Acta Oncologica, 2005; 44: 134–141

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ORIGINAL ARTICLE

Effect of anastrozole and tamoxifen on lipid metabolism in Japanese postmenopausal women with early breast cancer

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Abstract

Endocrine therapies that profoundly decrease estrogen levels potentially have a detrimental effect on the cardiovascular system. This study evaluated the effect on lipid metabolism of one such agent, the new generation aromatase inhibitor anastrozole, compared with tamoxifen, when used as adjuvant treatment in postmenopausal Japanese women with early breast cancer. All patients had completed primary surgery and were randomized to anastrozole 1 mg once daily (n = 22) or tamoxifen 20 mg once daily (n = 22). Anastrozole significantly reduced levels of triglycerides and remnant-like particle cholesterol, whereas tamoxifen significantly increased these. Activity of lipoprotein lipase and levels of high-density lipoprotein cholesterol significantly increased after anastrozole treatment. In contrast, activity of hepatic triglyceride lipase, also a key enzyme of triglyceride metabolism, significantly decreased following treatment with tamoxifen. We thus conclude that in our study anastrozole had a beneficial effect on lipid profiles of postmenopausal women with early breast cancer after 12 weeks of treatment.

Abbreviations: *T-C—total cholesterol, LDL-C—low-density lipoprotein cholesterol, HDL-C—high-density lipoprotein cholesterol, RLP-C—remnant-like particle cholesterol, Apo A-I—apolipoprotein A-I, Apo A-II—apolipoprotein A-II, Apo B—apolipoprotein B, Apo C-II—apolipoprotein C-II, Apo C-III—apolipoprotein C-III, Apo E—apolipoprotein E, LPL—lipoprotein lipase, HTGL—hepatic triglyceride lipase*

Introduction

Many breast cancers depend on estrogen for their continued growth, and depriving tumors of this stimulus is an established method of treating the disease [1,2]. Separate treatment strategies are available for reducing the effects of estrogens on breast cancer. One option is the use of selective estrogen receptor modulators (SERMs). These anti-estrogens block the effects of estrogen by binding to the estrogen receptor (ER) and interfering with receptor-mediated transcriptional events. Another option is to use an aromatase inhibitor to reduce plasma and intratumoral estrogen levels. Aromatase inhibitors block the rate-limiting step in the synthesis of estrogens—the conversion of androgens to estrogens by the cytochrome P-450 enzyme aromatase [3,4].

Tamoxifen is a SERM that is widely used in the treatment of breast cancer. For almost 30 years tamoxifen has remained the 'gold-standard' endocrine treatment of breast cancer [5]. However, the development of selective aromatase inhibitors has led to the availability of an alternative management approach for postmenopausal patients in whom hormonal therapy is indicated.

Anastrozole is a new-generation, oral aromatase inhibitor that substantially lowers both circulating plasma estrogens and intratumoral estrogen levels and has shown the highest degree of selectivity compared with letrozole and exemestane in terms of lack of effect on adrenosteroidogenesis [6,7]. Several trials comparing tamoxifen and anastrozole in postmenopausal women with advanced breast cancer have shown anastrozole to be superior to tamoxifen in terms of anti-tumor efficacy [8,9]. The

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(Received 9 July 2004; accepted 16 December 2004)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860510007585

most important issues now concern use of anastrozole in the adjuvant setting. In the "Arimidex", Tamoxifen alone or in Combination (ATAC) trial, adjuvant anastrozole was associated with significantly better disease-free survival and an overall favorable risk:benefit profile compared with tamoxifen in postmenopausal women [10,11]. It is therefore possible that anastrozole may, in the future, replace tamoxifen as the established adjuvant endocrine therapy for early breast cancer in these women.

Estrogen has been shown to have a beneficial effect on lipid metabolism [12], while the reduction of estrogen at the menopause has been associated with an increased rate of hyperlipidemia and a risk of hypoestrogenic-related disease, including myocardial infarction and stroke [13,14]. Estrogen deprivation following treatment for breast cancer may not be important in the metastatic setting. However, in the adjuvant setting or when used for the prevention of breast cancer, it is more important because patients are receiving long-term treatment.

In the present study, we compared, in a prospective, randomized fashion, the effect of two primary treatments, tamoxifen and anastrozole, on lipid metabolism in postmenopausal Japanese women with early breast cancer.

Material and methods

Patients

The study population consisted of 49 Japanese postmenopausal, primary operable breast cancer patients treated at the National Defense Medical College (Tokorozawa, Japan) from January 2002 to January 2003. Patients included in the trial satisfied the following entry criteria: (1) all demonstrated a postmenopausal status (defined as either no menses for more than 1 year or shorter duration of amenorrhea with follicle-stimulating hormone [FSH] levels in the postmenopausal range); (2) all had undergone breast surgery (either lumpectomy or mastectomy) and were considered to be potentially curable; (3) none had received either radiation or chemotherapy before breast surgery; (4) ER positivity was confirmed by histopathology; (5) none had either diabetes mellitus, renal or hepatic disease; (6) none had received drugs known to affect the lipid and lipoprotein levels; and (7) all were instructed to follow their usual diet and maintain weight during the study period. Informed consent was obtained from all participants. The study was conducted on an outpatient basis according to the principles of the Declaration of Helsinki and was approved by the medical ethics committee of the National Defense Medical College, and written consent was obtained from all participants.

All patients underwent surgery in the form of a total mastectomy or a breast-conserving resection with axillary evacuation. The subjects were randomly allocated to tamoxifen 20 mg once daily or anastrozole 1 mg once daily.

Sex hormone and lipid analyses

Overnight fasting blood samples were collected under identical conditions from the study patients, before and after 12 weeks of endocrine therapy, for measurement of FSH, estradiol, total cholesterol (T-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, remnant-like particle cholesterol (RLP-C), and apolipoprotein (apo) A-I, A-II, B, C-II, C-III and E levels. Serum FSH and estradiol levels were determined by modification with a fluorescence immunoassay kit (Perkin Elmer, Japan). T-C, LDL-C, HDL-C, and triglycerides were determined using enzymatic assay kits (Kyowa Medics, Japan). RLP-C was determined by an immune adherence method (Japan Immunoresearch Laboratories, Japan). Apo A-I, A-II, B, C-II, C-III, and E were measured with a turbidimetric immunoassay kit (Daiichi Pure Chemicals, Japan). The intra-assay coefficient of variance (%) (n = 20) for measurements of T-C = 1.1; LDL-C = 1.5; HDL-C = 1.2; triglycerides = 0.8; RLP-C = 3.7; apoA-1 = 2.2; apoA-II = 2.0; apoB = 1.9; apoC-II = 2.0; apoC-III = 2.0, and apoE = 2.4. The inter-assay coefficient of variance (%) (n = 20) for measurements of T-C = 0.6; LDL-C = 0.8; HDL-C = 0.6; triglycerides = 0.9; RLP-C = 3.1; apoA-1 = 0.8; apoA-II = 1.2; apoB = 0.8; apoC-II = 2.0; apo-CIII = 1.0, and apoE = 1.2.

Lipase activity assay

At the same time as fasting blood samples were collected, samples to determine the activity of lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) were collected in post-heparin plasma from all patients, 10 min after intravenous injection of heparin (30 U/kg body weight). The samples were separated immediately by centrifugation at 4°C and stored at −80°C until assay. The activities of LPL and HTGL were measured using previously described methods [15]. The intra-assay coefficient of variance (%) (n = 20) for measurements of LPL = 4.6 and for HTGL = 3.9. The inter-assay coefficient of variance (%) (n = 20) for measurements of LPL = 4.3 and for HTGL = 3.8.

Statistical analyses

Summary statistics are presented as the mean ± standard deviation (SD). Differences in the serum values from baseline to 12 weeks within each group were calculated as the median (interquartile range) and were compared by the Wilcoxon matched-pair signed-rank test. The differences in the serum values between the two groups were compared by the non-parametric Mann–Whitney test. All p-values of less than 0.05 were considered significant.

Assessment of T-C, LCL-C, HDL-C, and triglycerides before and after 12 weeks of endocrine therapy were classed as primary endpoints of the study.

Results

Table I gives the baseline values of all variables measured for all women included in the study. The two groups were generally well balanced. Forty-four women completed the 12-week follow-up. In the tamoxifen group, two women withdrew because of hot flushes and one withdrew due to the onset of diabetes. In the anastrozole group, one woman withdrew due to edema of the lower leg, and one due to administration of a hypolipidemic drug not authorized by the protocol. Both groups maintained their weight during the study period (data not shown).

Serum sex hormone levels

The baseline serum hormone levels and the response to tamoxifen and anastrozole are shown in Figure 1. Estradiol levels before treatment were low in both the tamoxifen and anastrozole group (34.9 and 32.0 pmol/L, respectively), thus indicating that patients in both groups were postmenopausal. Estradiol levels decreased significantly after treatment in the anastrozole group ($p < 0.001$). FSH levels were significantly decreased in the tamoxifen group ($p = 0.001$), whereas they increased significantly in the anastrozole group ($p < 0.001$).

Table I. Clinical characteristics of the study population.

Variables	Tamoxifen (n = 22)	Anastrozole (n = 22)
Age (years)	59.3 ± 5.9	58.7 ± 5.4
Height (cm)	153 ± 6.2	155 ± 6.7
Weight (kg)	54.7 ± 8.3	55.6 ± 5.6
Body mass index	23.4 ± 5.4	23.1 ± 5.5
Hypercholesterolemia, n (%)	13 (59)	12 (55)
Hypertension, n (%)	3 (14)	2 (9)
Previous coronary disease, n (%)	0 (0)	1 (5)
Duration of menopause (years)	7.3 ± 4.7	6.5 ± 3.9

Values indicate the frequencies or mean ± SD.

Serum lipid and lipoprotein levels

The baseline serum variables and the response to 12 weeks' treatment with tamoxifen and anastrozole are summarized in Table II, and the percentage change at 12 weeks from baseline for T-C, LDL-C, HDL-C, triglycerides, and RLP-C are shown in Figure 2.

Tamoxifen significantly decreased T-C by 13.4% ($p = 0.001$) and LDL-C by 23.5% ($p < 0.001$) (see Table II). Anastrozole did not induce any changes in T-C and LDL-C levels. The difference between the groups was statistically significant ($p < 0.001$).

Tamoxifen did not change HDL-C, but anastrozole significantly increased HDL-C by 10.2% ($p < 0.001$). The difference between the two groups was statistically significant ($p = 0.029$).

Tamoxifen increased triglycerides by 21.7% ($p = 0.005$) and RLP-C by 22.6%, ($p = 0.011$), while anastrozole decreased triglycerides by 20.1% ($p = 0.003$) and RLP-C by 22.2% ($p < 0.001$). The differences between the groups were also statistically significant ($p < 0.001$).

Serum apolipoprotein levels

The various serum lipoproteins have characteristic apoprotein compositions. The protein moiety of HDL particles consists primarily of apo A-I and apo A-II, while the protein moiety of LDL particles contains exclusively apo B. The levels of lipoproteins and apolipoproteins are important independent factors in the risk of coronary heart disease (CHD) that require assessment [16,17]. Tamoxifen significantly increased apo A-I by 12.9% ($p < 0.001$) and apo A-II by 7.1% ($p = 0.015$). Apo B decreased by 19.4% ($p < 0.001$) and apo E by 13.6% ($p = 0.002$) (see Table II).

Treatment with anastrozole was not associated with any significant changes in serum apoprotein levels (see Table II), although a slight increase in Apo A-I was observed (3.6%, $p = 0.02$).

Lipase activity

LPL and HTGL catalyze the hydrolysis of triglycerides. Table III shows the activity of HTGL and LPL before and after 12 weeks of treatment and Figure 3 shows percentage change in HTGL and LPL activities from baseline at 12 weeks.

Tamoxifen significantly decreased HTGL activity by 18.8% ($p < 0.001$), compared with anastrozole, which increased the HTGL activity by 9.7%

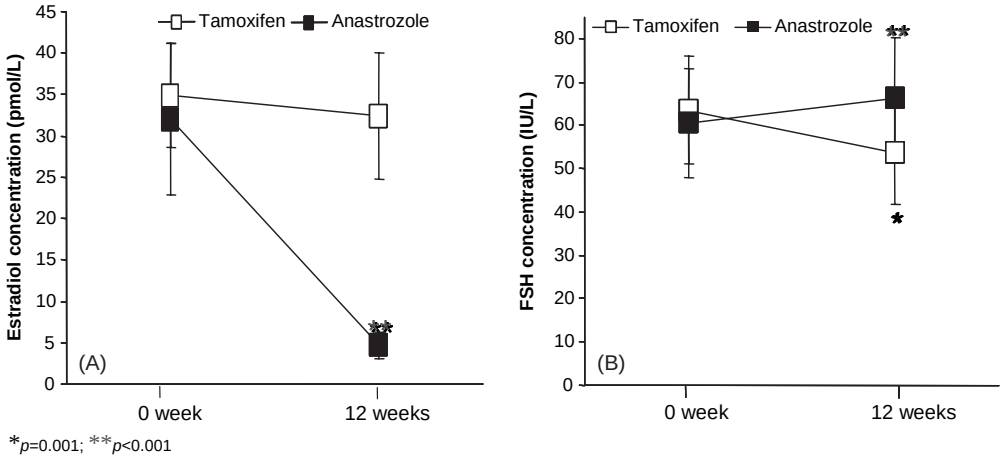

Figure 1. Effect of tamoxifen and anastrozole on the serum sex hormone levels. (A): Estradiol concentration; (B): FSH concentration. Data are the mean ± SD; p-values for the treatment difference from baseline to after 12 weeks of treatment were determined using the Wilcoxon matched-pair signed rank test. *p = 0.001 and **p < 0.001.

(p = 0.124). The difference between the groups was statistically significant (p = 0.005).

In contrast, anastrozole significantly increased the LPL activity by 10.0% (p = 0.01) compared with tamoxifen, which decreased the LPL activity by 10.3% (p = 0.051). The difference between the groups was statistically significant (p = 0.007).

Discussion

Epidemiologic studies have provided data to support the finding that elevated LDL-C and triglycerides levels, and reduced HDL-C levels are important risk factors for developing cardiovascular disease [16,17]. Overall, a 1 mg/dL increase in HDL cholesterol decreases the risk of CHD by 2–3% [18]. A 10 mg/dL increase in LDL cholesterol increases the risk of cardiovascular disease by 12%[19]. As a result, drugs that alter lipid profiles may increase the risk of developing cardiovascular disease. In the present study, we demonstrated that anastrozole administered at a dose of 1 mg once daily had no detrimental impact on fasted lipid profiles over a treatment period of 12 weeks. T-C and LDL-C levels remained unchanged; moreover, beneficial changes associated with anastrozole treatment were noted for HDL-C, triglycerides, and RLP-C levels. We also found that anastrozole treatment was associated with increased LPL activity, which could explain why it led to a decrease in triglyceride levels and an increase in HDL-C levels in this study.

Table II. Effect of tamoxifen and anastrozole on fasting lipids in 44 postmenopausal women with breast cancer.

	Tamoxifen (n = 22)		Anastrozole (n = 22)		Tamoxifen (n = 22)		Anastrozole (n = 22)	
Laboratory Test	0 week (mean ± SD [mg/dL])	12 weeks (mean ± SD [mg/dL])	0 week (mean ± SD [mg/dL])	12 weeks (mean ± SD [mg/dL])	Difference between 0 and 12 weeks (median [IQ range] mg/dL)	p-value	Difference between 0 and 12 weeks (median [IQ range] mg/dL)	p-value
T-C	217 ± 30	188 ± 33	213 ± 30	215 ± 31	−34.5 (−50.0, −15.0)	0.001	4.0 (−9.0, 17.0)	0.498
LDL-C	132 ± 29	101 ± 26	130 ± 27	126 ± 28	−35.5 (−44.0, −25.0)	<0.001	−3.5 (−23.0, 8.0)	0.358
HDL-C	61 ± 16	63 ± 16	59 ± 12	65 ± 16	0.5 (−2.5, 6.8)	0.367	6.0 (3.3, 11.9)	<0.001
Triglycerides	129 ± 41	157 ± 64	134 ± 61	107 ± 47	26.0 (0.0, 44.0)	0.005	−27.0 (−44.0, −9.0)	0.003
RLP-C	6.2 ± 1.7	7.6 ± 3.3	6.3 ± 2.8	4.9 ± 2.0	1.2 (−0.2, 1.8)	0.011	−1.3 (−2.2, −0.6)	<0.001
Apo A-I	139 ± 23	157 ± 23	138 ± 18	143 ± 22	15.5 (3.0, 24.0)	<0.001	9.0 (−2.0, 12.0)	0.020
Apo A-II	28 ± 4.4	30 ± 4.0	27 ± 4.4	27 ± 4.0	1.5 (−0.3, 4.6)	0.015	0.6 (−2.4, 2.6)	0.539
Apo B	103 ± 24	83 ± 26	103 ± 19	102 ± 25	−24.5 (−35.0, −6.0)	<0.001	1.5 (−15.0, 8.0)	0.788
Apo C-II	3.7 ± 1.3	3.6 ± 1.2	4.1 ± 1.3	4.2 ± 1.4	0.1 (−0.9, 0.6)	0.754	0.0 (−0.9, 0.9)	0.726
Apo C-III	8.8 ± 1.5	9.4 ± 2.4	9.3 ± 2.4	9.3 ± 2.2	0.4 (−0.8, 1.6)	0.265	0.1 (−1.0, 1.4)	0.975
Apo E	4.4 ± 0.8	3.8 ± 1.2	4.4 ± 1.0	4.5 ± 1.0	−0.6 (−1.3, −0.3)	0.002	0.1 (−0.3, 0.5)	0.256

P-values are for the difference between 12 weeks and baseline, using the Wilcoxon matched-pair signed rank test.

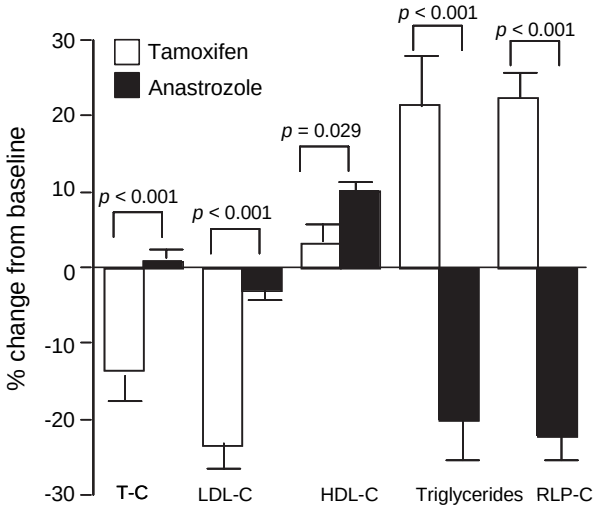

Figure 2. Effect of tamoxifen and anastrozole on serum lipids. Data are the mean ± SD; p values for the difference between the tamoxifen group and anastrozole group were determined using the Mann–Whitney test. T-C = total cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; RLP-C = remnant like particle cholesterol.

Anastrozole and LDL-C

Postmenopausal women have higher T-C and LDL-C levels than premenopausal women [20]; LDL-C levels increase by 10–20% after menopause [21]. Estrogen is known to reduce serum LDL-C levels by increasing LDL particle clearance through LDL receptor upregulation [22]. A large increase in LDL-C levels appears to occur early in the transition from premenopausal to postmenopausal status [23], when estrogen concentrations decrease from high levels (> 200 pmol/L) to low levels (≤ 50 pmol/L). In this study, anastrozole caused no change in LDL-C levels when the estrogen concentration decreased from a low level (50 pmol/L) to an even lower level (< 10 pmol/L) (see Figure 1). We speculate that the estrogen concentration threshold affecting cholesterol metabolism ranges between 50 pmol/L and 200 pmol/L. Therefore, in postmenopausal women, lowering the estrogen concentration below 50 pmol/L may not influence LDL-C levels.

Anastrozole and HDL-C, triglycerides, RLP-C

In this study, anastrozole increased HDL-C, and reduced triglycerides and RLP-C levels. RLP-C, which is reflected by remnant lipoprotein, is a new independent risk factor for cardiovascular disease [24]. A high level of RLP-C implies a delayed clearance of triglyceride rich lipoprotein.

LPL is the major enzyme responsible for hydrolysis of circulating triglycerides. It hydrolyzes the triglyceride moiety of chylomicrons and very low-density lipoproteins (VLDL), thus resulting in the biogenesis of HDL particles. Increased LPL activity leads to low levels of VLDL and high levels of HDL. This enzyme is mainly produced in adipose tissue and skeletal muscle [25]. Plasma LPL activity was correlated with LPL activity in adipose tissue [26] and in skeletal muscle [27].

LPL activity was investigated to determine whether or not anastrozole has a beneficial effect on triglyceride metabolism. Anastrozole was shown to increase LPL activity. Estrogen has been reported to inhibit LPL activity in plasma [26], which supports the finding that the effect of anastrozole on estrogen levels may increase LPL activity (see Table III and Figure 3). This increase in LPL activity leads to the hydrolysis of triglyceride-rich lipoprotein, generating HDL in the process, which could explain why anastrozole reduced triglycerides and increased HDL-C in this study.

Enhanced LPL activity is known to increase larger HDL particles, which are more lipid-rich and less protein-poor [28]. Anastrozole significantly increased HDL-C (10.2%, $p < 0.001$) but increased apoA-I slightly (3.6%, $p = 0.02$) (see Table II and Figure 2). As a result, anastrozole increased the

Table III. Effect of tamoxifen and anastrozole on HTGL and LPL in 44 postmenopausal women with breast cancer.

	Tamoxifen (n = 22)		Anastrozole (n = 22)		Tamoxifen (n = 22)		Anastrozole (n = 22)	
Laboratory Test	0 week (mean ± SD [μmol/ml/min])	12 weeks	0 week (mean ± SD [μmol/ml/min])	12 weeks	Difference between 0 and 12 weeks (median [IQ range] μmol/ml/min)	p-value	Difference between 0 and 12 weeks (median [IQ range] μmol/ml/min)	p-value
HTGL activity	0.32 ± 0.07	0.26 ± 0.05	0.31 ± 0.05	0.34 ± 0.05	−0.05 (−0.08, −0.02)	<0.001	0.04 (−0.01, 0.10)	0.124
LPL activity	0.39 ± 0.12	0.35 ± 0.12	0.40 ± 0.12	0.44 ± 0.17	−0.04 (−0.09, 0.02)	0.051	0.04 (−0.01, 0.06)	0.010

p-values are for the difference between 12 weeks and baseline, using the Wilcoxon matched-pair signed rank test.

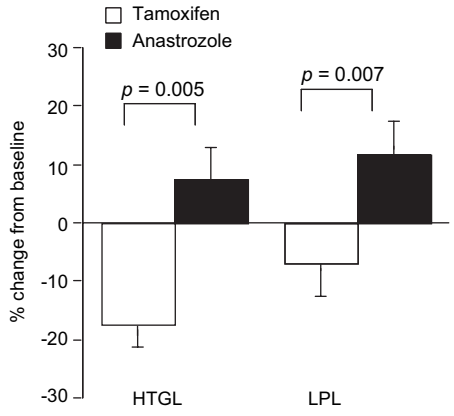

Figure 3. Effect of tamoxifen and anastrozole on the activity of lipase. Data are the mean ± SD; P-values for difference between the tamoxifen group and anastrozole group were determined using the Mann–Whitney test. LPL = lipoprotein lipase; HTGL = hepatic triglyceride lipase.

HDL-C (cholesterol)/apoA-I (protein) molar ratio, which indicates HDL particle size. This change of HDL particle size suggests that anastrozole changed lipoprotein profiles through increasing LPL activity.

Although HDL particle consists of apo-AI and additional lipids, the new synthesis of apo-AI, which is normally upregulated by estrogen, is reduced with anastrozole treatment. The increase in HDL-C with anastrozole treatment in this study does not therefore have to correlate with a significant increase in overall apo-AI and apo-AII.

Results from the ATAC trial indicate that anastrozole shows an advantage over tamoxifen in terms of fewer ischemic cerebral events and thrombotic events [10,11]. This may be a result of the favorable effects of anastrozole on triglycerides and HDL-C levels.

Other reports on the effects of aromatase inhibitors on lipid metabolism

There have been several reports on the effects of third-generation aromatase inhibitors on lipid profiles in postmenopausal women with advanced breast cancer. Dewar et al. reported that anastrozole did not alter the non-fasting lipid levels in comparison with baseline measurements [29].

In contrast, letrozole, which like anastrozole is a non-steroidal, third-generation aromatase inhibitor, has been found to increase T-C and LDL-C levels [30]. Exemestane, a steroidal aromatase inhibitor, may also have the potential to affect lipid profiles. One study found it increased T-C and LDL-C levels, decreased HDL-C and significantly decreased triglyceride levels [31]. A dose-escalation study found a significant decrease in T-C, HDL-C and total triglycerides [32]. Conversely, 3 months' treatment with exemestane indicated that it did not have a clinically relevant effect on lipid profiles [33]. In these studies exemestane caused a clinically significant change in HDL-C/LDL-C ratio, an important predictor of cardiovascular risk.

Fadrozole, another non-steroidal aromatase inhibitor, did not alter lipid profiles [34]. However, a high-dose subgroup receiving fadrozole 4 mg daily demonstrated a significant increase in the HDL-C level over time [34]. These data are similar to the study presented here in which anastrozole significantly increased HDL-C levels. Although it is difficult to extrapolate these data into the adjuvant setting, particularly because it is not known whether there will be any long-term clinical relevance in terms of cardiovascular morbidity, the results of these studies clearly show that these third-generation aromatase inhibitors appear to have different effects on the serum lipid levels.

Tamoxifen and lipid metabolism

In the present study, tamoxifen decreased T-C by 13.4% and LDL-C by 23.5%. This may be due to its partial estrogenic activity, since estrogen is known to reduce serum LDL-C levels by increasing LDL particle clearance through LDL receptor upregulation [35]. Tamoxifen has been previously reported as having no significant effect on HDL-C levels, whereas it is known to increase serum apo-AI levels [36]. Estrogen is known to upregulate hepatic apo-AI expression and hence the increase in apo-AI may represent an estrogen agonistic effect on apo-AI expression, leading to increased serum apo-AI levels but not HDL-C. In contrast, anastrozole did not alter apo-AI and apo-AII levels as it does not possess estrogenic effects similar to tamoxifen.

Tamoxifen increased triglyceride levels by 22% and RLP-C by 23%. In addition, it also decreased HTGL activity by 19%. Hozumi et al. reported tamoxifen decreased HTGL activity in postmenopausal women with adjuvant breast cancer [37]. Again, this may be due to its partial estrogenic activity, as it is well established that estrogen induces hypertriglyceridemia through its multiple effects on lipid metabolism, including increased synthesis of triglyceride and decreased HTGL activity. HTGL participates in the catabolism of triglyceride rich lipoprotein and the lowering of enzyme activity is accompanied by an increase in serum triglyceride levels [38,39].

In this way, tamoxifen is considered to exhibit a strong estrogen agonistic effect on lipoprotein metabolism.

Conclusion

It is clear that these two widely used methods of endocrine therapy show distinct differences in their effects on lipid metabolism. The significant favorable effects on lipid metabolism associated with anastrozole are important to consider for adjuvant breast cancer therapy.

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