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ORIGINAL ARTICLE

Assessment of Quality of Life and Safety in Postmenopausal Breast Cancer Patients Receiving Letrozole as an Early Adjuvant Treatment

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Purpose: There are few reports from Asian countries about the long-term results of aromatase inhibitor adjuvant treatment for breast cancer. This observational study aimed to evaluate the long-term effects of letrozole in postmenopausal Korean women with operable breast cancer. **Methods:** Self-reported quality of life (QoL) scores were serially assessed for 3 years during adjuvant letrozole treatment using the Korean version of the Functional Assessment of Cancer Therapy-Breast questionnaires (version 3). Changes in bone mineral density (BMD) and serum cholesterol levels were also examined. **Results:** All 897 patients received the documented informed consent form and completed a baseline questionnaire before treatment. Adjuvant chemotherapy was administered to 684 (76.3%) subjects, and 410 (45.7%) and 396 (44.1%) patients had stage I and II breast cancer, respectively. Each patient completed questionnaires at 3, 6, 12, 18, 24, 30, and 36 months after enrollment. Of 897 patients, 749 (83.5%) completed the study. The dropout rate was 16.5%. The serial trial outcome index, the sum of the physical and functional well-being subscales, increased gradually and significantly from baseline during letrozole treatment ($p<0.001$). The mean serum cholesterol level increased significantly from 199 to 205 after 36 months ($p=0.042$). The mean BMD significantly decreased from –0.39 at baseline to –0.87 after 36 months ($p<0.001$). **Conclusion:** QoL gradually improved during letrozole treatment. BMD and serum cholesterol level changes were similar to those in Western countries, indicating that adjuvant letrozole treatment is well tolerated in Korean women, with minimal ethnic variation.

Key Words: *Breast neoplasms, Letrozole, Quality of life, Treatment*

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INTRODUCTION

Breast cancer is the most prevalent malignancy among women, not only in Western countries, but also in Korea. More than half the newly diagnosed patients are postmenopausal women, even though women younger than 50 years

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old comprise a relatively large proportion [1]. More than 80% of those who undergo treatment for breast cancer have early breast cancer and around 70% have hormone receptor-positive disease. Anti-estrogen treatment is preferred over cytotoxic chemotherapy for hormone receptor-positive breast cancer as identified by advanced risk assessment tools such as molecular profiling [2].

A number of clinical trials indicate that third-generation aromatase inhibitors (AI) are more effective than tamoxifen in reducing disease recurrence in postmenopausal women with hormone receptor-positive tumors [3-5]. In contrast to tamoxifen, AI have specific adverse effects such as osteoporosis, joint pain, and change in serum lipoproteins, because of their estrogen-depriving function [6,7]. A number of clinical trials reported AI-specific adverse events; however, the majority of the patients studied were not Asian. There have been few reports from Asian countries about the long-term results of adjuvant AI treatment in postmenopausal women with breast cancer [8,9].

The primary aim of postoperative adjuvant therapy in early breast cancer is prevention of disease recurrence. Safety and tolerability of adjuvant treatment are important considering the relatively lower risk of recurrence in early breast cancer.

This observational study was performed to evaluate the long-term effects of letrozole in postmenopausal Korean women with early breast cancer. We analyzed the quality of life (QoL) of postmenopausal women who underwent adjuvant letrozole treatment. We also summarized the changes in bone mineral density (BMD) and serum cholesterol levels during adjuvant letrozole treatment.

METHODS

Study design and patients

Women from 30 institutes participated in this study. The study received institutional review board approval from individual ethics committees of the participating institutes. All the women were postmenopausal with histologically proven, operable, invasive breast carcinoma; had estrogen receptor-positive tumors; and were Korean. Women were eligible if they were at least 50 years of age and amenorrheic for at least 12 consecutive months before letrozole treatment, if they were younger than 50 years old but were postmenopausal or had undergone a bilateral oophorectomy, or if they had postmenopausal levels of follicle-stimulating hormone.

All patients had completed primary treatment for breast cancer (surgery and/or systemic chemotherapy and/or radiation therapy) according to the individual institutes' treatment principles. Systemic chemotherapy was started within 8 weeks of surgery and completed within 8 weeks of entry to the study. Patients were excluded if the investigator believed that they would be unable to comply with the protocol because of psychological or literacy issues.

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Each subject received a documented informed consent form to participate in the study and this study was approved by Institutional Review Board of Ajou University (Protocol No. AJIRB-CRO-07). The study is registered with ClinicalTrials.gov (number: NCT00913016).

Procedures

Each subject completed a baseline questionnaire before adjuvant letrozole treatment. A follow-up questionnaire was completed by each patient without help from a medical person, before visiting their clinician 3, 6, 12, 18, 24, 30, and 36 months after enrollment.

QoL was assessed using the Korean version of the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire (version 3) [10]. FACT-B is a 23-item questionnaire that measures physical (seven items) and functional (seven items) well-being and includes additional subscales more specific to breast cancer (nine items).

Outcomes

The primary endpoint of the QoL study was the trial outcome index (TOI) of FACT-B questionnaires, which is the sum of the physical and functional well-being and breast cancer-specific subscales. The sum of TOI scores was converted to the mean TOI score at every visit and the changes in mean TOI were analyzed.

Serum total cholesterol levels were measured every 6 months for 3 years, while the BMD was measured every year. Subsequently, all these values were analyzed.

Statistical analysis

The primary end point of the TOI was used to determine an appropriate sample size. It was noted that a 5-point change in TOI compared to the baseline was clinically relevant [10,11]. According to Fallowfield et al. [12] the mean TOI score for the primary disease group, which was similar to that in our study population, was 72.3 after a 3-month follow-up. We presumed that this mean TOI score would be maintained for 3 years unless adjuvant treatment was administered.

Meanwhile, Fallowfield et al. [13] showed that an average 3.49 point (with an estimated standard deviation [SD] of 12.45) change in TOI was achieved during 2 years of follow-up in the tamoxifen group. Hence, we should expect an increase of 1.51 points in the TOI with adjuvant letrozole treatment. This implied that in order to achieve an average TOI score of 73.8 rather than 72.3 with an SD of 12.45 for adjuvant therapy during the study period, a total of 717 subjects were needed. This sample size would ensure at least 90% statistical power based on a one-sample t-test with a two-sided significance level of 5%. Assuming a follow-up loss rate of 20%, a total of 897 patients were recruited.

The primary endpoint for QoL was analyzed using the intention-to-treat (ITT) population, which included all patients who received at least one dose of treatment. The per-protocol population was used for sensitivity analysis, excluding individuals from the ITT population without any QoL and TOI evaluation for the baseline and final visit (at 36 months).

Patients' demographics are summarized as mean ± SD or number of subjects (percentage), as appropriate. QoL scores were calculated for those with valid questionnaires. Changes in the QoL and BMD scores over the study period were assessed using the generalized estimating equations (GEE) method to incorporate the longitudinal nature of the data. In subgroup analyses, QoL scores were compared between the chemotherapy and non-chemotherapy groups and femur and spine BMDs were compared between the calcium and non-calcium groups. The Student t-test was used to compare baseline differences between groups. Overall changes during the study period and linear or quadratic patterns of the trend were examined using GEE. The significance of the mean TOI score changes between the baseline and each follow-up visit were also examined using contrasts within the GEE model.

All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, USA), and a p-value < 0.05 was considered statistically significant.

Table 1. Distribution of study subjects in the intention-to-treat population

Category	No. (%)
Enrolled subjects	897 (100)
Completed study	749 (83.5)
Early dropouts	148 (16.5)
Reasons for dropouts	
Adverse events	45 (30.4)
Abnormal laboratory tests	19 (12.9)
Protocol violation	7 (4.7)
Withdrawal of informed consent	18 (12.2)
Follow-up loss	52 (35.1)
Death	7 (4.7)

RESULTS

In total, 897 patients were enrolled and available for ITT analysis. Of the 897 patients, 749 (83.5%) completed the study, while 148 (16.5%) dropped out. The main reasons for dropout were loss to follow-up (35.1%), adverse events (30.4%). Other reasons for dropouts are described in Table 1.

The median age of the enrolled patients was 57 years (range, 51–79 years). The estrogen receptor was positive in 849 patients (94.6%) and the progesterone receptor was positive in 84.4% (n = 757). The numbers of patients with stage I and stage II disease were 410 (45.7%) and 396 (44.1%), respectively. Ninety-one patients (10.2%) had stage III disease, while 575 women (64.1%) had node-negative disease (Table 2).

Table 2. Demographic characteristics of the study subjects (n = 897)

Variable	No. (%)
Age (yr)*	57.1 ± 5.7
Estrogen receptor status	
Positive	849 (94.6)
Negative	48 (5.4)
Progesterone receptor status	
Positive	757 (84.4)
Negative	140 (15.6)
Stage	
I	410 (45.7)
II	396 (44.1)
III	91 (10.2)
Tumor size	
T1	533 (59.4)
T2	330 (36.8)
T3	34 (3.8)
Axillary lymph node metastasis	
N0	575 (64.1)
N1	225 (25.1)
N2	64 (7.1)
N3	33 (3.7)
Adjuvant treatment	
Radiation treatment	598 (66.7)
Chemotherapy	684 (76.3)
Operative method	
Modified radical mastectomy	379 (42.3)
Breast-conserving surgery	518 (57.7)
Types of adjuvant chemotherapy	
Anthracycline-based treatment	
Yes	468 (68.4)
No	216 (31.6)
Taxane-based treatment	
Yes	251 (36.7)
No	487 (63.3)
Bone mineral density*	
Femur	–0.21 ± 1.07
Spine	–0.44 ± 1.16

*Mean ± SD.

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Women who had undergone breast-conserving surgery numbered 518 (57.7%), and 684 women (76.3%) underwent adjuvant chemotherapy before entry into the study. Anthracycline-containing chemotherapy was administered to 468 (68.4%) women, and 251 women (36.7%) received taxane-based adjuvant chemotherapy.

Of the 897 women included in the analyses, 95.1% completed the questionnaire at 6 months, 92.4% at 12 months, 87.2% at 24 months, and 79.3% at 36 months. For QoL analysis, the TOI scores at each follow-up were converted to mean TOI scores, which were the sum of all the question scores divided by the number of question items.

The mean TOI score was 2.58 at baseline, increased at the 6-month follow-up (mean TOI, 2.63), and reached 2.78 at the end of the study (Table 3). The change in the TOI was statistically significant ($p<0.0001$), when its trend was analyzed using GEE analysis.

The changing QoL pattern was analyzed to see whether adjuvant chemotherapy could affect QoL during letrozole treatment. The mean TOI score was significantly lower ($p=0.0025$) in women who underwent adjuvant chemotherapy than in women who were at the nadir of adjuvant chemotherapy (mean TOI, 2.55 vs. 2.68) at the beginning of the study (Table 3). However, the mean TOI increased more rapidly in women who underwent adjuvant chemotherapy before letrozole treatment than in women who did not (Figure 1). The mean TOI increased steadily and linearly in both groups. The increase in the mean TOI was not different between the two groups during letrozole treatment.

The mean BMD of long bones (femur) was –0.21 at the beginning of the study and decreased steadily during the follow-up period, reaching –0.46 36 months after enrollment (Table 4). The decrease in the BMD of long bones with the use of letrozole was statistically significant ($p<0.0001$) (Figure 2A). The findings were similar when we measured the mean spine BMD. It decreased from –0.44 at enrollment to –0.84 at the end of the study (Table 4, Figure 2B).

The change in BMD was also analyzed according to calcium supplement intake during the letrozole treatment. Mean BMD

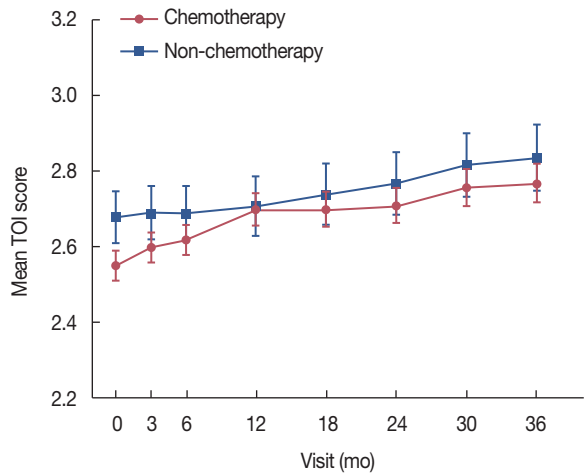

Figure 1. Comparison of mean trial outcome index (TOI) score changes between the chemotherapy-receiving and non-chemotherapy groups.

Table 3. Changes in the mean TOI score over the study period in the intention-to-treat population

Mean TOI	Baseline*	Months							*p*-value
		3	6	12	18	24	30	36	
Total									
N	888	853	822	762	697	652	576	554	<0.0001†
Mean	2.58	2.62	2.63	2.70	2.71	2.72	2.77	2.78	<0.0001‡
SD	0.53	0.52	0.53	0.53	0.56	0.54	0.53	0.54	
p-value§	-	0.0023	0.0004	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Chemotherapy									
N	676	652	633	592	538	501	450	436	0.2039‖
Mean	2.55	2.60	2.62	2.70	2.70	2.71	2.76	2.77	0.0311¶
SD	0.53	0.52	0.53	0.53	0.57	0.55	0.55	0.56	<0.0001‡
p-value§	-	0.0008	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Non-chemotherapy									
N	210	199	188	168	157	149	124	115	0.0122‡
Mean	2.68	2.69	2.69	2.71	2.74	2.77	2.82	2.84	
SD	0.51	0.52	0.52	0.53	0.53	0.53	0.49	0.48	
p-value§	-	0.8009	0.6947	0.6722	0.3305	0.0549	0.0531	0.0184	

TOI = trial outcome index; SD = standard deviation.
*$p=0.0025$ using Student t-test for equality of mean baseline TOI scores between the chemotherapy and non-chemotherapy groups; †For equality of mean TOI scores across visits using the generalized estimating equation (GEE); ‡For a linear trend test of mean TOI scores across visits using GEE analysis; §For comparisons of mean TOI score changes between baseline and each follow-up visit using contrasts within the GEE; ‖For an interaction effect between the chemotherapy/non-chemotherapy group and visits using the GEE; ¶Overall equality of mean TOI scores between the chemotherapy and non-chemotherapy groups using the GEE.

Table 4. Changes in femur/spine BMD compared to the baseline in the intention-to-treat population during letrozole treatment

BMD	Baseline*	Months			*p*-value
		12	24	36	
Femur BMD					
Total					
N	891	751	645	288	<0.0001†
Mean	–0.21	–0.38	–0.52	–0.46	<0.0001‡
SD	1.07	1.09	1.03	0.93	0.0031§
p-value‖	-	<0.0001	<0.0001	<0.0001	
Calcium					
N	165	144	134	52	0.3707¶
Mean	–0.49	–0.66	–0.88	–0.69	<0.0001**
SD	1.12	1.13	1.02	0.97	0.0066§
p-value‖	-	<0.0001	<0.0001	0.0001	
Non-calcium					
N	726	607	511	236	<0.0001‡
Mean	–0.14	–0.32	–0.43	–0.41	
SD	1.05	1.07	1.02	0.92	
p-value‖	-	<0.0001	<0.0001	<0.0001	
Spine BMD					
Total					
N	887	752	644	286	<0.0001†
Mean	–0.44	–0.76	–0.92	–0.84	<0.0001‡
SD	1.16	1.21	1.13	1.06	<0.0001§
p-value‖	-	<0.0001	<0.0001	<0.0001	
Calcium					
N	162	145	134	51	0.1060¶
Mean	–0.79	–1.09	–1.36	–1.25	<0.0001**
SD	1.06	1.10	0.97	1.00	0.0010§
p-value‖	-	<0.0001	<0.0001	0.0001	
Non-calcium					
N	725	607	510	235	<0.0001§
Mean	–0.36	–0.69	–0.81	–0.75	
SD	1.17	1.23	1.14	1.05	
p-value‖	-	<0.0001	<0.0001	0.0001	

BMD = bone mineral density; SD = standard deviation.
*$p = 0.0001$ for equality of mean baseline femur/spine BMD between the calcium and non-calcium groups using the Student t-test; †For equality of mean femur/spine BMD across visits using the generalized estimating equation (GEE); ‡For a linear trend test of mean femur/spine BMD across visits using GEE analysis; §For a quadratic trend test of mean femur/spine BMD across visits using GEE analysis; ‖For comparisons of mean femur/spine BMD changes between baseline and each follow-up visit using contrasts within the GEE; ¶For an interaction effect between the calcium/non-calcium group and visits using the GEE; **For overall equality of mean femur/spine BMD between the calcium and non-calcium groups using the GEE.

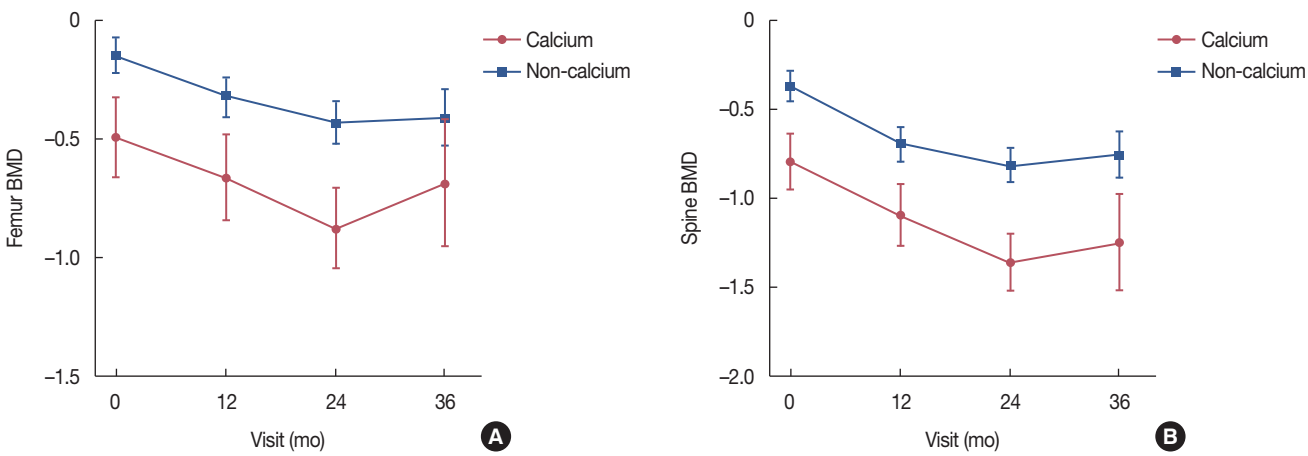

Figure 2. Changes in bone mineral density (BMD) compared to baseline with or without calcium medication during letrozole treatment. (A) Femur BMD. (B) Spine BMD.

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Table 5. Changes of total cholesterol from baseline during letrozole treatment with intention-to-treat population

Total cholesterol	Baseline	Months			*p*-value
		12	24	36	
N	881	778	672	281	0.0423*
Mean (mg/dL)	198.9	202.1	201.1	203.7	0.0211†
SD (mg/dL)	35.9	35.4	35.0	31.4	
p-value‡	-	0.0130	0.0391	0.0142	

SD = standard deviation.
*For an equality of mean total cholesterol across visits using generalized estimating equation (GEE); †For a linear trend test of mean total cholesterol across visits within GEE analysis; ‡For comparisons of mean total cholesterol change from baseline to each of following visits using contrasts within GEE.

at enrollment was –0.49 in women who received calcium supplements, while the mean BMD was –0.14 in women who did not take calcium supplements. The difference between the groups was statistically significant ($p < 0.0001$) at the beginning of the study (Table 4) and was maintained until the end of the study (Figure 2).

Serum cholesterol for all patients was monitored annually. Mean total cholesterol levels increased after 12 months of letrozole treatment from 198 at enrollment to 203 and the increasing trend was maintained until the end of the study. The increase was statistically significant ($p = 0.0423$) (Table 5).

DISCUSSION

Most clinical trials testing the clinical efficiency of AI have concentrated on the therapeutic superiority of AI to tamoxifen [3-5]. Based on the results of large-scale clinical trials, AI are now the standard treatment for postmenopausal women with hormone receptor-positive breast cancer. In these trials, patients' QoL was assessed as a subprotocol in a relatively small population of patients. There were no significant differences in TOI scores over time in most large-scale clinical trials [13-15].

In this study, patients' QoL significantly and continuously increased during letrozole treatment. This finding is somewhat different from other studies where QoL was maintained during AI treatment. Contrary to other studies, the TOI score increased during the follow-up period and the increase was statistically significant. This could be due to a younger population in our study or due to an ethnic difference, since all the patients in this study were Korean.

In some studies, older age was a predictor of worsening QoL in terms of overall physical health and bodily pain [14,16]. In the MA.17 trial, the majority of the patients were older than 60 years of age, while the mean age in this study was about 57 years. A review of adjuvant endocrine treatment in elderly patients revealed that QoL is minimally affected; however, more long-term data may be needed [17].

Maintenance of QoL is especially important in the adjuvant AI treatment of postmenopausal women with early breast cancer. The standard treatment duration for adjuvant AI in hormone receptor-positive patients is currently 5 years. Compliance with AI treatment is critical for an improved patient outcome in breast cancer. In daily practice settings, it has been reported that around one-third of patients failed to complete a 5-year adjuvant tamoxifen treatment course for various reasons [18]. Deterioration of QoL can affect the patients' compliance with adjuvant letrozole treatment. Of the 148 patients who dropped out, 40 patients discontinued the medication due to joint pain, although this symptom has been known to be associated with a better outcome [19].

A stable QoL status during letrozole treatment indicates that adjuvant letrozole treatment is well tolerated in postmenopausal Korean women with breast cancer.

During letrozole treatment in the current study, the BMD of the spine and femur decreased steadily. Subgroup analysis of the Breast International Group (BIG) 1-98 indicates that any type of adjuvant letrozole treatment, upfront or sequential, results in a decrease in BMD; however, BMD is not a perfect surrogate marker for predicting the bone fracture rate [20]. An association between the increased bone fracture rate and decreased BMD was observed in letrozole-treated patients in the BIG 1-98 trials. The MA.17 study also demonstrated a significant decrease in lumbar spine BMD and total hip BMD [21]. An increased risk of bone loss and bone fracture in AI-treated patients was reported in another large-scale clinical trial [15]. The finding was consistent with that in the current study. The mean spine and femur BMD decreased steadily in the current study. The decrease in BMD was not corrected by calcium supplementation. Results from the current and other large-scale studies indicate that prophylactic management for bone loss such as bisphosphonate treatment is necessary along with adjuvant letrozole treatment, since zoledronic acid is reported to have a prophylactic effect on bone loss during adjuvant letrozole treatment [22]. A recent large population study demonstrated that simultaneous use of oral bisphosphonate can counterbalance the effect of AI-induced bone loss in osteopenic and osteoporotic women [23].

We monitored serum cholesterol levels on an annual basis. Serum cholesterol increase did not affect the compliance of letrozole treatment, but the increase was statistically significant.

Complete estrogen deprivation because of letrozole is known to affect the serum lipid level. However, the results are not consistent among different studies. The National Cancer Institute of Canada Clinical Trial Group MA.17 lipid substudy

reported no remarkable changes in total cholesterol levels for patients treated with letrozole after 5 years of tamoxifen treatment [24]. However, the frequency of hypercholesterolemia in patients treated with anastrozole was significantly increased compared to that in patients treated with tamoxifen [6]. Another clinical trial with Japanese postmenopausal early breast cancer patients reported that AI had no clinically significant effect on serum lipids [9]. However, the study used exemestane and anastrozole, but did not include letrozole. Thus, direct comparison with the current study was not feasible.

This study has several limitations. It was an open label, single arm study without a control group. The questionnaire results might be influenced by the patients' community group or public medical information. Moreover, records of detailed adverse events and endocrine symptoms were missed. Despite these limitations, this study is meaningful in several points. It was performed with a considerable number of postmenopausal Asian women with primary breast cancers. While most large-scale QoL studies have been intended for a Western population, this study was targeted toward Asian women to make a comparison based on ethnic differences.

In conclusion, QoL significantly and continuously improved during letrozole treatment in postmenopausal Korean women with early breast cancer. The changing profiles for BMD and serum cholesterol levels were similar to those of Western countries. The results of this study indicate that adjuvant letrozole treatment is well tolerated in Korean women, with minimal ethnic variation compared to Western populations.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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