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ORIGINAL ARTICLE / *ARTIGO ORIGINAL*

Factors associated with adherence and persistence to hormonal therapy in women with breast cancer

Fatores associados à adesão e à persistência na hormonioterapia em mulheres com câncer de mama

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ABSTRACT: ***Introduction:*** Hormonal therapy in breast cancer is essential to the transition from active treatment to care survival, because it improves long-term survival and provides a better quality of life. reducing hospital costs as well. However, adherence and persistence in the recommended treatment are important to achieve the desirable results. ***Methodology:*** This is a cohort retrospective study of 182 women on hormonal treatment identified at a high complexity oncology unit, in the southeastern region of Brazil, and followed-up until 2014. We performed a bivariate analysis to analyze the factors associated with adherence and we conducted the multivariate Cox regression to identify variables associated with discontinuity of treatment over time. ***Results:*** Overall adherence was 85.2% and persistence was 45.4% at the end of 5 years. No association was found between the studied independent variables and adherence. Women with advanced stage (HR = 2.24; 95% confidence interval 1.45 – 3.45), who did not undergo surgery (HR = 3.46; 95%CI 2.00 – 5.97), and with three or more hospitalizations (HR = 6.06; 95%CI 2.53 – 14.54) exhibited increased risk of discontinuity. ***Discussion:*** The variables associated with persistence reflect the relation between the highest disease severity and the discontinuity of adjuvant hormonal treatment. ***Conclusion:*** Despite the high adherence level, there is a progressive increase in non-persistence among women on hormonal therapy, influenced by characteristics related to disease severity, which contributes to an inadequate therapeutic response.

Keywords: Breast neoplasms. Antineoplastic agents, Hormonal. Medication adherence. Patient dropouts. Risk factors. Drug therapy.

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RESUMO: ***Introdução:*** A hormonioterapia no câncer de mama é fundamental para a transição do tratamento ativo aos cuidados de sobrevivência, pois melhora significativamente os resultados de sobrevida em longo prazo, além de propiciar melhor qualidade de vida e reduzir os custos de hospitalização. Porém, para atingir resultados desejáveis, são importantes a adesão e a persistência no tratamento recomendado. ***Metodologia:*** Estudo de coorte retrospectivo com 182 mulheres em tratamento hormonal identificadas em unidade oncológica de alta complexidade da Região Sudeste do Brasil e acompanhadas até 2014. Foram realizadas análise bivariada, para investigar os fatores associados à adesão, e regressão multivariada de Cox, para identificar variáveis associadas à descontinuidade do tratamento ao longo do tempo. ***Resultados:*** A adesão geral foi de 85,2% e a persistência, de 45,4% após 5 anos. Não foi encontrada associação entre as variáveis independentes estudadas e a adesão. Mulheres com estadiamento avançado (*hazard ratio* – HR = 2,24; intervalo de confiança de 95% – IC95% 1,45 – 3,45), que não realizaram cirurgia (HR = 3,46; IC95% 2,00 – 5,97) e com 3 ou mais internações hospitalares (HR = 6,06; IC95% 2,53 – 14,54) exibiram maior risco de descontinuidade. ***Discussão:*** As variáveis associadas à persistência refletem a relação entre a maior gravidade da doença e a interrupção do tratamento hormonal adjuvante. ***Conclusão:*** Apesar da alta adesão, observa-se aumento progressivo do número de pacientes que não persistem no tratamento, devido a características relacionadas à gravidade da doença, contribuindo para uma resposta terapêutica inadequada.

Palavras-chave: Neoplasias da mama. Antineoplásicos hormonais. Adesão à medicação. Pacientes desistentes do tratamento. Fatores de risco. Tratamento farmacológico.

INTRODUCTION

Use of the hormonal therapy to treat breast cancer has a main role in the transition from active treatment to survival care, because it significantly improves long-term survival results. Studies show that using such drugs to treat breast cancer at early stages may decrease the risk of recurrence and mortality to 15 years and, therefore, it is recommended as a preventive measurement in 75 to 80% of the disease cases[1,2]. In addition, considering that oral medications are used, hormonal therapy may also provide better quality of life to ill subjects with more feeling of control on the therapeutics and less interference in social life[3]. Another benefit of the hormonal therapy in comparison with the conventional chemotherapy is its cost-effective strategy in hospitalization, equipment, and human resources[4,5].

The main hormonal agents used in breast cancer treatment include the selective estrogen receptor modulators — tamoxifen (TMX) — and the aromatase inhibitors (AIs), such as anastrozole. To update the guideline of clinical practice in adjuvant endocrine therapy, the American Society of Clinical Oncology (ASCO) conducted a systematic review on the optimal treatment duration throughout the years 2009-2013. They found survival, recurrent disease and occurrence of adverse events as the outcomes of interest. The earlier guidelines of ASCO recommended five years of treatment with TMX or AIs. However, current evidence suggests the treatment should last ten years[1]. The last protocol presented in

2011, by the Brazilian Medical Association [*Associação Médica Brasileira* (AMB)] and by the Supplementary Health Brazilian Agency [*Agência Nacional de Saúde Suplementar* (ANSS)], during the project *"Diretrizes – Câncer de Mama: Terapia Endócrina e Terapia-Alvo"*, recommends that hormonal therapy should also be used for all patients with a positive hormone receptor and during a 5-year period, without considering complementary benefits after treatment prolongation.

All benefits of hormonal therapy are well-known, including increase of survival. In addition, the medication is distributed by the Brazilian Unified Health System (SUS) for free. Nevertheless, the desirable results many times are not achieved due to problems such as low adherence and low persistence in the recommended treatment, whose associated factors should be carefully evaluated. Evidence ensures that benefits in the change from the mortality and disease recurrence rates only happen effectively if the treatment is completely followed[6,7].

Attention has been given to adherence and persistence studies (A & P) due to the concept that clinical results of the treatment are not only affected by how patients take the drugs, but also by the period of uninterrupted use[8]. Therefore, adherence and persistence should be separately defined and measured to characterize the medication intake in a broader manner, thus providing more understanding on this conduct[8,9].

It is known that adherence and persistence may be influenced by several factors related to the patient, such as treatment, health services, beliefs, and life habits[2,10]. The performance of researches able to measure such phenomena and to portray them in a defined context represents an important strategy for comparing, understanding and producing evidence for health services and professionals to promote the success of the employed therapy, the improvement of patient's quality of life and, finally, the reduction of mortality[2,10,11].

Hence, this study aimed to determine the adherence, persistence, and associated factors among breast cancer patients that received adjuvant hormonal therapy in a reference hospital from the city of Muriaé, Minas Gerais State, Brazil.

METHODOLOGY

We performed an analytical and longitudinal study based on secondary data collection of breast cancer women who underwent adjuvant hormonal therapy, receiving treatment in a high-complexity oncology hospital that is known for its cancer treatment and that provides treatment for more than four million residents in Muriaé, Minas Gerais[12].

The study population comprised a cohort of women diagnosed with breast cancer, older than 18 years and treated in the mentioned hospital, who had begun hormonal therapy in the year of 2009 and had their medications dismissed more than once until December 31st, 2014, according to data from the hospital pharmacy department. The study removed patients without registration in such database with the record of at least two different dates.

We collected the following information available in registrations from different service departments:

1. dismissal control of hormonal therapy drugs from the pharmacy department – electronic database created to enable funding at SUS, which provides information for the A & P calculation in each patient's treatment, such as kind of drug (TMX or anastrozole), dismissal date, and quantity;
2. electronic medical record, through which we collected information regarding the sociodemographic, clinic, and support characteristics of the patient receiving treatment, which are important to identify factors that influence such behaviors. We used the women's number of enrollment to integrate data.

This study adopted the recommendation of one daily tablet of hormonal therapy for 5 years[13-15]. TMX and AIs, such as anastrozole, play the role of medications distributed for free by SUS in the study hospital for breast cancer treatment. All the cohort women began their hormone therapy between January 1st and December 31st in 2009, without censure on the left in the observations; the follow-up of women receiving hormonal therapy for more than 5 years was incomplete by the end of the period established for observation.

The study dependent variables included adherence and persistence. According to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), adherence is the level in which the patient works accordingly to the prescribed daily treatment regarding the time, dose and frequency; and persistence is understood as the time since the beginning until the interruption of the drug therapy[8].

The method used for adherence calculation was the medication possession rate (MPR), based on the group of individual prescriptions in the following way: (total of days with the required medication)/(last date of drug dismissal – date of beginning + amount of medication delivered in the last dismissal). The result of this equation was converted into percentage and patients that obtained a value equal or higher than 80%[16] were considered adherents.

We calculated the persistence measurement through the estimated level of persistence with therapy (ELPT) method, which considers the time between the beginning of the hormonal therapy and its abandonment or discontinuity for 60 days or longer by doing the accounting of the last supply of the obtained medication[6,17]. Non-persistent was the patient that discontinued treatment during the mentioned term and without death confirmation. We considered therefore women who changed medications during the treatment by medical recommendation and satisfied the principles of A & P proportionally to the time of use of each medication.

The independent variables of interest were divided into three subgroups and, then, they were categorized to facilitate comparison with other studies:

1. sociodemographic characteristics – age at diagnosis (until 40 years old; 50-69 years old; 70 years old or older)[18]; educational level in years of complete studies (low,

intermediate or high educational level)[18]; marital status (with or without partner)[6]; and self-reported race (white or non-white)[19];

2. clinical characteristics – staging, according to the classification of malignant tumors (TNM)[20] (initial – stages 0, I and II; and advanced – III and IV)[6]; comorbidities described in medical record (yes or no); family history of cancer; Charlson comorbidity index (CCI)[21] (attributing two points in the report of only one neoplasm, and three points, four or more according to the quantity of self-reported comorbidities);
3. support characteristics – kind of hormonal therapy (TMX or anastrozole); performance of chemotherapy, radiotherapy and surgery; number of appointments in clinical oncology (up to 13 appointments and 14 or more)[6]; number of hospitalizations during the observation period (none; up to 2; 3 or more)[19].

To analyze the factors associated with adherence, we performed bivariate analyses using the chi-square test. To verify the factors associated with persistence, we used the methodology of survival analysis. The beginning of persistence counting time was considered as the date of hormonal therapy beginning. To analyze survival, we considered the discontinuity (loss of persistence) occurred until the end of the study follow-up. The follow-up time was censored in 60 months for women who persisted until the end of the follow-up or for those who died. The cases confirmed as follow-up loss were censored in the date of the last follow-up in the pharmaceutical department.

The persistence probabilities were calculated according to the method proposed by Kaplan-Meier and then compared, regarding the variables through the log-rank test. To evaluate the prognostic factors, we used the model of Cox proportional risks by computing the hazard ratio (HR) and their corresponding values of 95% confidence interval (95%CI). We chose the variables through the significance obtained in the univariate Cox model ($p \leq 0.2$) and its clinical relevance. The variables included in the multiple analysis were removed according to the backward elimination process. The final model included women who remained statistically significant ($p < 0.05$). We used the likelihood-ratio test to verify the significance of the parameters of the reduced models and Schoenfeld's residual diagnosis test to assess the proportionality of Cox models[22]. Input and descriptive analysis of data were conducted in the Statistical Package for the Social Sciences (SPSS) program, version 15.0, and we used the STATA program, version 12.0, to analyze survival and prognostic factors.

We submitted the study for the Research Ethics Committee from *Universidade Federal de Juiz de Fora* (UFJF) that approved the project under protocol number 844.852.

RESULTS

182 women began hormonal therapy in the study period. The average age at diagnosis was 58.2 years old (± 13.5), varying from 31 to 88 years old. Most of the women were not

white (54.4%), had educational level from 1 to 8 years (62.1%) and were married (47.3%). Regarding the menopause condition, 121 (66.5%) were in the post-menopausal period. Infiltrating ductal carcinoma was the most frequent histological type (n = 136; 74.7%). All cases were positive for estrogen (ER) and/or progesterone receptor (PgR), distributed into: 120 positive cases only for the ER (66%), 11 positive cases only for the PgR (6%) and 51 cases positive for both receptors (28%). Most of the women were diagnosed with the disease in the initial stage (EC 0, I and II) (67.5%). Exclusive treatment with TMX was described in 72.0% of the sample. All women received chemotherapy (except for hormonal therapy); most of them performed radiotherapy (77.5%) and surgery (78.0%). The mean of appointments with an oncologist was equal to 9.00 (IIQ 3.62), whereas the mean of hospitalizations during the study period was 2.00 hospitalizations (IIQ 2.00) (Table 1).

Adherence between the participants was 85.2% (95%CI 79.2 – 89.8); of whom 47.7% (95%CI 39.8 – 55.7) remained under treatment. Treatment persistence after 5 years was 49.5% (95%CI 42.2 – 56.7); however, such behavior changed throughout time and presented rates of 83.5% in the end of the first year, 66.5% in two years; 53.4% in three years, 51.6% in 4 years, and 45.2% in the last year (Figure 1).

We did not observe any statistically significant association between adherence to hormone therapy and the independent variables studied (Table 2). The factors associated with more probability of persistence include: initial stage of the disease at diagnosis; use of TMX; undergoing radiotherapy and surgery; number of appointments with oncologist based on recommendations ($n \geq 14$). and lower frequency of hospitalizations (Table 3). None of the variables related to socioeconomic characteristics seemed to be associated with higher probability of persistence.

Table 4 shows crude and adjusted HR values of the variables chosen for the multivariate model. Advanced stage at diagnosis, non-performance of surgery and larger number of hospitalizations showed higher risk of hormonal therapy discontinuity. Such variables did not violate the risk proportionality principle, with a non-significant p-value of Schoenfeld residual tests for the overall result (0.56) and for each variable.

DISCUSSION

We observed, in the studied population, that most of the patients (85.2%) adhered to hormonal therapy, but only 49.5% finished their treatment without significant interruptions. Such results, similarly to those found by other authors[2,23,24], confirm that even though adherence to adjuvant hormonal therapy is, in general, high (70 – 80%), there is a progressive increase of the non-persistent patients in the treatment throughout time.

Although these results were closer to those observed in previous studies, slight differences are seen regarding the eligibility criteria of the studied population (some studies include only patients with initial tumors; others analyze prospective or retrospective cohorts of young or aged women, among other aspects) and regarding the methodology used to define

Table 1. Distribution of clinical and support characteristics of women with breast cancer undergoing hormonal therapy, Brazil, 2015.

Variable	Absolute frequency (n)	Relative frequency (%)
Clinical characteristics		
Family history of cancer		
Yes	75	41.2
No	84	46.2
Comorbidities		
Yes	91	50.0
No	91	50.0
Charlson Comorbidity Index		
2 (presence of neoplasm only)	91	50.0
3	76	41.8
4 +	15	8.2
Stage		
I	50	27.5
II	69	37.9
III	55	30.2
IV	7	3.8
Support characteristics		
Hormonal therapy		
Tamoxifen	131	72.0
Anastrozole	51	28.0
Clinical oncology (number of appointments)		
1 to 4	41	22.5
5 to 13	76	41.8
14 +	65	35.7
Hospitalizations (number)		
None	26	14.3
Up to 2	71	39.0
3 +	85	46.7

P.S.: We did not include information that were not in the consulted databases and medical records.

and calculate the A & P (such as the use of the proportion of days covered for the adherence analysis, among other methods, and serum dosage or concentration in the urine of the drug under use for persistence evaluation), which many times make comparisons with other findings more difficult[25-27]. Among the variety of methods to estimate the A & P, those based on retrospective data are still more used due to their easiness of calculation and low cost, besides presenting closer rates to the real ones, when compared with studies that use direct methods to determine such behaviors[14,28,29]. Regarding persistence estimates, we need to relativize the results, given the adopted concept considers the interruption of treatment for more than or 60 days. Women considered non-persistent may have returned to complete the treatment during the recommended period and, therefore, they can be considered adherent according to the used method. Nevertheless, women who experience larger lacks in the endocrine treatment for breast cancer will not probably enjoy the benefits regarding disease recurrence and survival[30,31].

The association between independent variables and adherence based on the bivariate analysis was more difficult due to the high index of adherent women in the study. We assume that calculation, based on the medication possession ratio (MPR), might overestimate such behavior when considering only the time with medication on hands in the denominator, instead of the entire period of treatment[32]. This is a limitation, but we believe

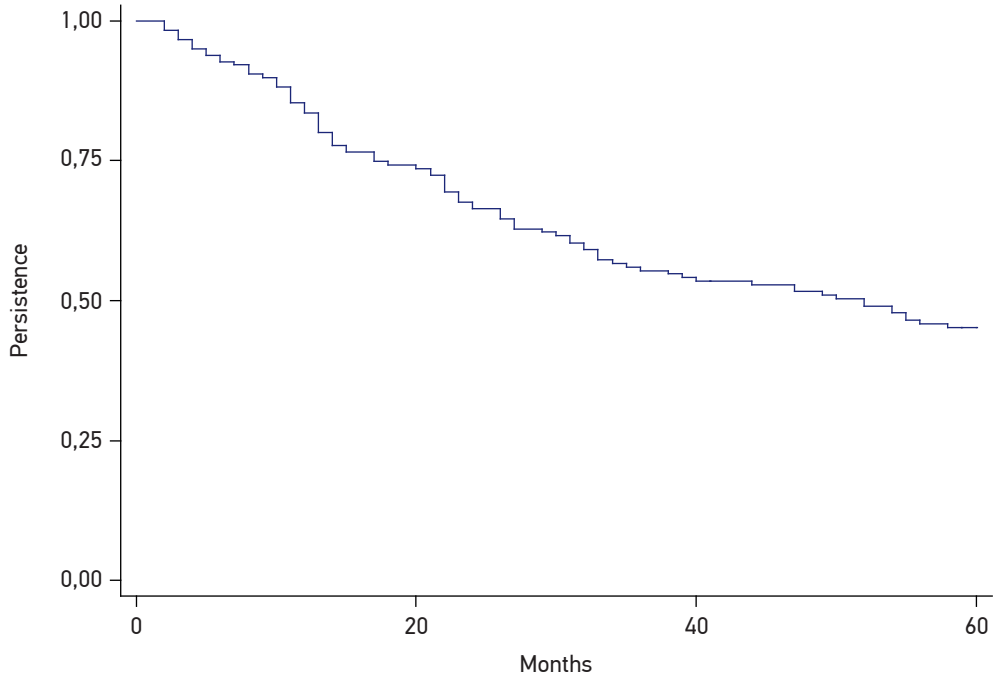

Figure 1. Kaplan-Meier estimator curve for persistence to hormonal therapy in a cohort of women with breast cancer undergoing treatment between 2009 and 2014, Brazil, 2015.

this bias may be understated when such estimates are made from the secondary database of great populations[33].

We observed that variables associated with persistence, which were maintained in the final model of the multivariate analysis, reflect the relation between the highest disease severity and the interruption of the adjuvant hormonal treatment. Women with advanced stage

Table 2. Bivariate analysis of independent characteristics according to adherence to hormonal therapy in breast cancer.

Variable	Adherence		
	%	OR (95%CI)	p-value
Family history of cancer			
No	81.0	1	0.223
Yes	88.0	1.402 (0.239 – 1.402)	
Stage			
Advanced	88.7	1	0.323
Initial	83.2	0.630 (0.251 – 1.584)	
Comorbidities			
≥ 1	89.0	1	0.144
None	81.3	0.537 (0.231 – 1.248)	
Hormonal therapy			
Anastrozole	88.2	1	0.468
Tamoxifen	84.0	0.698 (0.264 – 1.845)	
Clinical oncology (number of appointments)			
≥ 14	84.6	1	0.877
≤ 13	85.5	1.070 (0.458 – 2.496)	
Surgical treatment			
No	82.5	1	0.591
Yes	85.9	1.294 (0.504 – 3.332)	
Radiotherapy			
No	87.8	1	0.589
Yes	84.4	0.751 (0.266 – 2.166)	
Hospitalization (number)			
≥ 3	84.7	1	0.342
Up to 2	81.7	0.806 (0.347 – 1.871)	
None	96.2	4.154 (0.562 – 36.284)	

OR: odds ratio; 95%CI: 95% confidence interval.

are more susceptible to discontinuing the treatment. This relation has also been observed in previous studies[6,23], in which women with more involved lymph nodes presented a higher rate of discontinuity and, as a consequence, lower success in the employed therapy, which also reaffirms the known inverse relation between the survival rate and the cancer stage at the moment of diagnosis[7].

Table 3. Probability of non-adjusted persistence of breast cancer hormonal therapy treatment according to characteristics of the studied population.

Variable	Persistence probability		
	%	95%CI	p-value
Family history			
No	50.5	38.94 – 60.94	0.341
Yes	40.9	29.00 – 52.39	
Stage			
Initial	56.6	47.01 – 65.07	≤ 0.001
Advanced	18.4	8.54 – 31.15	
Comorbidities			
≥ 1	44.6	33.65 – 54.99	0.832
None	45.9	34.97 – 56.15	
Hormonal therapy			
Tamoxifen	57.5	48.30 – 65.67	≤ 0.001
Anastrozole	8.0	2.10 – 19.22	
Clinical oncology (number of appointments)			
≥ 14	88.2	76.77 – 94.19	≤ 0.001
≤ 13	19.8	12.78 – 28.02	
Surgical treatment			
Yes	48.2	39.35 – 56.51	0.036
No	32.4	19.49 – 49.63	
Radiotherapy			
No	23.2	11.00 – 37.95	≤ 0.002
Yes	51.3	42.32 – 59.47	
Hospitalization (number)			
None	66.2	43.55 – 81.55	≤ 0.001
Up to 2	61.2	48.11 – 71.97	
≥ 3	26.5	17.32 – 36.56	

95%CI: 95% confidence interval.

Non-performance of surgery was also related to a higher probability of non-persistence to treatment, which is in agreement with other studies[32,34]. A possible explanation for this relation is that the surgical procedure is many times indicated for patients with earlier stage, whereas in women with advanced disease, this therapeutic modality is often forgotten, considering the systemic treatment is prioritized[6,25]. According to Kemp, women undergoing more aggressive treatment may notice their condition as more severe and recognize their increased need of endocrine therapy. Risk of non-persistence increased with the number of hospitalizations. For Brito et al., although many studies do not associate this variable directly, such relation may be explained by the disease severity and the presence of other comorbidities and side effects, producing different responses to treatment[6]. Presence and severity of disease symptoms are factors that might interfere in the treatment follow-up[35].

We must emphasize that although there has been significance only in the non-adjusted survival analysis, the number of specialized appointments is considered relevant. The direct relation between a higher number of appointments and the higher probability in persisting to treatment reflects the importance of the doctor-patient relationship, both in the provision of information regarding the treatment and also in the appearance of side effects and their handling, as well as in the emotional support even after the disease active treatment. Evidence shows that most of the patients, after completing the "initial" phase of treatment (i.e. surgery, chemotherapy and radiotherapy), do not continue using the oncologist figure as his/her main care provider, which makes the maintenance of hormonal therapy more difficult[2,36,37]. Reasons for therapy discontinuation may change throughout the treatment; therefore, the professional must understand them to overcome them, by emphasizing the importance of its follow-up to patients[38].

Table 4. Crude and adjusted hazard ratios of the variables chosen for the multivariate model for persistence to hormonal therapy.

Variables	Gross HR	95%CI	Adjusted HR	95%CI
Stage				
Initial	1		1	
Advanced	2.53	1.66 – 3.86	2.24	1.45 – 3.45
Surgical treatment				
Yes	1		1	
No	1.63	1.03 – 6.01	3.46	2.00 – 5.97
Hospitalization (number)				
None	1		1	
Up to 2	1.21	0.55 – 2.69	2.21	0.92 – 5.29
≥ 3	3.04	1.49 – 6.37	6.06	2.53 – 14.54

HR: hazard ratio; 95%CI: 95% confidence interval.

CONCLUSION

Although adherence is higher in this cohort (85.2%), we found an important decrease in the persistence rates year by year that reached a percentage value below 50% in the last year of treatment, which reinforces the importance of measuring such behaviors together. We must adopt such measurement not only to better understand the related factors and identify patients requiring more intervention in a more effective way, but also to assess the clinical and economic results, considering that low rates have been associated with side results and with high health care costs.

Increase in the discontinuity risk to hormonal therapy has been associated with characteristics related to the disease severity, which also reflects a high number of breast cancer diagnoses in advanced stages. Considering that the use of adjuvant hormonal therapy in these cases significantly reduces the appearance of secondary tumors and, consequently, improves the survival rates, strategies should be thought so that women may experience the benefits of this therapeutic modality.

Due to the retrospective character and secondary base of this study, we could not assess important questions regarding the patients, such as appearance and handling of side effects, as well as their beliefs and habits, which are described in literature as potentially associated with treatment discontinuation. Therefore, identifying such determiners that may be modifiable is an important factor for the development of interventions that aim to improve such behaviors.

This study aimed to contribute with information that enable the discussion on questions related to the operationalization of A & P studies for chronic pathologies, especially considering Brazilian results. Thus, it provides important reflections on the joined approach of A & P with hormonal therapy and collaborates for the analysis of the Brazilian Policy of Oncological Attention.

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