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.

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

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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.

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 Al 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
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-
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The authors declare no conflict of interest.

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Submitted: 5.11.2013
Accepted: 9.06.2014