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CLINICAL TRIAL

Tamoxifen adherence and its relationship to mortality in 116 men with breast cancer

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Abstract Recent studies have revealed that many, perhaps most women with hormone-responsive breast cancer have low adherence to tamoxifen adjuvant hormonal therapy. However, limited data are available on tamoxifen adherence in male breast cancer (MBC) patients. The goal of this study was to assess tamoxifen adherence and its relationship to mortality in MBC patients. A cohort of 116 men who were diagnosed with receptor-positive breast cancer between June 1987 and July 2012 was recruited for the study using the cancer prevention and treatment system database of Heilongjiang Province. From the 116 patients who received a five-year tamoxifen prescription, only 64.6 % were still taking their medication 1 year later, and this percentage decreased to 46.4 and 28.7 % after 2 and 3 years, respectively, to 25.8 % after 4 years, and to 17.7 % in the last year. After multivariate adjustment, factors that significantly decreased tamoxifen adherence were low social support [Hazard ratio (HR) = 2.45, 95 % CI 1.32–4.55], age (HR = 1.10, 95 % CI 1.01–1.21), and adverse effects (HR = 2.19, 95 % CI 1.57–3.04). The primary endpoints in the adherence or low-adherence groups from this study were overall survival (OS) and disease-free survival (DFS) of the MBC patients. The five- and ten-year OS of the patients was 97.9 and 79.6 %, respectively, in the adherence group, and 84.7 and 50.4 %, respectively, in the low-adherence group ($p = 0.008$). The five- and ten-year DFS of the patients was 95.4 and 72.8 %, respectively, in the adherence group, and 72.6 and 42.3 %, respectively, in the low-adherence group ($p = 0.007$). The consequences of low treatment adherence in men, who have a potentially long life expectancy, may be significant. In light of these findings, there is an urgent need to acknowledge and tackle the issue of tamoxifen adherence in this patient group.

Keywords Adherence · Male breast cancer · MBC · Tamoxifen · Overall survival · OS · Disease free survival · DFS · Adjuvant endocrine treatment

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Introduction

Male breast cancer (MBC) is an uncommon disease, accounting for less than 1 % of all breast cancer cases worldwide [1–3]. Compared with female breast cancer (FBC), MBC occurs later in life and resembles postmenopausal breast cancer [4]. MBC is a specific subgroup of breast cancer. First, due to its rarity, the principles of management are largely derived from randomized trials performed in women. Second, the prognosis of MBC may be more severe than in women if the diagnosis is delayed as a result of ignorance with regard to the existence of this condition in

males. Third, as a result of endocrine therapy, MBC patients report more side effects, such as decreased libido and weight gain, as well as serious complications, such as deep venous thrombosis, as compared to women, and the drop-out rate is about 20 % in less than a year [5, 6].

Tamoxifen, an estrogen receptor antagonist in the breast tissue, is considered the standard therapy for hormone receptor-positive breast cancer in pre-menopausal women, as it may reduce the risk of recurrences and it increases survival rates in FBC patients [7]. Meanwhile, tamoxifen is also generally accepted as the standard of care for adjuvant hormonal therapy in MBC patients [8]. Several retrospective studies have compared the outcomes of MBC patients who were treated with tamoxifen in an adjuvant setting with those who received no hormonal therapy, and found improved overall survival (OS) and disease-free survival (DFS) rates in men receiving adjuvant tamoxifen [9–11].

Nonadherence to oral medication is an increasingly recognized concern in the care of patients with breast cancer [12]. Studies on adherence to tamoxifen have mainly focused on FBC patients, while little has been discussed on MBC patients. Low levels of tamoxifen adherence are likely to result in significantly worse outcomes for FBC patients [13–18]. We do not know whether the outcomes with respect to this issue, for MBC patients, are similar to the ones for FBC patients. Reliance on tamoxifen endocrine therapy, as revealed by studies conducted in women, is based on the assumption that MBC and FBC are the same disease and may be managed identically, but it is not certain whether this is really true. It is therefore crucial to evaluate tamoxifen adherence and its relationship to mortality in MBC patients.

Methods

Data sources

The Cancer Prevention and Treatment System database of Heilongjiang Province (CPTS) constituted the primary data source for patient selection. The study area covered four administrative regions comprising over 10 million inhabitants. The treatment of MBC patients, reported to the CPTS database by their physicians, includes information on drug characteristics such as name, dosage, and the number of pills.

Study population

The study cohort, established in June 1987 to document the impact of the patients' quality of life and survival, comprised 181 MBC patients by the end of July 2012. Pathology samples collected from eligible participants diagnosed with primary breast cancer were rechecked by pathologists. Men with a previous history of breast cancer, serious cognitive problems, or psychiatric diseases were excluded. The study was approved by the Medical Ethics Committee of Heilongjiang Province. All members received at least one supply of tamoxifen, as registered in the CPTS medical database.

Data collection

All eligible MBC patients registered in the CPTS database were sent an explanatory letter about the study. Men who agreed to participate were sent a self-administered questionnaire. In parallel with each interview, a medical questionnaire was sent to the patient's physician who was in charge of the cancer treatment. This questionnaire covered the patient's medical history, physical examination, histology, tumor staging and grading, HR/PR/Her-2 status, and primary treatment, such as surgery, chemotherapy, radiation therapy, and endocrine therapy.

Twelve months after diagnosis, a telephone interview was used to collect data on treatment, socio-demographic characteristics, and self-reports of adherence. Men's perception of their quality of life (QOL) was collected using the WHOQOL-BREF questionnaire [19–21]. To evaluate whether they had low social or material support, participants were asked about the numbers of persons who brought them material and mental support.

Definition of adherence

Adherence was calculated via patient self-reports with a detailed questionnaire. Tamoxifen adherence was defined as the number of days covered by tamoxifen divided by the number of days between the cohort entry date and the date of the last tamoxifen prescription [22]. This proportion equals the medication possession ratio (MPR) [23]. Men whose MPR exceeded 80 % were considered adherent. Conversely, MPR values under 80 % were regarded as showing low adherence [24–28].

Assessment of survival

The primary endpoints of this study were OS and DFS in MBC patients with or without tamoxifen. Five- and ten-year OS and DFS were assessed in this study. OS was calculated from the date of diagnosis to the date of death; DFS was calculated from the date of diagnosis to the date of disease recurrence or death.

Statistical analysis

The analysis was conducted with men who received at least one tamoxifen prescription. Cohort entry was the date of the

first tamoxifen prescription. Follow-up of the participants ceased upon death, disease recurrence, or on July 31st 2012, whichever came first. Time to tamoxifen adherence was calculated using the Kaplan–Meier method. Different subgroups were compared using the log-rank test.

A multivariate analysis was performed to identify independent predictors of adherence using the Cox proportional hazards model. Variables with a p value <0.20 in the univariate analysis were included in the initial multivariate model. Only variables significantly associated with tamoxifen adherence, with a p value <0.10, were kept in the final model.

OS and DFS curves were also calculated using the Kaplan–Meier method to compare the difference between the adherence and the low-adherence groups. A multivariate analysis was applied to identify independent predictors of OS and DFS using the Cox proportional hazards model. All statistical analyses were performed using the SPSS version 13.0 software program.

Results

Population characteristics

From June 1987 to July 2012, 181 MBC patients were identified from the CPTS database. Among the patients, 12 (6.6 %) were found to be non-eligible because they presented metastases at diagnosis, 31 (17.1 %) did not agree to participate, 10 did not complete the questionnaire, and 12 had no medical data available. Our analysis of the factors associated with tamoxifen adherence was therefore conducted among the remaining 116 men.

The 116 men were followed for a median period of 7.08 years (interquartile range = 5.02–11.00 years). Patients' socio-demographic, medical, and psychological characteristics are described in Table 1. At the time of diagnosis, the mean age of the patients was 62.8 years (SD = 12.3). With respect to medical history, 8 patients had severe co-morbidities (such as asthma, diabetes, cardiac complaints, tuberculosis, and/or Hodgkin's disease). Twenty-seven (23.3 %) men were diagnosed in stage 1, 70 (60.3 %) in stage 2, and 19 (16.4 %) in stage 3 of the disease. Most tumors were estrogen—(91.4 %) and progesterone—(82.8 %) receptor positive. HER-2/neu proto-oncogene over-expression was seen in 7 (6.0 %) patients using the combination of fluorescence in situ hybridization and immunohistochemistry. Twelve months after diagnosis, 16 (13.8 %) patients reported, in telephone interviews, low adherence during the preceding month.

Adherence to tamoxifen

Among the 116 participants fulfilling the inclusion criteria, 15 (8.3 %) who did not fill any prescriptions and 50 (43.1 %) who had MPR values lower than 80 % were regarded as having low adherence. The remaining 51 men were considered tamoxifen-adherent for the whole duration of the endocrine therapy. At the beginning, the adherence rate was 86.2 %; after 1 year of tamoxifen intake, 64.6 % of the participants continued their treatment; this percentage decreased to 46.4 % after 2 years, 28.7 % after 3 years, 25.8 % after 4 years, and 17.7 % in the 5th year. The rate of treatment adherence decreased sharply during years 1 and 2 of treatment and moderately during years 3–5 (Fig. 1). After multivariate adjustment, tamoxifen adherence decreased significantly with low social support ($p = 0.002$), young age ($p = 0.038$), and drug-induced side effects ($p = 0.007$) (Table 2).

Cox proportional hazards model for all-cause mortality

A multivariate model was subsequently used to investigate the adjusted effect of covariates on the participating subjects. After adjusting for all factors, we found that a higher TNM stage, negative estrogen receptor status, and positive Her-2 and AR status increased mortality risk. With respect to adherence, patients in the low-adherence group (adherence <80 %) were at significantly higher risk of death than those in the high-adherence group (adherence ≥80 %) (HR = 2.93, 95 % CI = 1.19–7.24). We found that body index, chemotherapy, radiotherapy, and family tumor history may play a minor role in the mortality risk ($p = 0.468$, 0.333, 0.542, and 0.98, respectively) (Table 3).

Relationship between tamoxifen adherence and survival

OS and DFS differences between the adherence and low-adherence groups were calculated using the Kaplan–Meier method. The five- and ten-year OS in MBC patients were 97.9 % and 79.6 % in the adherence group, and 84.7 % and 50.4 % in the low-adherence group, respectively ($p = 0.008$). The five- and ten-year DFS in the participating patients was 95.4 and 72.8 %, respectively, in the adherence group, compared to 72.6 and 42.3 %, respectively, in patients from the low-adherence group ($p = 0.007$) (Figs. 2, 3).

Adverse effects

Seventy-four (63.8 %) of the 116 patients reported one or more adverse effects from tamoxifen. Adverse effects reported by MBC patients in this study included sweating, sleep disorders, anxiety, decreased libido, weight gain, fatigue, rash, myalgia, and other manifestations, such as visual blurring, loose stools, and abnormal liver function tests. Fatigue, the most common adverse effect, accounted for 21 % of the adverse effects, followed by anxiety and

Table 1 Factors associated with tamoxifen adherence in the cohort ($n = 116$)

		n (%)	Crude RR[a] (95 % CI)	p value
Age				
>60		70 (60.3)	1.0	0.023
≤60		46 (39.7)	1.47 (1.05–2.05)	
Level of education				
Less than middle school certificate		39 (33.6)	1.0	0.333
Middle school certificate or higher		77 (66.4)	1.23 (0.81–1.86)	
Body index				
≤24.0		72 (62.1)	1.0	0.83
>24.0		44 (37.9)	1.01 (0.91–1.12)	
Breast surgery				
Modified radical mastectomy		74 (63.8)	0.94 (0.47–1.88)	0.87
Mastectomy		42 (36.2)	1.0	
Chemotherapy				
No		17 (14.7)	0.89 (0.48–1.65)	0.70
Yes		99 (85.3)	1.0	
Radiotherapy				
No		9 (8.1)	0.76 (0.51–1.11)	0.16
Yes		107 (91.9)	1.0	
Clinical stage				
Stage I		38 (34.1)	1.04 (0.66–1.65)	0.85
Stage II/III		78 (65.9)	1.0	
Adverse effects				
Yes		74 (63.8)	1.96 (1.46–2.62)	<0.001
No		42 (36.2)	1.0	
Physical QOL	$n = 116$	76.2 (17.6)	0.87 (0.53–1.45)	0.6
Social relationships QOL	$n = 116$	63.6 (20.4)	1.00 (0.56–1.77)	0.98
Psychological QOL	$n = 116$	60.8 (19.8)	1.00 (0.64–1.56)	0.97
Self-reported adherence				
No		17 (14.7)	2.37 (1.21–4.64)	0.012
Yes		99 (85.3)	1	
Low social support				
Yes		95 (81.9)	2.49 (1.24–4.98)	0.001
No		21 (18.1)	1	

[a] *RR* relative risk estimated by the hazard ratio calculated

sleep disorders, which represented 20 % and 19 % of the adverse effects, respectively, as shown in the pie chart from Fig. 4 .

Discussion

Many retrospective studies have evaluated tamoxifen adherence in women, but reports discussing adherence in MBC patients are lacking. In our study, low social support, young age, and adverse reactions emerged as predictive factors leading to low treatment adherence in MBC patients. This study supports the idea that the lower tamoxifen adherence is, the greater the hazard ratio of death will be in a MBC patient. Patients in the adherence group who were prescribed tamoxifen had longer survival and DFS in the long run.

For research on tamoxifen adherence in FBC patients, approximately 20 % of tamoxifen users had adherence below 80 % [29–31]. Adherence to tamoxifen may be different in FBC patients after 1 year. A research study on a group of 246 patients reported that 17.0 % of the FBC patients discontinued tamoxifen treatment [32], and in a study on 328 patients, Margaret C reported a non-adherence rate of 16.4 % [33]. Interestingly, at three and a half years, the adherence was at similar levels as in FBC patients [34, 35]. However, for MBC patients in this study, tamoxifen adherence is different from the values reported in other published work, despite the same characteristics of tamoxifen use. An aspect that should be emphasized is the

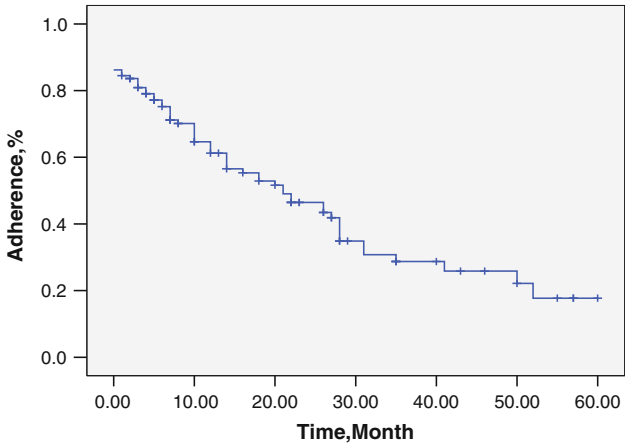

Fig. 1 Curve of tamoxifen adherence

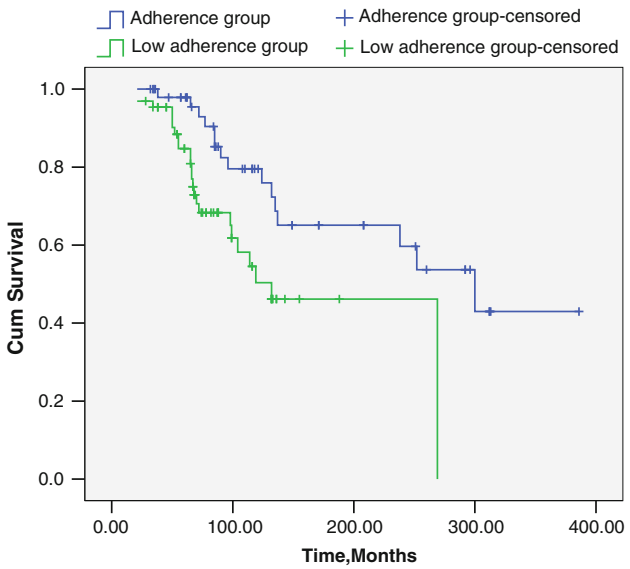

Fig. 2 Overall survival of patients in the adherence versus the low-adherence group

Table 2 Independent factors associated with tamoxifen adherence in a multivariate analysis $n = 116$

		Adjusted hazard ratio[a] (95 % confidence interval)	p value
Low social support			
No	95 (81.9)	1.0	
Yes	21 (18.1)	2.45 (1.32–4.55)	0.0048
Age			
>60	70 (60.3)	1.0	
≤60	46 (39.7)	1.10 (1.01–1.21)	0.046
Adverse effects			
No	74 (87.4)	1.0	
Yes	42 (12.6)	2.19 (1.57–3.04)	<0.001

[a] Hazard ratio calculated in a Cox proportional hazards model

Table 3 Multivariate association between covariates and all-cause mortality

Predictor	Adjusted for covariates		
	HR	95 % CI	p value
TNM stage			
I	1.0		
II	1.47	1.10–1.97	0.009
III	2.86	1.64–4.97	0.0002
ER status			
Positive	1.0		
Negative	1.55	1.16–2.08	0.033
Her-2 status			
Negative	1.0		
Positive	1.59	1.14–2.21	0.006
AR status			
Negative	1.0		
Positive	1.24	1.08–2.36	0.024
Adherence status			
Adherence	1.0		
Low adherence	2.93	1.19–7.24	0.019
Body index			
≤24.0	1.0		
>24.0	1.41	0.92–2.33	0.468
Chemotherapy			
Yes	1.0		
No	1.23	0.81–1.86	0.333
Radiotherapy			
Yes	1.0		
No	1.13	0.76–1.82	0.542
Family tumor history			
No	1.0		
Yes	1.00	0.56–1.77	0.98

link between low treatment adherence and increased disease recurrence and mortality. A study reported a significant increase in DFS and OS in a series of patients who underwent tamoxifen therapy for less than 2 years [11]. Another study found that the five-year survival rate was 61 % in MBC patients treated with adjuvant tamoxifen for 1 or 2 years, and 44 % in participants from a control group that did not take tamoxifen [36]. In our study, the five- and ten-year OS in patients from the adherence group was 97.9 and 79.6 %, and the same values were 84.7 and 50.4 % in patients from the low-adherence group. The five- and ten-year DFS of the patients were 95.4 and 72.8 % in the adherence group, respectively, compared to 72.6 and 42.3 % in the low-adherence group. Indeed, adherence was shown to improve OS and DFS in men with hormone receptor-positive breast cancer.

Many previous studies focused mainly on personal characteristics, without considering the patients' surroundings.

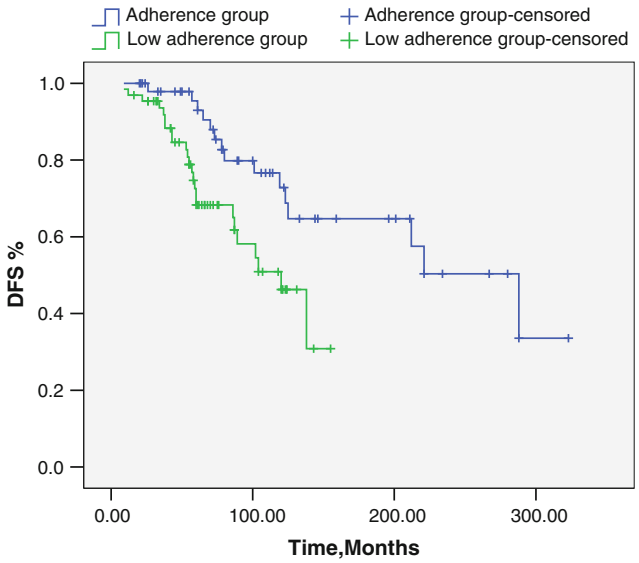

Fig. 3 Disease-free survival of patients in the adherence versus the low-adherence group

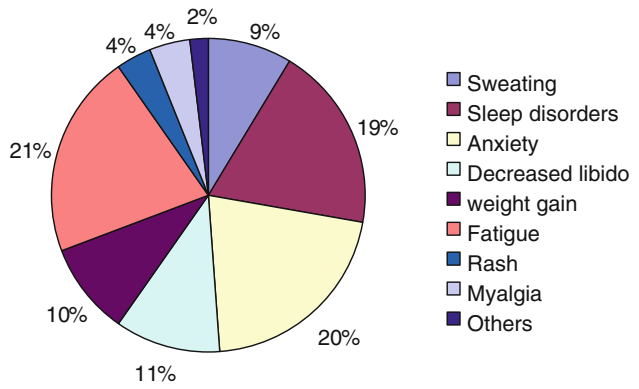

Fig. 4 Distribution of adverse effects from tamoxifen

In this study, we found that low social support was associated with low tamoxifen adherence. There may be many reasons for this finding. For one thing, people from Chinese cities who were enrolled in this study and have low social support may have medical insurance problems. The high cost for examinations and therapy in breast cancer patients may lead to low adherence to tamoxifen and ineffective results of the therapy. Another aspect is that most of the 116 patients enrolled in this study are farmers who are always involved with farm work, have a poor understanding of the disease, and poor economic conditions, and these factors may also contribute to their medical condition. Finally, many of the patients lived alone, or lost their companions, and had few children or children who lived far away from them. Therefore, the less effective supervision may also have resulted in low adherence to therapy. Thus, patients' psychosocial environment should be taken into consideration in future studies, to develop better predictors of treatment adherence.

Young age might be one of the factors associated with lower rates of adherence in FBC patients [33]. Interesting, in our study, we similarly concluded that young age is an independent factor associated with low adherence to tamoxifen treatment. The mean age at breast cancer diagnosis is different in males, and was reported to vary between 64 and 71 years [36, 37]. While the mean age at diagnosis for the 116 patients included in our study was 62.8 years, it was 55.7 years in the low-adherence group. Therefore, MBC patients in China may be younger at the time of diagnosis than MBC patients from other countries, and the low tamoxifen adherence always affects the younger patients. We could not explain why some younger men were more likely to have low adherence to tamoxifen. It is possible that adherence to therapy may be affected by their busy work schedules, by the adverse effects of therapy, or by a perception of low benefits from taking the medication, and all these factors result in lower adherence in younger men as compared to other patient groups, such as FBC patients [38, 39].

Although tamoxifen therapy is known to cause multiple toxicities of varying severity, not all patients report adverse effects. Patients may have different metabolic responses, depending on the activity of cytochrome P4502D6 (CYP2D6), an enzyme that converts tamoxifen into its active metabolite, endoxifen [40]. Treatment efficacy seems high in patients who are extensive metabolizers [41, 42]. One series reported a 21 % rate of side effects in MBC patients [5]. This value was higher than the 4–7 % rate that was reported in women receiving adjuvant tamoxifen [43]. Thus, tamoxifen tolerance may be worse in men as compared to women, and the amount and activity of CYP2D6 may be lower in MBC patients than in FBC patients. In our study, 44.8 % of the men reported one or more adverse effects from tamoxifen. Adverse effects were different in their constitution, fatigue accounting for 21 %, anxiety for 20 %, sleep disorders for 20 %, decreased libido for 11 %, weight gain for 10 %, sweating for 9 %, myalgia for 4 %, and rash for 4 %. The results suggest that the amount or activity of CYP2D6 in MBC patients from China may be much lower than in patients from other countries. More investigations need to be performed to evaluate the large differences that are reported in this respect.

Improving tamoxifen adherence over the entire treatment period may be a complex task. Tamoxifen adherence is partially dependent on the effective and timely communication between patients and their physicians. The importance of adherence to adjuvant tamoxifen therapy and the potential adverse effects from the prescribed therapy should be explained adequately [44]. A simple measure consists of systematically and repeatedly providing information, at each office visit, about the importance of adhering to treatment. Knowing the clinical importance of

adherence to medication and the potential benefits of therapy could improve the quality of life [45]. As adverse effects emerge as a major contributor to the low rates of adherence to tamoxifen treatment in the current study, it is crucial that physicians and nurse practitioners take the time to explain and prepare the patients for the possibility of adverse effects. Dedicating greater attention to managing treatment-related adverse effects, which were cited as the primary reason for low adherence or withdrawal from a clinical trial among respondents, might promote therapy adherence [46–48]. Another strategy is to identify discrepancies between clinicians and patients in the reporting of the adverse effects. However, although these adverse effects are not life-threatening, they might lower the quality of life in patients and affect the choice of treatment and adherence [49]. Initiating a conversation on adverse effects, or waiting less time once certain adverse effects present, may encourage patients to feel better while undergoing therapy. Another innovative measure is to apply reminder systems, such as text messages on cell phones or timely follow-up calls, to improve adherence in breast cancer patients. In fact, these measures that are intended to increase adherence should target patients who are particularly fragile or ignore their treatment early on [47]. However, to our knowledge, these reminder systems have been mainly tested in women using oral anti-cancer drugs. It still may be a problem to apply this reminder system to evaluate their effect in MBC patients.

Two limitations of our study need to be mentioned. First, as the incidence of MBC is low, the size of our study cohort is small. Determinants of adherence to tamoxifen may be influenced by the size of the group of participants into this study. Second, the real adherence to medication may not be accurately measured by the method that was used. Although this method of measuring adherence is not equivalent to measuring the actual adherence of a patient, it may eliminate the bias caused by the subjectivity in recalling acceptable answers.

The consequences of extending the potential life expectancy of MBC patients with low tamoxifen adherence are significant. Low adherence to tamoxifen therapy occurred in over half of the patients prescribed tamoxifen in this study. Our findings suggest that low tamoxifen adherence in breast cancer patients has a negative effect on survival, and patients face a greater risk of death and disease recurrence. Patients need to be encouraged to continue taking their medication for the full five-year period that is recommended, to insure their best chances for survival. Because of the significant decrease in adherence to adjuvant treatment in MBC patients, adherence issues in this field need to be urgently acknowledged and the possibility of preventive measures needs to be further evaluated.

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Conflict of interest Authors declare that they have no conflict of interest.

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