Adverse effects of endocrine therapy in breast cancer: single institute experience

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Aim of the study: The main purpose of this study is to assess the known adverse effects of adjuvant endocrine therapy for non-metastatic breast cancer patients and to present our single center experience with light of literature.

Material and methods: The breast cancer patients treated with adjuvant radiotherapy in Medical School of Ege University between January 2007 and December 2009 were evaluated for this trial after obtaining their acceptance. Vital findings, bone mineral densitometry, endometrium thickness measured with trans-vaginal ultrasonography, biochemical results including liver function tests and blood lipid profile (total cholesterol, HDL, LDL, VLDL, triglyceride) were recorded for each controls. Socio-demographic data, financial statuses, medical history, co-morbid diseases were obtained from first controls. Patients were followed without any local recurrence and distant metastases until June 2011.

Results: Endometrium thickness was not seen in AI using patients. As compared with tamoxifen group, lack of thickness in AI group was statistically significant (p = 0.000). When compared the values before AI, the number of patients who had osteoporosis was gradually increasing. The decrease was seen in the number of patients with osteopenia. The number of patients with normal lipid profile was gradually increasing up to the second evaluation for tamoxifen group (p = = 0.000). On the other hand, the number of patients with hyperlipidemia was increasing for AIs group in follow-up period statistically (p = 0.006).

Conclusions: With the aid of careful patient follow and effective disease management strategies, the negative effect over the QoL can be minimized and also the greatest benefit from endocrine therapy can be obtained.

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Introduction

Breast cancer is the most common type of cancer and it is the second most common cause of cancer death among women [1, 2]. In recent years advanced techniques have helped facilitate early-stage diagnosis of breast cancer and have prolonged the survival of patients with this disease. Long survival expectancy brings also the concept of quality of life (QoL) [3]. Breast cancer treatment includes a combination of surgery, chemotherapy, radiotherapy, and endocrine therapy. Adjuvant endocrine therapy (AET) is applied to hormone receptor-positive patients. AET is generally well tolerated and is not associated with acute or serious adverse effects, which are seen in chemotherapy. However, the need for long-term usage is a disadvantage of AET. Regular use is required to obtain the benefits of AET. Endocrine therapy is not only used in breast cancer but also in ovarian cancer [4]. Therefore, management of the adverse effects of AET composes an important part of treatment.

Clinical trials report that AIs and tamoxifen are well tolerated and that they do not negatively influence patients' routine life. Additionally, the results of FACE (comparing anastrozole and letrozole) and MA.27 (comparing exemestane and anastrozole), which are comparing AIs with each other directly, are pending, but thus far no differences between AIs have been found.

Notwithstanding the proven activities and acceptable tolerability profiles of endocrine treatment approaches, their adverse effects are generally underestimated [5, 6]. The main purpose of this study is to assess the known adverse effects of AET for non-metastatic breast cancer patients and to present our single-centre experience in light of the literature. We planned to give confirmatory results of hormonal treatment side effects before QoL evaluations.

Material and methods

Breast cancer patients treated in the Medical School of Ege University between January 2007 and December 2009 were evaluated for this trial after obtaining their approval. All of the included patients completed the whole treatment deemed appropriate for cancer, except for endocrine therapy.

Assessments

The patients were assessed in their routine policlinic controls. Vital findings, bone mineral densitometry (BMD), endometrial thickness measured with trans-vaginal ultrasonography (TVUSG), and biochemical results including liver function tests and blood lipid profile (total cholesterol, HDL (high-density lipoproteins), LDL (low-density lipoproteins), VLDL (very low-density lipoproteins), triglyceride), were recorded. First evaluation was

done after applying whole adjuvant cancer treatment except hormonal therapy, and it was coded as 'basal assessment'. Second evaluations were done after 6–12 months from the first control. Last evaluations were obtained within 18–24 months of the follow-up period.

Statistical analyses

Data were analysed using SPSS v15 (Statistical Package for Social Sciences version 15, SPSS Inc., Chicago, USA). For measuring descriptive statistics, frequency of distributions, average of whole scores, and 'Student's *t* test' were used to compare socio-demographic variables, clinical variables, and adverse effect data. In the analyses $p \leq 0.05$ was accepted as statistically significant.

Table 1. Clinical features of patients

	Number	%
Menopausal status		
Premenopausal	56	45.9
Postmenopausal	66	54.1
Co-morbid disease		
(+)	58	47.5
(–)	64	52.5
Operation type		
Partial mastectomy	78	63.9
Total mastectomy	44	36.1
Hormone receptor level		
Positive	102	83.6
Negative	20	16.4
Axillary dissection		
(+)	80	65.6
(–)	42	34.4
Stage group		
Early stage	95	77.9
Locally advanced stage	27	22.1
Chemotherapy		
(+)	84	68.9
(–)	38	31.1
Hormonal treatment type		
(–)	19	15.6
Tamoxifen Group	50	41.0
Aromatase Inhibitors	51	43.5

Results

One hundred and twenty-two breast cancer patients were included in this research. Clinical features of patients are illustrated in Table 1.

Evaluation of endometrial thickness

Endometrial thickness changes were measured with TVUSG for 50 patients using tamoxifen during the follow-up period as shown in Fig. 1. Before tamoxifen therapy, three patients had thickening of the endometrium in basal evaluation. After tamoxifen therapy, this number increased to 30 ($p = 0.000$). The detected rise was seen as statistically significant. All patients were referred to a gynaecologist for vaginal curettage. The results of curettages were reported as endometrial hyperplasia, except for in one patient. That patient's pathologic result included not only hyperplasia but also single invasive focus. Operation was suggested and applied with the patients' approval. Endometrial thickness was not seen in AI-using patients. Compared to the tamoxifen group, the lack of thickness in AI group was statistically significant ($p = 0.000$).

Evaluation of bone loss

BMD results for the AI group are shown in Fig. 2. When compared the values before AI, the number of patients who had osteoporosis gradually increased during therapy. A decrease was seen in patients with osteopaenia. These results were interpreted as the osteopaenia results shifting towards the osteoporosis side by use of AIs. BMD data for the tamoxifen group are also shown in Fig. 2. No significant change was seen during the follow-up period.

Evaluation of lipid profiles

The number of patients with normal lipid profile was gradually increasing up to the second evaluation for the

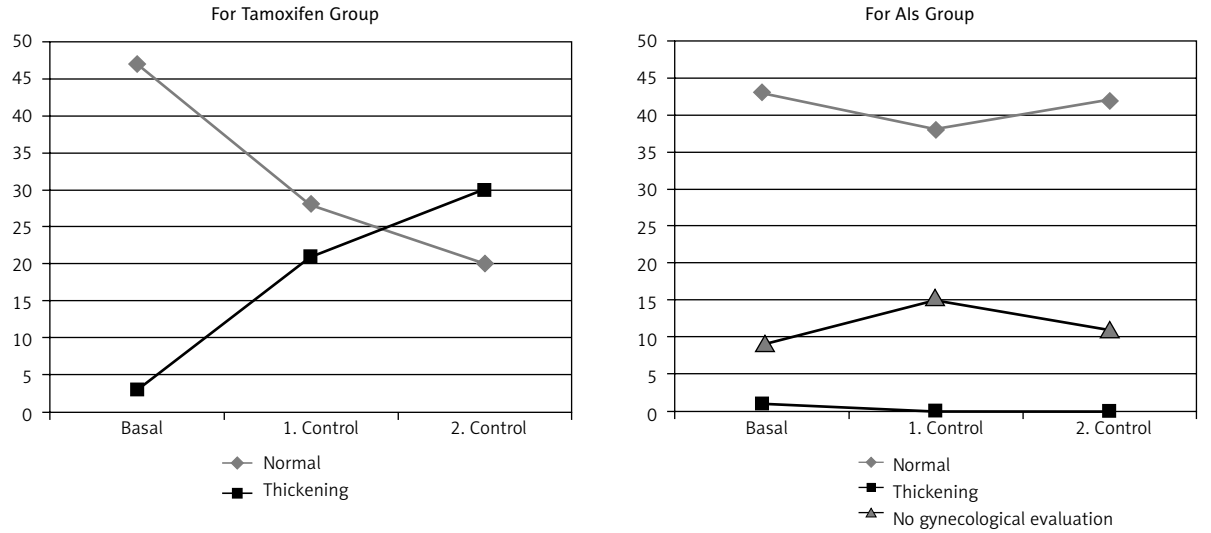

Fig. 1. Evaluation of endometrial thickness

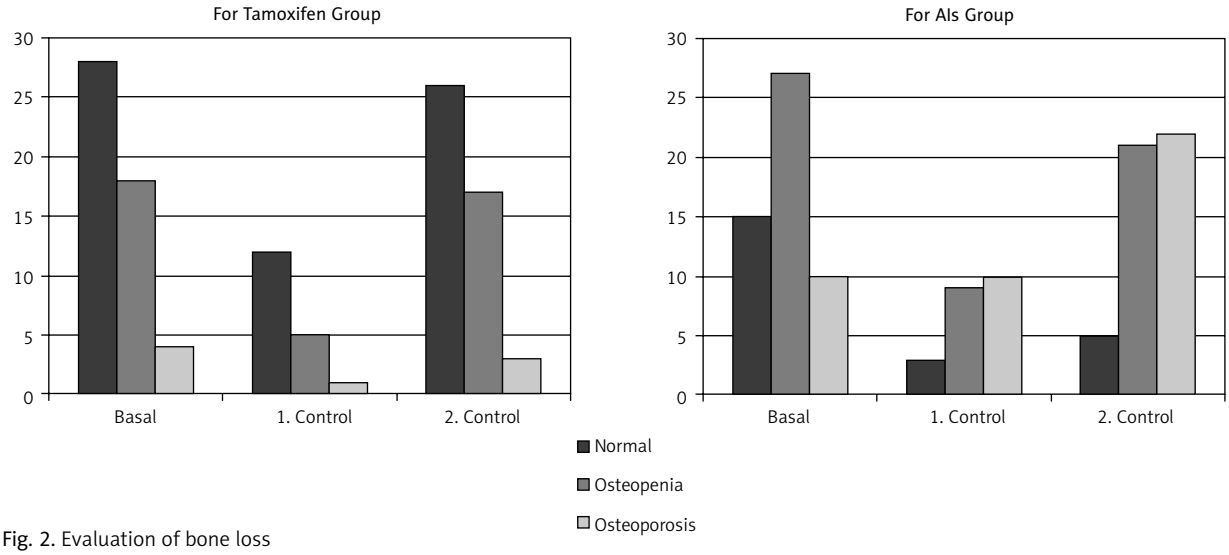

Fig. 2. Evaluation of bone loss

tamoxifen group (p = 0.000). Blood lipid profile changes for the tamoxifen group can be seen in Fig. 3. On the other hand, the number of patients with hyperlipidaemia increased for the AI group in the follow-up period (p = 0.006).

Discussion

Vaginal bleeding is an important symptom that can significantly affect the routine life of a patient. It is often associated with thickening of the endometrium. The probability of endometrium cancers should be considered. Tamoxifen was found to be associated with vaginal bleeding and endometrial thickness in The Arimidex, Tamoxifen Alone or in Combination (ATAC) and The Breast International Group (BIG) 1-98 studies [7, 8]. Vaginal bleeding caused by endometrial thickening was detected in 5.4% of the anastrozole group and 10.2% in the tamoxifen group (p < 0.0001). According to BIG 1–98 data, this ratio was 3.3% for the letrozole group and 6.6% for the tamoxifen group (p < 0.001). However, no statistical difference between tamoxifen and anastrozole arms was found in terms of vaginal bleeding and endometrium thickness in the combined analysis of the Austrian Breast and Colorectal Cancer Study Group 8 (ABCSG8) and Arimidex-Nolvadex 95 (ARNO95) trials [9]. The International Exemestane Study (IES) reported that increased endometrium thickness and vaginal bleeding was seen in the tamoxifen group than in the exemestane group (p = 0.05) [10]. Greater endometrial thickness and bleeding were determined in the placebo arm than in the letrozole arm in the MA.17 study (8% versus 6%, p = 0.005). The researchers argued the view that AI could repress the endometrial proliferation [11]. Endometrium thickness was detected only in three patients using tamoxifen before AET in our study. After tamoxifen therapy, the number of patients with endometrial thickness increased to 30 in the control assessment. This result was similar to that seen in the literature (p = 0.000).

BMD is a good indicator for osteoporosis evaluation. According to literature, AIs can cause an annual 2–3% decrease in BMD [12]. Postmenopausal BMD loss is increased with AIs. This can be explained by the increase in bone resorption through AIs. BMD data were investigated in ATAC subgroup analysis evaluating osteoporosis [13]. Osteopo-

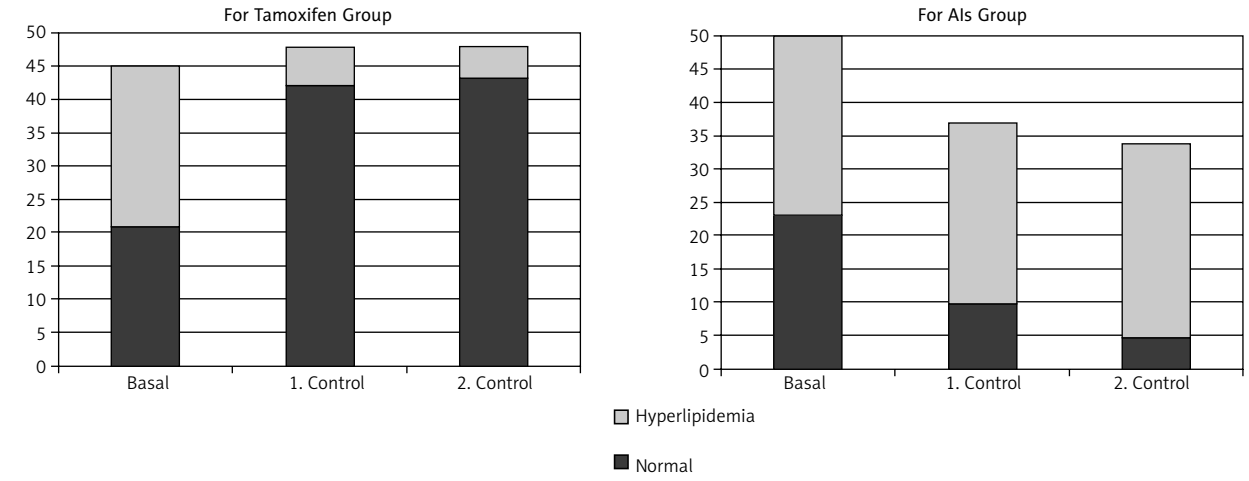

Fig. 3. Evaluation of lipid profiles

rosis was seen 3.3% more often in the tamoxifen group than in the anastrozole group. The osteoporosis rate was 11% for the anastrozole arm and 7.7% for the tamoxifen arm ($p < 0.0001$). BMD and bone pain were assessed after five years of follow-up for women using tamoxifen for 2-3 years followed by anastrozole in the ARNO95/ABCSG8 combined trial [9]. A significantly higher rate of osteoporosis was seen in the arm that switched to anastrozole (2%) than in the the tamoxifen arm ($p = 0.015$). More bone pain was reported in the anastrozole arm (19% vs. 16%, $p = 0.05$). Bone fractures were detected more often in the letrozole arm than in the tamoxifen arm in the BIG 1-98 trial ($p < 0.001$) [8]. BMD results of patients using AIs, before and after endocrine therapy, were compared in our study in order to evaluate osteoporosis. There was no significant difference between basal (obtained before endocrine therapies) and first control results. On the other hand, it was seen that osteoporosis was statistically higher in the second evaluation ($p = 0.000$).

The effect of AIs upon blood lipid levels is another issue to be discussed. Blood lipid profile changes were compared between the patients using tamoxifen alone and the patients using anastrozole after 5 years of tamoxifen in the Italian Tamoxifen Anastrozole (ITA) trial [14]. Statistically significant blood lipid profile changes were seen in the anastrozole group (9.3% vs. 4.0%, $p = 0.03$). However, there was no difference regarding hypercholesterolaemia in the anastrozole arm according to the ARNO95/ABCSG8 study results [9]. The effect of exemestane on blood lipid profile was evaluated in a randomised controlled study by Krang *et al.* [15], in which placebo and exemestane arms were compared. While the value of HDL-C decreased by 6–9% in the exemestane arm, there was a 1–2% increase in the placebo arm ($p < 0.001$). Blood lipid profile differences were compared between placebo and letrozole arms in a 36-month follow-up in the MA.17 trial [11, 16]. There were no statistically significant differences in terms of total cholesterol, HDL-C, LDL-C, triglyceride, or lipoprotein A levels between the two arms. Three hundred and forty patients were included in the Adjuvant Post-Tamoxifen Exemestane vs. Nothing Applied (ATENA) study [17]. A patient group using exemestane for 5 years and a patient group using nothing after 5–7 years of tamoxifen were compared in the ATENA study. There was no difference in subgroup analysis of ATENA in terms of total cholesterol, LDL-C, HDL-C, and triglyceride levels. We detected that blood lipid levels were gradually increasing in the AI group during the follow-up period ($p = 0.006$). This increasing result was seen similarly in the ARNO95/ABCSG8 trial and in the study by Krang *et al.*

In conclusion**,** most of the adverse effects of endocrine therapy consist of oestrogen suppression, as well as the side effects of predicted natural menopause. Nevertheless, these adverse effects can still be annoying and troublesome in the patients' routine daily life. Effective management options are available in order to cope with undesired side effects of AI treatment. On the other hand, the management of the side effects derived from tamoxifen is more difficult than for AI. Side effects experienced with AI, like bone loss, lipid profile changes and arthralgia, are controlled and managed easier than the effects, like thromboembolic events and endometrium cancer, experienced primarily with tamoxifen. With the aid of careful patient follow-up and effective disease management strategies, the negative effect on the patients' routine daily life can be minimised and the greatest benefit from endocrine therapy can be obtained. In order to give certain behaviour approaches, we need multi-institutional research projects on large numbers of people, including QoL assessments. With the help of future research, we can improve the disease prognosis through increased treatment adherence and belief of patients.

The authors declare no conflict of interest.

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