, research by Partridge AH. and colleagues showed that between 50 and 68% of patients remained on HT after 3 years[32]. Furthermore, a review highlighted that premature discontinuation of HT occurs in 23 to 28% of

patients in clinical trials and between 30 and 50% in routine clinical practice[33].

Our research identified that the main reason for poor treatment adherence, as reported by 72.7% of patients with low adherence (n=16), was forgetting to take the medication. Additionally, 31.8% of these patients indicated intentionally interrupting the treatment, either when feeling well (4 patients) or when experiencing discomfort (3 patients). These findings underscore the need to address the underlying causes of non-adherence to hormonal therapy. Specifically, two crucial aspects are highlighted: the tendency to forget the treatment and the decision to interrupt it based on perceived well-being or the presence of adverse symptoms. These elements should be considered when developing strategies to improve treatment adherence, emphasizing the importance of patient education and continuous support to manage both forgetfulness and reactions to changes in their health status.

In our study, we observed higher treatment adherence in patients treated with aromatase inhibitors compared to those who received tamoxifen. However, the results in the literature are varied in this aspect. Some international studies have found higher adherence in patients treated with tamoxifen[3,5], while other studies, both international[2] and national[9], have not reported significant differences in adherence between the two types of drugs.

Several studies have shown that patients living with a partner tend to have higher treatment adherence[34,35], although there are also studies indicating the opposite[36]. In our study, we observed that patients living alone exhibited higher treatment adherence. This could be attributed to several factors: greater autonomy and self-management in healthcare, fewer family responsibilities interfering with treatment, greater control over daily routines, a more focused approach to self-care, and potentially less stress due to complicated family dynamics.

In our study, although we observed that patients who received chemotherapy this was not significant. This trend has been evident in various studies[2,3], and can be explained by several interconnected factors. These patients tend to have a greater awareness of the severity of their illness due to the intensive experience of chemotherapy, which possibly reinforces their commitment to complete treatment, including hormone therapy. Additionally, their more frequent engagement with the healthcare system provides them with better access to education about the importance of treatment and more regular follow-up, facilitating adherence. It is also possible that their experience in managing the side effects of chemotherapy better prepares them to cope with those of hormone therapy, and they perceive a greater overall benefit in following all treatment recommendations to improve their chances of success in the fight against cancer.

Future research could employ longitudinal designs to better understand the dynamics of treatment adherence over time. Additionally, it would be beneficial to explore specific interventions based on the identified risk factors and assess their effectiveness in improving treatment adherence.

The key strengths of our study include the fact that patients were only treated at 2 centers,

which limits differences in their follow-up and management, and the detailed use of the Morisky-Green questionnaire to assess adherence, thus providing reliable and relevant data. Additionally, the comprehensive evaluation of demographic, occupational, and tumor-related variables contributes to a comprehensive understanding of the factors influencing treatment adherence. However, a notable limitation is that our study is based on a cross-sectional evaluation and self-reported data, which could introduce biases, although complete anonymity was ensured to minimize the possibility of inaccurate responses.

It is recommended that future research adopt longitudinal approaches to gain a deeper understanding of how treatment adherence evolves over time. Additionally, it would be beneficial to investigate and test interventions specifically designed to address the identified risk factors, in order to determine their impact on increasing treatment adherence.

Conclusion

Low adherence to adjuvant HT treatment in BC is a well-recognized challenge, and our research adds valuable insight into this issue. Although the specific causes of non-adherence were not evaluated, our study provides a unique perspective on real-life patient subgroups with a high prevalence of non-adherence. To the best of our knowledge, this is one of the first studies in our setting to address this specific issue. The findings are crucial for designing future intervention studies that focus on high-risk patients, with the aim of improving their treatment adherence. These studies should incorporate comprehensive interventions that combine behavioral, educational, and affective aspects to be effective.

Conflict of Interest:

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