

Adherence to endocrine therapy among Chinese patients with breast cancer: current status and recommendations for improvement

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Background: Postoperative endocrine therapy is known to reduce recurrence and mortality in patients with estrogen receptor (ER)- or progesterone receptor (PR)-positive breast cancer. Correlates and determinants of compliance with endocrine therapy among Chinese patients with breast cancer are not known. The aim of this study was to elucidate the efficacy and adherence of endocrine therapy in China and suggest effective improvements on the adherence.

Patients and methods: We analyzed the survival of 1,110 patients eligible for endocrine therapy and adherence of 699 patients to endocrine therapy. Kaplan–Meier curves, log-rank tests and Cox proportional hazard models were used to evaluate survival, and logistic regression models were used to assess variables associated with treatment adherence.

Results: Long-term endocrine therapy was associated with lower recurrence rate (HR 0.72; 95% CI 0.56–0.93; $p=0.013$). Adherence to endocrine therapy was only 63.1%. Sociodemographic characteristics of patients, clinical- and medication-related characteristics and patients' attitudes were associated with adherence to endocrine therapy.

Conclusion: Adherence to endocrine therapy in Chinese patients with ER+/PR+ breast cancer was <65%. Both patients and physicians should take progressive steps to improve the rate of adherence.

Keywords: breast cancer, endocrine therapy, adherence

Introduction

Breast cancer is the most common cancer in females around the world.¹ Nearly half of these cases and 60% of breast cancer-related deaths occur in developing countries.¹ Although the incidence of breast cancer in Asia is lower than that in the USA and European countries,¹ the annual incidence of breast cancer in China is increasing by 3% each year.^{2,3} In patients with estrogen receptor (ER)- or progesterone receptor (PR)-positive breast cancer, endocrine therapy has been shown to reduce the incidence of recurrence, metastasis and death.⁴ According to the National Comprehensive Cancer Network guidelines, patients with ER-/PR-positive invasive breast cancer are eligible for treatment with tamoxifen (TAM) or aromatase inhibitors (AIs), and there is an additional benefit from ovarian ablation or suppression in premenopausal women.⁵ Nonadherence to the full course of treatment is one of the major reasons for the failure of endocrine therapy. In multicenter clinical trials, such as the Arimidex, Tamoxifen Alone or in Combination trial, the reported nonadherence to endocrine therapy was of the order of 8%–28%.^{6,7} In the real-world clinical settings, however, nonadherence rates are likely to reach about 50%.^{8,9} Several factors may influence adherence,

such as age, occurrence of complications, financial constraints, lack of information, therapeutic regimen and adverse events.^{9–11}

China is a developing country with a large population and several minority groups. Although the incidence of breast cancer is increasing every year, very few studies have assessed the treatment efficacy and adherence among Chinese patients with breast cancer. The aim of this study was to assess the correlation between survival of patients with hormone receptor-positive breast cancer and treatment adherence. In addition, we assessed the reasons for nonadherence and have suggested feasible strategies to improve adherence.

Patients and methods

Study design and participants

All patients in this retrospective analysis were identified from the First Hospital of Jilin University via the Bethune-Laval Oncology Unit database system (established in 1998, in collaboration with Laval University, Canada). A total of 1,110 patients were enrolled in this study. There was no restriction of age or sex. The inclusion criteria were as follows:

- Primary breast cancer diagnosed by histopathological examination or biopsy specimens between April 1, 2005 and December 31, 2010.

- ER- and/or PR-positive status (>1% positive on immunohistochemical staining).
- T stage < T4 and the absence of distant metastasis.

Out of the 1,110 patients, 699 completed a survey on factors associated with endocrine therapy either telephonically or via face-to-face interview. Data collection was completed on December 31, 2016. The data were analyzed anonymously. The patient selection criteria are shown in Figure 1. Written informed consent was obtained from all patients, and the study was approved by the ethics committee of the First Hospital of Jilin University.

Definition

Adherence includes compliance and/or persistence. Compliance was defined as adherence to the prescribed medications (TAM 20 mg, anastrozole 1 mg or letrozole 2.5 mg) and interruption of <180 days. Persistence was defined as continuation of endocrine therapy for at least 5 years or until the first recurrence, metastasis or death.^{12,13} In our study, very few of the nonadherent patients belonged to the noncompliance group. Therefore, we mainly focused on the analysis of persistence.

Overall survival (OS) was defined as the time from the the date of diagnosis or date of surgery. Disease-free survival (DFS) was defined as the time from the date of the primary surgery to the date of relapse.

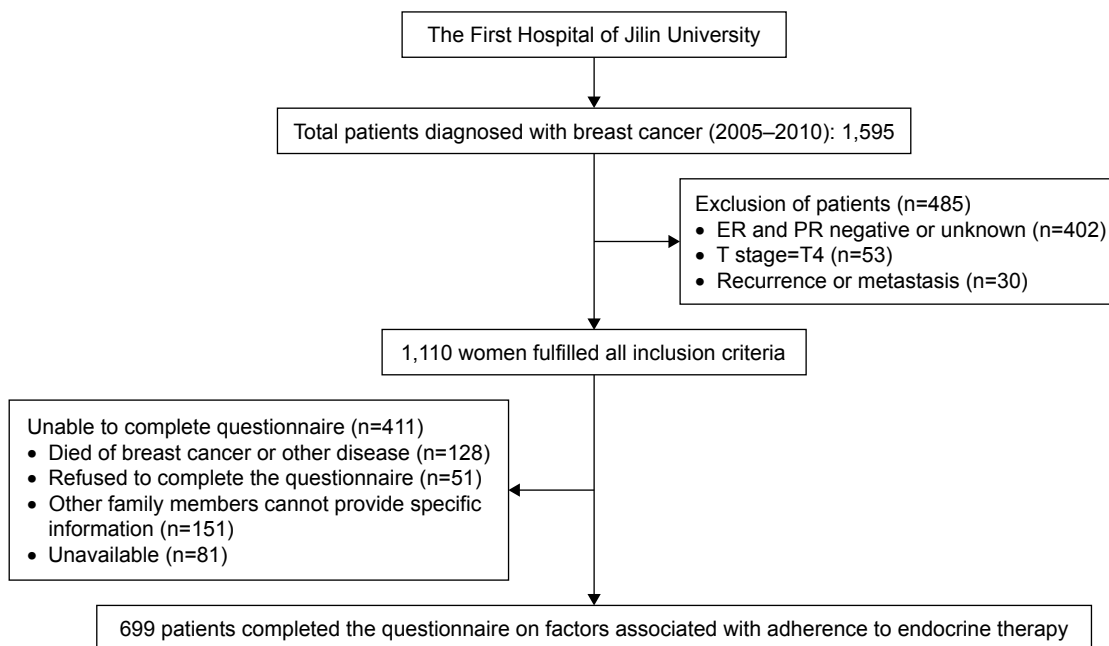


Figure 1 Study sample selection.

Notes: A total of 1,110 patients were eligible for the inclusion criteria; 699 patients completed the questionnaire on factors associated with adherence to endocrine therapy.

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

Statistical analyses

Data pertaining to 1,100 ER+/PR+ patients were included in this analysis. Non-normally distributed continuous variables are presented as median (25th to 75th percentiles), and between-group differences were assessed by Kruskal–Wallis test or Mann–Whitney *U* test. Normally distributed continuous variables are expressed as mean \pm SD, and between-group differences were assessed by independent *t*-test and analysis of variance. Data pertaining to categorical variables are expressed as frequencies and percentages, and between-group differences were assessed by chi-squared test and Fischer's test, as appropriate. Follow-up began at the time of diagnosis of breast cancer. Patients who were lost to follow up at the first interview were excluded from the survival analysis. Survival analysis of endocrine therapy and related factors was performed using Kaplan–Meier method and compared by log-rank test. Median survival was estimated by the Kaplan–Meier method. Factors associated with adherence to endocrine therapy were assessed using univariate and multivariate logistic regression models. OR and their 95% CIs were used for quantitative analysis. Independent-risk factors associated with *p*-values <0.05 were identified on multivariate analysis after adjusting for confounding variables. All analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA).

Results

Nonadherence to endocrine therapy is associated with poor clinical outcome

A total of 1,110 patients with hormone receptor-positive breast cancer met the patient selection criteria. The demographic and clinical characteristics are summarized in Table S1. In our study, 92.6% of these patients were followed up for a median duration of 79 months (range 1–122) until December 31, 2016. Among these, 38 patients experienced a relapse, 18 developed contralateral breast cancer, 99 developed distant recurrence, 28 died of breast cancer and 17 patients died of other diseases. DFS and OS at 5 years were 83% and 89%, respectively. Completion of 5 years of endocrine therapy decreased recurrence and death by 28% and 15%, respectively (Table 1). Improvement in DFS was apparent after the completion of adjuvant endocrine therapy (Figure 2A; HR 0.72; 95% CI 0.56–0.93; *p*=0.013). However, improvement in OS was not obvious (Figure 2B; HR 0.85; 95% CI 0.60–1.20; *p*=0.347). Survival analysis of other factors is presented in Table S2. Because of the sensitivity of immunohistochemistry, there are still many patients diagnosed as

Table 1 Survival analysis of the completion of ET

Variables	DFS		OS	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Completed ET ^a				
No	1.00		1.00	
Yes	0.72 (0.56–0.93)	0.013	0.85 (0.60–1.20)	0.347

Note: ^aUnknown $<15\%$.

Abbreviations: CI, confidence interval; DFS, disease-free survival; ET, endocrine therapy; HR, hazard ratio; OS, overall survival.

having ER–/PR+ breast cancer.^{14,15} Therefore, these patients were also included in survival analysis.

Adherence to endocrine therapy in China is not lower than that in other countries

Out of the 699 patients who completed the survey, only 441 (63.1%) completed endocrine therapy, whereas 258 (36.9%) patients did not (80 of these never initiated endocrine therapy). Out of these 699 patients, 351 (50.2%) received only TAM, 177 (25.3%) received only AIs and 55 (7.9%) received both TAM and AI. Adherence to AIs and TAM was 75.7% and 69.2%, respectively. Causes of nonadherence are shown in Figure 3. Of the patients who discontinued the treatment (Figure 3), 36% of patients discontinued endocrine therapy because of its side effects, another 14% stopped treatment after reading the package insert about side effects rather than after having experienced by themselves. There are 35% of patients doubting about the efficacy of endocrine therapy, and 12% were not aware of the necessity.

Association between sociodemographic characteristics and adherence to endocrine therapy

According to our survey results (Table 2), financial constraints (OR 0.55; 95% CI 0.34–0.89; *p*=0.015), insurance coverage (OR 0.60; 95% CI 0.42–0.88; *p*=0.01) and education level of patient (OR 2.32; 95% CI 1.35–3.79; *p*=0.01) had a significant influence on adherence rate. Occupation was not found to be a significant factor. Although we hypothesized that patients employed in a healthcare-related field would have a better understanding of the necessity of endocrine therapy, this subgroup of patients did not exhibit significantly higher adherence than others (Table 2).

Association between clinical- and medication-related characteristics and adherence to endocrine therapy

Poor adherence among patients who were diagnosed with breast cancer before the year 2008 was largely driven by

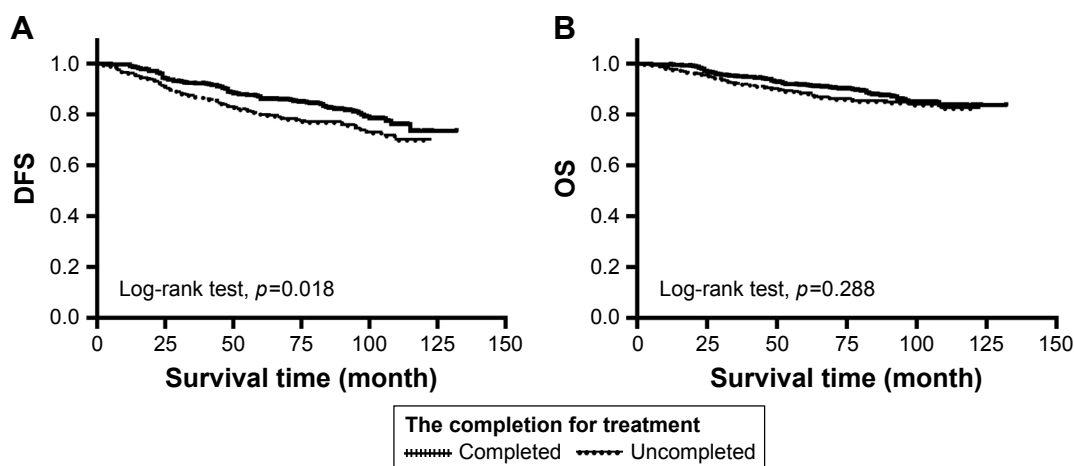


Figure 2 Kaplan–Meier survival curves for DFS and OS demonstrating the relationship between completion of endocrine therapy and survival.

Notes: (A) Kaplan–Meier survival curves for DFS. Improvement in DFS is apparent after completion of adjuvant endocrine therapy (HR 0.72; 95% CI 0.56–0.93; $p=0.013$). (B) Kaplan–Meier survival curves for OS. Improvement in OS is not obvious (HR 0.85; 95% CI 0.60–1.20; $p=0.347$).

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

suboptimal endocrine therapy as compared with patients who were diagnosed after the year 2008 (OR 0.63; 95% CI 0.46–0.87; $p=0.005$). Patients diagnosed with more advanced stage of breast cancer usually had higher adherence rate. For example, patients with one to three metastatic lymph nodes were more likely to take standard medications than their node-negative counterparts (OR 1.56; 95% CI 1.07–2.27; $p=0.02$). Patients with node-positive breast cancer, especially those with involvement of >4 nodes, are often prescribed adjuvant radiotherapy. Of these patients, the ones who received radiotherapy were more likely to complete endocrine therapy (OR 2.45; 95% CI 1.77–3.38; $p<0.001$). Completion of the recommended six to eight cycles of chemotherapy was also observed to positively influence adherence (OR 2.43; 95% CI 1.75–3.38; $p<0.001$). These results showed that adherence for a patient was reflected not only in long-term endocrine therapy but also in other adjuvant therapies. Long-term

treatment of TAM can cause adverse effects, such as hot flashes, gynecologic complications, sexual problem, sleeping disorders, bone loss, arthralgia and myalgia, some are even unbearable.^{16,17} Adverse effects of endocrine therapy are another obstacle to the completion of treatment (OR 0.22; 95% CI 0.13–0.3; $p<0.01$). As shown in Figure 3, side effect (36%) was the top reason for nonadherence in this study, especially the intolerable adverse effects (OR 0.93; 95% CI 0.05–0.19; $p=0.041$). Other factors associated with adherence, identified on univariate and multivariate analyses, are summarized in Table 3.

Association between patient's attitude, education level and adherence to endocrine therapy

A patient's attitude is shaped by the belief on the diagnosis or treatment protocol by physicians, the understanding of endocrine therapy and their access to information (Table 4). Patients who had a skeptical attitude (OR 0.18; 95% CI 0.10–0.33; $p<0.001$) or those who were not convinced about the efficacy of endocrine therapy (OR 0.02; 95% CI 0.01–0.06; $p<0.001$) were more likely to show poor adherence to endocrine therapy. Adherence rates were higher when patients had a good understanding of the efficacy, mechanisms of action and the potential adverse effects of treatment (OR 0.10; 95% CI 0.05–0.19; $p<0.01$). Well-educated patients, according to previous results, are more likely to accept new information and tend to have higher incomes. Such patients are likely to be more aware of cancer-related information because of better exposure to print and electronic media or have friends with access to medical education and

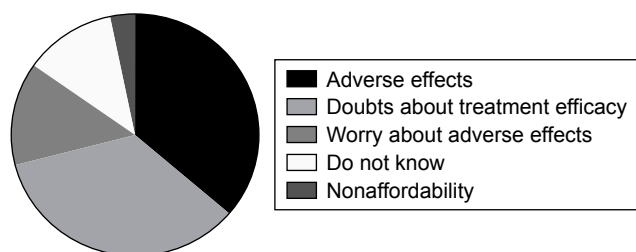


Figure 3 Reasons for nonadherence to endocrine therapy among Chinese patients with breast cancer.

Notes: Adverse effects (36%) and doubts pertaining to treatment efficacy (35%) were the most commonly cited reasons. Fourteen percent of patients worried about the adverse effects rather than having experienced by themselves. There were 12% of these patients even not aware of the necessity of endocrine therapy. Only 3% of the patients cited nonaffordability of endocrine treatment as the reason for nonadherence to treatment.

Table 2 The association between the sociodemographic characteristics and adherence to endocrine therapy

Variables	AD, n (%)	NAD, n (%)	Univariate			Multivariate		
			OR	95% CI	p-value	OR	95% CI	p-value
Age								
<40 years	72 (16.3)	34 (13.2)	1.00	Reference				
40–59 years	304 (68.9)	177 (68.6)	0.81	0.52–1.27	0.360			
≥60 years	65 (14.7)	47 (18.2)	0.65	0.38–1.14	0.312			
Ethnicity								
Han	418 (94.8)	246 (95.3)	1.00	Reference				
Minorities	23 (5.2)	12 (4.7)	1.13	0.55–2.31	0.74			
Financial problems								
No	182 (41.3)	67 (26.0)	1.00	Reference		1.00	Reference	
Yes	259 (58.7)	191 (74.0)	0.50	0.36–0.70	<0.001	0.55	0.34–0.89	0.015
Medical insurance								
UB insurance	307 (69.6)	150 (58.1)	1.00	Reference		1.00	Reference	
RC insurance	50 (11.3)	40 (15.5)	0.61	0.39–0.97	0.04	2.43	0.85–6.98	0.09
No insurance	84 (19.0)	68 (26.4)	0.60	0.42–0.88	0.01	0.92	0.46–1.82	0.80
Education								
Elementary school	55 (12.5)	47 (18.2)	1.00	Reference		1.00	Reference	
Middle school	283 (64.2)	173 (67.1)	1.40	0.91–2.16	0.13	1.09	0.40–2.93	0.87
University or more	103 (23.4)	38 (14.7)	2.32	1.35–3.97	0.01	0.73	0.22–2.40	0.60
Occupation								
Farmer or worker	123 (27.9)	83 (32.2)	1.00	Reference				
Office staff	176 (39.9)	92 (35.7)	1.29	0.89–1.88	0.183			
Medicine related	29 (6.6)	17 (6.6)	1.15	0.60–2.23	0.676			
Service	28 (6.3)	19 (7.4)	0.99	0.52–1.90	0.986			
Others	30 (6.8)	18 (7.0)	1.13	0.60–2.15	0.722			
No	55 (12.5)	29 (11.2)	1.28	0.75–2.17	0.361			

Abbreviations: AD, adherence; CI, confidence interval; NAD, nonadherence; OR, odds ratio; RC insurance, Rural Cooperative Medical Insurance; UB insurance, Urban Residents Basic Medical Insurance.

are more likely to comply with endocrine therapy (OR 2.76; 95% CI 1.47–5.42; $p=0.003$) than those who depend only on the doctor's advice for treatment-related information.

Improvement of endocrine therapy in clinical practice

As shown in Figure 3, most of the patients discontinued endocrine therapy because of doubts about treatment efficacy and the adverse effects. Therefore, physicians can help improve treatment adherence by inculcating a positive attitude among patients toward endocrine therapy and control of adverse effects.

First, establishment of a good relationship with patients, counseling them regarding their disease condition and convincing them about the necessity of full course of endocrine therapy, is a challenge for every physician. In the real-world clinical settings in China, some families tend to conceal the seriousness of the disease from the patients in order not to perturb them.¹⁸ However, patients who underestimate the severity of their condition are more likely to pay inadequate attention to adjuvant therapy. In our study, 54% of the patients in the adherence group and only 11.2% in the nonadherence

group believed in the efficacy of endocrine therapy. Among patients with poor adherence, 7.8% were not even aware of the necessity of endocrine therapy and 42.1% believed that they had recovered from breast cancer and that the oral tablets were not of much use. From the year 2007 onward, multidisciplinary consultations are routinely provided for breast cancer patients after surgery in our hospital. This may be an effective way to improve adherence to endocrine therapy among patients treated at our hospital. Oncologists discuss the various available treatment options and involve the patients and their families in treatment decision-making. Such an approach also enables the family members to support the patient in adhering to treatment.

Second, helping patients manage their side effects is very important. Medication toxicity can be relieved by pharmacological or nonpharmacological means. For example, nonsteroidal anti-inflammatory drugs, analgesics, cyclooxygenase-2 inhibitors, opioids and vitamin D supplements can be used to alleviate arthralgia and myalgia.¹⁹ Sometimes, switching of treatment from an AI to TAM or from one AI to another AI may also alleviate toxic effects of endocrine therapy.^{20,21}

Table 3 The association between the clinical- and medication-related characteristics and adherence to endocrine therapy

Variables	AD, n (%)	NAD, n (%)	Univariate			Multivariate		
			OR	95% CI	p-value	OR	95% CI	p-value
Year of diagnosis								
2008–2010	218 (49.4)	103 (39.9)	1.00	Reference		1.00	Reference	
2005–2007	223 (50.6)	155 (60.1)	0.63	0.46–0.87	0.005	0.92	0.53–1.62	0.781
Comorbidities								
0	365 (83.1)	216 (83.7)	1.00	Reference				
I	68 (15.4)	36 (14.0)	1.12	0.72–1.73	0.62			
>I	8 (1.8)	6 (2.3)	0.79	0.27–2.30	0.67			
Other drug exposures								
None	388 (88.0)	232 (89.9)	1.00	Reference				
For treatment	37 (8.4)	19 (7.4)	1.16	0.65–2.07	0.61			
Chinese herbs	16 (3.6)	7 (2.7)	1.38	0.55–3.37	0.50			
ER								
Negative	32 (7.3)	33 (12.8)	1.00	Reference		1.00	Reference	
I+	42 (9.5)	34 (13.2)	1.27	0.66–2.48	0.48	0.93	0.07–12.02	0.96
2+	73 (16.6)	47 (18.2)	1.60	0.87–2.95	0.13	0.97	0.08–11.75	0.97
3+	294 (66.7)	144 (55.8)	2.11	1.25–3.56	0.01	1.86	0.16–21.51	1.86
PR								
Negative	55 (12.5)	36 (14.0)	1.00	Reference				
I+	94 (21.3)	54 (20.9)	1.14	0.67–1.95	0.63			
2+	87 (19.7)	66 (25.6)	0.86	0.51–1.46	0.58			
3+	205 (46.5)	102 (39.5)	1.32	0.81–2.13	0.27			
Primary tumor size ^a								
<5 cm	411 (98.6)	234 (96.3)	1.00	Reference				
≥5 cm	6 (1.4)	9 (3.7)	0.38	0.13–1.08	0.069			
Node status								
N0	266 (60.3)	181 (70.2)	1.00	Reference		1.00	Reference	
N1	119 (27.0)	52 (20.2)	1.56	1.07–2.27	0.02	1.83	0.91–3.65	0.09
N2	41 (9.3)	19 (7.4)	1.47	0.83–2.61	0.19	0.63	0.24–1.67	0.35
N3	15 (3.4)	6 (2.3)	1.70	0.65–4.47	0.28	3.16	0.49–20.58	0.23
HT utilization pattern ^b								
TAM only	243 (55.1)	108 (60.7)	1.00	Reference		1.00	Reference	
AIs only	134 (30.4)	43 (24.2)	1.39	0.92–2.09	0.12	1.00	0.55–1.81	0.97
TAM to AIs	45 (10.2)	10 (5.6)	2.00	0.97–4.12	0.06	2.86	1.02–7.46	0.04
Unknown	19 (4.3)	17 (9.6)	0.50	0.25–0.99	0.05	0.69	0.23–2.08	0.51
CT								
0–5 procedures	107 (24.3)	113 (43.8)	1.00	Reference		1.00	Reference	
6–8 procedures	334 (75.7)	145 (56.2)	2.43	1.75–3.38	<0.001	1.56	0.88–2.76	0.13
RT ^c								
No	212 (48.1)	179 (69.4)	1.00	Reference		1.00	Reference	
Yes	229 (51.9)	79 (30.6)	2.45	1.77–3.38	<0.001	0.99	0.55–1.78	0.98
Adverse effects								
No	289 (65.5)	150 (58.1)	1.00	Reference		1.00	Reference	
Yes	152 (34.5)	108 (41.9)	0.73	0.53–1.00	0.05	0.22	0.13–0.37	<0.001
Severity of adverse effects ^d								
Tolerable	65 (42.8)	28 (29.5)	1.00	Reference				
Intolerable	14 (9.2)	65 (60.2)	0.93	0.05–0.19	0.041			
Unknown	73 (48.0)	15 (13.9)	2.32					

Notes: ^aUnknown=5.6%. ^bFor patients ever initiated. ^cFor node-positive breast cancer patients. ^dFor patients with adverse effects.

Abbreviations: AD, adherence; AI, aromatase inhibitor; CI, confidence interval; ER, estrogen receptor; HT, hormone therapy; NAD, nonadherence; OR, odds ratio; PR, progesterone receptor; RT, radiotherapy; TAM, tamoxifen.

Periodic reminder to patients is another way to improve treatment adherence. In the Patient's Anastrozole Compliance to Therapy trial, standard therapy plus reminders were shown to improve compliance with adjuvant endocrine therapy.²² Other methods such as marked-up calendars, reminder notes, pill boxes and frequent monitoring have been used to enhance adherence as well.²²

Discussion

TAM for premenopausal ER+/PR+ breast cancer patients and AIs alone or in combination with TAM for postmenopausal patients have been shown to prolong DFS and OS in many randomized controlled clinical trials.^{4,7,23} Completion of 5 years of treatment was shown to be associated with significantly longer DFS and OS when compared to only

Table 4 The association between the patients' attitude-related characteristics and adherence to endocrine therapy

Variables	AD, n (%)	NAD, n (%)	Univariate			Multivariate		
			OR	95% CI	p-value	OR	95% CI	p-value
Patients' attitudes toward efficacy ^a								
Believe	241 (54.6)	29 (11.2)	1.00	Reference		1.00	Reference	
Doubt	189 (42.9)	139 (53.9)	0.16	0.11–0.26	<0.001	0.18	0.10–0.33	<0.001
Deny	8 (1.8)	82 (31.8)	0.01	0.01–0.03	<0.001	0.02	0.01–0.06	<0.001
Understanding HT-related information								
Yes	428 (97.1)	198 (76.7)	1.00	Reference		1.00	Reference	
No	13 (2.9)	60 (23.3)	0.10	0.05–0.19	<0.001	0.73	0.22–2.46	0.73
Access to information								
Doctors only	382 (88.6)	237 (95.6)	1.00	Reference		1.00	Reference	
Doctors+others	49 (11.4)	11 (4.4)	2.76	1.41–5.42	0.003	2.74	0.90–8.36	0.08

Note: ^aUnknown=1.6%.

Abbreviations: AD, adherence; CI, confidence interval; HT, hormone therapy; NAD, nonadherence; OR, odds ratio.

1–2 years of treatment.⁴ Although the patients in this study have longer DFS, the OS was not longer. Sequence therapy with TAM and AIs will improve DFS significantly;²⁴ therefore, it may be a good choice for postmenopausal patients with early breast cancer.

TAM was not introduced to Chinese breast cancer patients until the 1990s, which is much later than that in other developed countries. Prehn et al²⁵ found that Chinese patients are less likely to receive adjuvant therapy after surgery; however, the status of adherence to endocrine therapy in China is not clear. This study focuses on the patients in Jilin province, which is located in the northeast of China, and is famous for agriculture. A majority of the population is of Han ethnic origin. The GDP and the education level in Jilin province rank in the middle level among all provinces in China. The First Hospital of Jilin University caters to patients from nearby provinces, both from urban and rural areas. Therefore, patients who attend our hospital are representative of a large geographic area. We used the patient information at our hospital to evaluate the status of endocrine therapy in China.

In clinical practice, the adherence is not very high across the world. In previous studies, the rates of non-adherence or discontinuation were found to be as high as 50% around the world.⁹ Improvement in adherence to endocrine therapy is a global priority. In our study, the adherence rates for of AIs and TAM were 69.2% and 75.7%, respectively, which are at par with those reported from developed countries (77%–81% for AI^{26,27} and 49%–63% for TAM^{28,29}). This observation is not consistent with the results of Prehn et al's²⁵ study, in which Chinese women were shown to be less likely to receive adjuvant treatment. This may be because the patients in China were more likely to accept doctors' advice in recent years. In the current study, sociodemographic, clinical- and medication-related and patients' attitude-related

characteristics were found to be the three major factors associated with adherence to endocrine therapy. Physicians have many ways to help improve endocrine therapy adherence.

Over the years, there has been a gradual improvement in access to treatment for breast cancer and awareness regarding endocrine therapy. Therefore, treatment adherence among patients diagnosed before 2008 was not optimal (60.1% vs 39.9%). In previous studies, extreme age (age >65 or <35 years) of patient,^{9,30} presence of comorbidity and concurrent treatment for chronic diseases were associated with nonadherence of endocrine therapy,^{10,31,32} which is inconsistent with our results (Tables 2 and 3). In contrast to our hypothesis, we did not observe improved treatment adherence among breast cancer patients who had a positive family history of breast cancer. Adherence to endocrine therapy among patients belonging to minority population groups was not significantly inferior than that among patients from majority groups; this implies that language difficulties or poor access to education among minority groups may not be a significant contributor to nonadherence to endocrine therapy.

Consistent with the results of Fink et al's³² study, in which a positive correlation was observed between treatment adherence and metastatic involvement of >4 lymph nodes, we also observed a positive correlation between treatment adherence and involvement of one to three metastatic lymph nodes. This suggests that patients with more advanced disease were more likely to follow the doctors' advice and adhere to treatment. Endocrine therapy may cause some adverse effects. Consistent with the results of other studies,^{10,33} side effects were a major cause of nonadherence in this study. This phenomenon indicates a flawed perception of the efficacy and adverse effect profile of endocrine therapy among the Chinese women. Indeed, adverse effects of endocrine therapy have been reported to be a predictor of good efficacy.³⁴

However, patients' awareness of the benefits and risks of endocrine therapy is also important. Informing patients about both the benefits and the risks of endocrine therapy has a positive effect on adherence. Healthcare providers are better equipped to facilitate improved compliance with endocrine therapy among their patients. Patients who underwent follow-up examinations at the oncology unit were found to be more likely to adhere to endocrine therapy than those who received follow-up care at other units.¹⁰ A good relationship between patients and healthcare providers is known to have a positive impact on adherence.³³ In a study on postmenopausal women in Europe, only 26% of the patients were aware of the risk of recurrence and only 15% were aware of the side effects of long-term endocrine therapy.^{35,36} Effective patient–physician communication is known to improve adherence to endocrine therapy.³¹ Oncologists should ensure adequate patient education regarding their medical condition, importance of endocrine therapy, the prescribed medications, their dosage, mechanism of action, potential side effects, possible severity and the potential decrease in the severity of side effects over time.^{37,38}

Conclusion

In this study, greater adherence to endocrine treatment significantly reduced the recurrence of breast cancer. Unfortunately, patient adherence to endocrine therapy in clinical practice is not more than 65%. Both patient- and medical-related factors were found to affect patient adherence. Adequate patient education and management of side effects are key steps by which healthcare providers can help improve treatment compliance. Sustained efforts by both physicians and patients will help improve survival rate and quality of life of patients with ER+/PR+ breast cancer.

Advantages and limitation

This is the first study that investigated the efficacy of endocrine therapy and the associated adherence rates among women with hormone receptor-positive breast cancer treated at a single center in the northeast China. An analysis of the factors with nonadherence is presented. Information pertaining to treatment adherence was obtained directly from the patients. The reasons for nonadherence reflect the patients' attitudes and the barriers faced by Chinese breast cancer patients in the real-world setting. However, 37% (411/1,110) of the eligible patients did not complete the survey, which may have affected our results.

Acknowledgments

We thank all the staff members in the Department of Breast Surgery at the First Hospital of Jilin University who helped

collect patients' information in the past 10 years. This work was supported by a grant from Canada International Development Agency (PSCLU010-282/19156) and another grant from National Natural Science Foundation of China (No 30872194).

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Demographic and clinical characteristics of the study population

Variables	Value, n (%)
Menstrual condition	
Postmenopausal	534 (48.1)
Premenopausal	569 (51.3)
Unknown	7 (0.6)
Initial treatment	
Surgery	846 (76.2)
Neo-adjuvant chemotherapy	54 (4.9)
Unknown	210 (18.9)
Year of surgery	
2005	54 (4.9)
2006	153 (13.8)
2007	202 (18.2)
2008	315 (28.4)
2009	103 (9.3)
2010	283 (25.5)
Surgery details	
Modified radical mastectomy	873 (78.6)
Breast-conserving surgery	174 (15.7)
Mastectomy and SLNB	42 (3.8)
Segmental mastectomy and SLNB	21 (1.9)
Cancer stage	
I	57 (5.1)
II	355 (32.0)
III	148 (13.3)
Unknown	550 (49.5)
ER ^a	
Negative	101 (9.1)
1+	133 (12.0)
2+	191 (17.2)
3+	685 (1.7)
PR ^a	
Negative	140 (12.6)
1+	229 (20.6)
2+	261 (23.5)
3+	480 (43.2)
HER2	
Negative	754 (67.9)
1+	90 (8.1)
2+	94 (8.5)
3+	97 (8.7)
Unknown	75 (6.8)
CT	
Yes	918 (82.7)
No	192 (17.3)
RT	
Yes	464 (41.8)
No	646 (58.2)
Completed recommended ET	
Yes	619 (55.8)
No	399 (35.9)
Unknown	92 (8.3)
ET utilization pattern	
Never initiated	206 (18.6)
TAM	550 (49.5)
AI	259 (23.3)
TAM + AI	56 (5.0)
Forgotten	39 (3.5)

Notes: ^aNegative: <1%; 1+: 1%–25%; 2+: 25%–75%; 3+: >75%.

Abbreviations: AI, aromatase inhibitor; CT, chemotherapy; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; RT, radiotherapy; SLNB, sentinel lymph node biopsy; TAM, tamoxifen.

Table S2 Survival analysis of ET and related factors

Variables	DFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Hormone receptor status				
ER+/PR+	1.00		1.00	
ER+/PR-	1.43 (0.95–2.13)	0.083	1.46 (0.89–2.40)	0.135
ER-/PR+	1.97 (1.35–2.89)	<0.001	1.98 (1.24–3.18)	0.004
HER2				
Negative	1.00	0.009	1.00	0.008
1+	1.39 (0.85–2.26)	0.186	1.57 (0.87–2.84)	0.123
2+	1.44 (0.92–2.28)	0.115	1.07 (0.55–2.07)	0.855
3+	2.28 (1.55–3.37)	<0.001	2.86 (1.83–4.49)	0.001
Unknown	0.91 (0.50–1.65)	0.761	0.98 (0.47–2.03)	0.951
Duration of ET				
<1 year	1.00		1.00	
1 year	1.44 (0.90–2.30)	0.13	2.18 (1.15–4.14)	0.017
2 years	1.56 (0.83–2.94)	0.17	1.77 (0.75–4.17)	0.192
3 years	1.16 (0.65–2.05)	0.62	0.96 (0.41–2.20)	0.914
4 years	1.41 (0.70–2.86)	0.34	1.42 (0.53–3.84)	0.490
5 years	0.18 (0.10–0.30)	<0.001	0.23 (0.11–0.48)	<0.001
Unknown	0.38 (0.14–1.02)	0.054	0.71 (0.22–2.27)	0.568

Abbreviations: CI, confidence interval; DFS, disease-free survival; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PR, progesterone receptor; OS, overall survival.

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