JBUON 2013; 18(4): 838-844
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Comparative efficacy study of 5-year letrozole or anastrozole in postmenopausal hormone receptor-positive early breast cancer

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Summary

Purpose: *To compare the efficacy of adjuvant anastrozole and letrozole in hormone receptor-positive postmenopausal patients with early breast cancer.*

Methods: *A total of 569 hormone receptor-positive postmenopausal early breast cancer patients were included and analyzed in this study. Of them 238 were taking adjuvant anastrozole and 331 adjuvant letrozole. Demographic and medical data including age, menopausal status, weight, height, treatment history and comorbid diseases were collected from their medical charts.*

Results: *In both anastrozole and letrozole users, the baseline clinicopathologic characteristics and the treatment history with radiotherapy and chemotherapy were similar. The median patient follow-up was 26.4 months. In the anastrozole arm disease free survival (DFS) was 94.9, 81.3 and 66.0%, whereas in the letrozole arm DFS was 90.6, 78.7 and 68.5% in the first, third and fifth years, respectively (p=0.25). Median overall survival (OS) could not be reached due to the low number of events in both arms. Three-year survival rate in the anastrozole arm was 98.8%, whereas in the letrozole arm it was 96.7% (p = 0.20).*

Conclusion: *This study showed that both letrozole and anastrozole have similar effects on DFS and OS in the adjuvant hormonal treatment of postmenopausal hormone receptor-positive breast cancer. We believe that this retrospective study is the first to directly compare the efficacy of letrozole and anastrozole.*

Key words: *anastrozole, breast cancer, letrozole, postmenopausal*

Introduction

Breast cancer is the most commonly diagnosed cancer type and the second leading cause of death due to cancer among women worldwide [1]. Patients with invasive breast cancer and positive estrogen receptor (ER) and/or progesterone receptor (PR) should be treated with adjuvant endocrine therapy regardless of disease stage, age, prior chemotherapy and menopausal status [2]. Randomized controlled trials show that adjuvant tamoxifen treatment for hormone receptor-positive postmenopausal breast cancer patients prolongs DFS and OS [3]. With 5-year tamoxifen treatment breast cancer recurrence decreased by 47% and risk of death decreased by 26% [2]. Thus, until the last decade, 5-year tamoxifen administration was the standard adjuvant endocrine treatment for postmenopausal women with hormone receptor-positive early breast cancer.

In recent years, aromatase inhibitors have been widely used in the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer. In this setting, most of the trials have shown superiority of aromatase inhibitors over tamoxifen [4-13]. Two studies have directly examined the effectiveness of initial tamoxifen or an aromatase inhibitor for postmenopausal hormone receptor-positive breast cancer. In the first results evaluation of ATAC (Arimidex, Tamoxifen, Alone or Combination) trial, 3-year DFS rate and incidence of contralateral breast cancer were significantly better with anastrozole than with tamoxifen [4]. After completion of 5-year adju-

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Received: 12/10/2012; Accepted: 22/04/2013

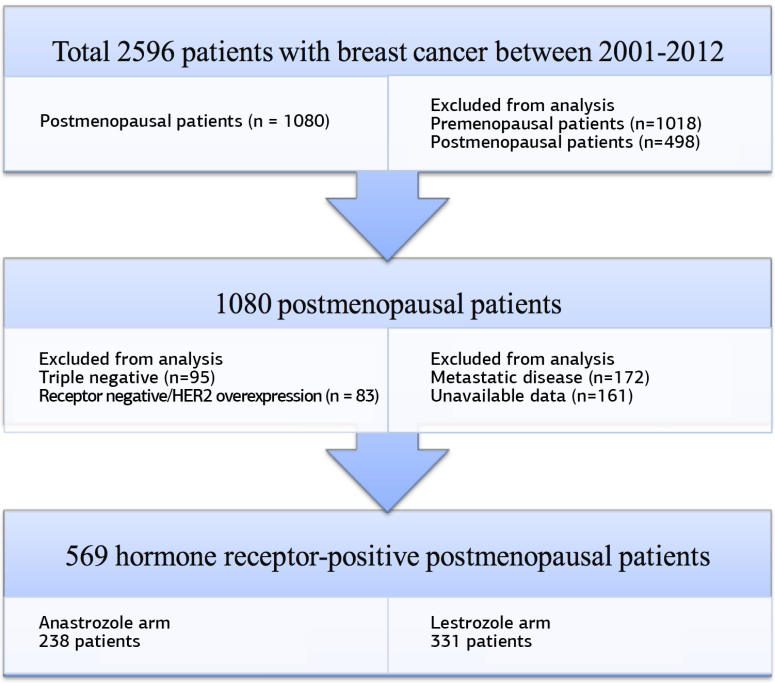

Figure 1. CONSORT diagram of the study.

vant treatment in the ATAC trial, results showed that anastrozole significantly prolonged DFS and time-to-recurrence (TTR) and significantly reduced the distant metastases and contralateral breast cancer occurrence compared to tamoxifen [10]. With a median follow-up of 100 months in the ATAC trial, significantly fewer recurrences and prolonged DFS and TTR were also reported in the anastrozole arm compared to the tamoxifen arm in postmenopausal hormone receptor-positive early breast cancer patients [8]. No OS difference was observed between tamoxifen and anastrozole arms.

The BIG 1-98 (Breast International Group 1-98) trial was a randomized, phase III, double-blind trial that compared 5 years of letrozole or tamoxifen alone or sequentially (tamoxifen followed by letrozole and letrozole followed by tamoxifen) [13]. An early analysis of this trial showed that DFS was significantly prolonged and the risk of distant recurrences was significantly reduced with letrozole compared to tamoxifen in postmenopausal hormone receptor-positive breast cancer [13]. No OS difference was observed between letrozole and tamoxifen in the BIG 1-98 trial.

There is no reported randomized study to directly compare the efficacy of 5-year exemestane and tamoxifen. Exemestane, a steroidal aromatase inhibitor, significantly prolonged DFS and reduced contralateral breast cancer risk compared to 5-year tamoxifen administration when given for 2-3 years after 2-3 years of tamoxifen in postmenopausal estrogen receptor-positive breast cancer patients [14].

In a meta-analyses of breast cancer outcomes in adjuvant trials of aromatase inhibitors vs tamoxifen, aromatase inhibitors significantly lowered recurrence rates compared to tamoxifen either as initial monotherapy or after 2-3 years of tamoxifen [15]. Due to better progression free survival rate and lower recurrence rates with aromatase inhibitors compared to tamoxifen in early breast cancer, aromatase inhibitors have been accepted as first line treatment in the adjuvant treatment of hormone receptor-positive postmenopausal breast cancer patients [16].

However, no comparison between letrozole and anastrozole in the adjuvant setting has been carried out.

In this study we aimed to retrospectively compare the efficacy of adjuvant letrozole and anastrozole in hormone receptor-positive postmenopausal patients with early breast cancer.

Methods

Patients with newly diagnosed breast cancer, treated and followed in our clinic from 2001 to 2012, were retrospectively analyzed. During this time period 2596 patients with breast cancer were admitted to our clinic. Breast cancer patients who were postmenopausal at

the time of diagnosis were enrolled onto the study. Of the 1080 postmenopausal breast cancer patients, triple negative (N=95) and hormone receptor-negative plus HER2 overexpression (N=83), patients with metastatic disease at the time of the diagnosis (N=172) and patients with missing data (N=161) were excluded from analysis, leaving 569 hormone receptor-positive postmenopausal early breast cancer patients for analysis (Figure 1). Anastrozole 1 mg/day was administered to 238 patients and letrozole 2.5 mg/day to 331 patients. Demographic and medical data including age, menopausal status, weight, height, treatment history and comorbid diseases were collected from the patient medical charts. Body mass index (BMI) was calculated according to baseline height and weight. Tumors were graded according to the modified Bloom–Richardson scoring system and staged according to the TNM criteria. ER, PR and HER2/neu estimations were obtained using immunohistochemistry (IHC) for ER and PR and the HerceptTest for HER2/neu. ER and PR receptor positivity was based on > 1% of cells being positive.

Statistics

Statistical analyses were performed using SPSS for Windows version 18.0.(SPSS, Chicago, IL) Baseline characteristics of normal-weight patients were compared with overweight and obese patients by x^2 tests (for categorical variables) or two sample t-test (for continuous variables). Cases with missing data were omitted from analyses. DFS and OS were assessed according to the hormonal treatment history. Kaplan–Meier survival analysis was carried out for DFS and OS and log-rank test was used to examine statistical significance of the differences observed between the groups. Two-sided p-values of <0.05 were considered statistically significant.

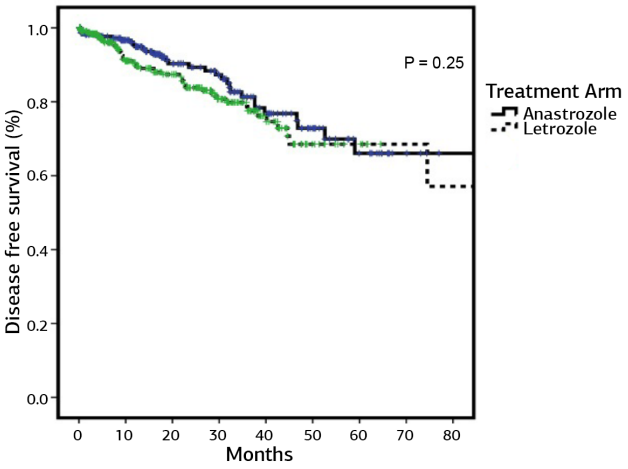

Figure 2. Disease free survival according to hormonal treatment.

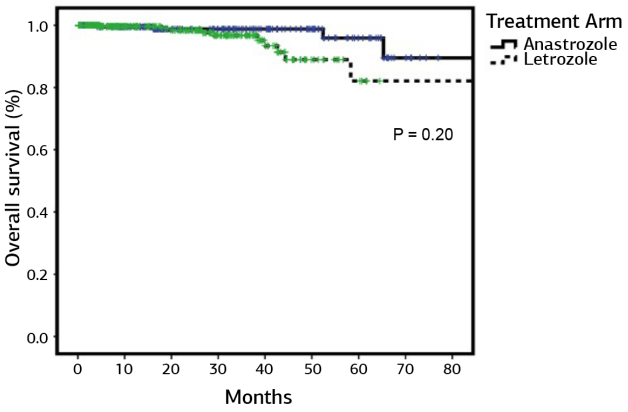

Figure 3. Overall survival of according to hormonal treatment.

Results

The mean patient age was 59.2±8.5 and 60.1±8.4 years in the anastrozole and letrozole arms, respectively (p=0.19) and the median follow-up time was 26.4 months (range 2-112). The mean BMI was 29.4±5.0 kg/m^2 in the anastrozole arm, whereas it was 29.3±5.2 kg/m^2 in the letrozole arm (p=0.84). Baseline clinical characteristics of the participants are described in Table 1. In both arms, histology of the primary tumor and type of surgery was similar. Also in both arms the incidence of lymphovascular invasion, perineural invasion, HER2 positivity and histological grade were similar. There were no apparent differences in baseline nodal status (p=0.43), tumor size (p=0.58) and tumor stage (p=0.15) between the two treatment arms. Both ER and PR were positive in 193 (81.1%) patients in the anastrozole arm and in 270 (81.6%) patients in the letrozole arm, whereas 45 (18.9%) patients in the anastrozole arm and 61 (18.4%) patients in the letrozole arm had only ER or PR positivity. The distribution of the receptor pattern in both arms was not statistically significant (p=0.74)

Baseline treatment modalities of the patients in both arms are described in Table 2. In both arms the treatment history with radiotherapy (p = 0.85) and chemotherapy (p=0.81) was similar. Also in both arms, the chemotherapeutic agents used were similar (p=0.23).

In the anastrozole arm DFS rate was 94.9, 81.3 and 66.0%, whereas in the letrozole arm it was 90.6, 78.7 and 68.5% in the first, third and fifth years, respectively (p=0.25) (Figure 2). Median OS could not be reached due to the low number of events in both arms (Figure 3). Three-year OS survival rate in the anastrozole arm was 98.8%, whereas it was 96.7% in the letrozole arm (p=0.20).

Table 1. Baseline patient demographics and clinical characteristics by aromatase inhibitor of postmenopausal hormone receptor-positive breast cancer patients

Characteristics	*Hormonal treatment*				
	Anastrozole		*Letrozole*		
	N	*(%)*	*N*	*(%)*	*p-value*
Total	238	100	331	100	
Age (years)					
<50	25	10.5	30	9.1	0.19
50-60	119	50.0	149	45.0	
≥ 60	94	39.5	152	45.9	
Body mass index (kg/m^2)					
<25	34	16.8	62	20.9	0.50
25-30	81	40.1	110	37.2	
≥ 30	87	43.1	124	41.9	
Histology of primary tumor					
IDC	202	84.9	274	82.8	0.27
ILC	7	2.9	9	2.7	
Mixed	19	8.0	33	10.0	
Other	10	4.2	15	4.5	
Types of operation					
BCS	75	31.5	88	26.6	0.54
MRM	163	68.5	243	73.4	
LVI					
Negative	104	43.7	121	36.6	0.24
Positive	134	56.3	210	63.4	
PNI					
Negative	210	88.2	280	84.6	0.47
Positive	28	11.8	51	15.4	
HER2					
Negative	195	81.9	270	81.6	0.94
Positive	43	18.1	61	18.4	
Receptor status					
ER+/PR+	193	81.1	270	81.6	0.74
ER+/PR-	26	10.9	40	12.1	
ER-/PR+	19	8.0	21	6.3	
Histologic grade					
I	39	16.4	51	15.4	0.76
II	130	54.6	174	52.5	
III	69	29.0	106	32.0	
Tumor stage at diagnosis					
T1	76	31.9	86	26.0	
T2	118	49.6	170	51.4	0.58
T3	34	14.3	56	16.9	
T4	10	4.2	19	5.7	
Lymph node status					
N0	103	43.3	120	36.3	
N1	81	34.1	108	32.6	0.43
N2	30	12.6	64	19.3	
N3	24	10.0	39	11.8	
TNM stage					
I	60	25.2	81	24.5	
IIA	65	27.3	88	26.6	0.15
IIB	47	19.8	54	16.3	
IIIA	31	13.0	59	17.8	
IIIB	11	4.7	10	3.0	
IIIC	24	10.0	39	11.8	

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, ER: estrogen receptor, PR: progesterone receptor, BCS: breast-conserving surgery, MRM: modified radical mastectomy, LVI: lymphovascular invasion, PNI: perineural invasion

Table 2. Prior treatment modalities according to hormonal treatment

Characteristics	*Hormonal treatment*				
	Anastrozole		*Letrozole*		
	N	*(%)*	*N*	*(%)*	*p-value*
Total	235	100	331	100	
Chemotherapy					0.81
No	77	32.3	112	33.8	
Adjuvant	145	60.9	197	59.5	
Neoadjuvant	16	6.8	22	6.7	
Chemotherapeutic agents					0.23
Anthracycline	38	16.0	48	14.5	
Anthracycline+taxanes	67	28.2	83	25.0	
Taxanes	9	3.8	26	7.9	
Trastuzumab	35	14.7	51	15.4	
Other	12	5.0	11	3.3	
Radiotherapy					0.85
No	72	30.3	104	31.4	
Yes	166	69.7	227	68.6	

Discussion

Five-year adjuvant aromatase inhibitors administration is recommended in hormone receptor-positive postmenopausal breast cancer [16-18]. In direct-comparison studies, 5-year administration of anastrozole and letrozole was significantly superior to 5-year tamoxifen [8,13]. Also 5 trials that studied the use of adjuvant tamoxifen for 2-3 years followed by a third generation of aromatase inhibitor vs continued tamoxifen showed that the use of aromatase inhibitors after 2-3 years of tamoxifen produced significantly lower recurrence rates compared to tamoxifen alone [11,14,19-21].

Both letrozole and anastrozole were superior to tamoxifen in clinical studies, but letrozole seems to be a more potent inhibitor of aromatase than anastrozole used at their conventional doses, and letrozole leads to more complete inhibition of whole-body aromatase. Geisler et al. reported that the mean percentage of aromatase inhibition with anastrozole was 97.1%, whereas > 99.1% suppression of aromatase was observed with letrozole in standard treatment doses [22]. In this study, the suppression of estrone and estrone sulphate was significantly better with letrozole compared to anastrozole. In another study, Dixon et al. reported that letrozole significantly suppresses plasma estradiol and estrone sulphate levels compared to anastrozole in postmenopausal women taking adjuvant aromatase inhibitors for hormone receptor–positive breast cancer [23]. In a recent trial, the ALIQUOT (Anastrozole vs Letrozole, an Investigation of Quality Of Life and Tolerability) study has shown that baseline plasma estradiol and estrone sulfate levels were significantly correlated with BMI and letrozole induced significantly greater suppression of both estradiol and estrone sulfate compared to anastrozole [24]. But the clinical benefit of this complete inhibition of letrozole compared to anastrozole is still unclear, because of there is no randomized phase III clinical trial that directly compares the efficacy of both letrozole and anastrozole. In postmenopausal patients, a randomized phase II trial compared the efficacy of aromatase inhibitors in the neoadjuvant setting. This study has shown that in the neoadjuvant setting both letrozole and anastrozole had similar rates of clinical response [25]. In the subgroup analysis of our previous study on the efficacy of aromatase inhibitors according to the BMI have showed that both letrozole and anastrozole had similar efficacy in both normal weight and overweight hormone receptor-positive postmenopausal breast cancer patients [26].

Our study showed equal efficacy in both anastrozole and letrozole arms. To our knowledge, this is the first study to directly compare the efficacy of both adjuvant letrozole and anastrozole in postmenopausal hormone receptor-positive early breast cancer patients. A recently published phase III randomized trial (MA.27 trial) was designed to compare the efficacy of adjuvant steroidal aromatase inhibitor exemestane and the non-steroidal aromatase inhibitor anastrozole for 5 years in hormone receptor-positive patients [27]; both exemestane and anastrozole showed similar outcomes.

Our study has some limitations that are inherent to its retrospective nature. Despite the proven clinical efficacy of aromatase inhibitors in breast cancer patients with hormone receptor-positive disease, the adherence to aromatase inhibitors ranged from 41 to 72 % and non-adherence ranged from 31 to 73 %, measured at the end of 5 years of treatment in previous studies [28,29]. Due to the retrospective na-

ture of our study, the adherence to aromatase inhibitors was not known in both arms. The short duration of follow-up is another limitation of our study, as is the lack of safety and toxicity data in both arms. Our study showed that the 1, 3 and 5 years of DFS rate and the 3-year OS rate were similar in both anastrozole and letrozole arms.

The ongoing Femara versus Anastrozole Clinical Evaluation (FACE) trial is a phase IIIb open-label, randomized, multicenter trial designed to test whether letrozole or anastrozole have superior efficacy as adjuvant treatment of postmenopausal women with hormone receptor and lymph node-positive breast cancer [30]. Eligible patients are randomized to receive either letrozole 2.5 mg or anastrozole 1 mg daily for up to 5 years. The primary objective is to compare DFS at 5 years. Secondary endpoints include safety, overall survival, time to distant metastases, and time to contralateral breast cancer. The FACE trial will determine whether or not letrozole offers a greater clinical benefit compared to anastrozole in postmenopausal women with hormone receptor-positive early breast cancer.The estimated study completion date is April 2013.

In conclusion, the present study showed that both third generation non-steroidal aromatase inhibitors (letrozole and anastrozole) have similar effects on DFS and OS in the adjuvant hormonal treatment of postmenopausal hormone receptor-positive breast cancer. This retrospective study is the first to directly compare the efficacy of adjuvant letrozole and anastrozole.

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