The effect of exemestane, anastrozole, and tamoxifen on lipid profiles in Japanese postmenopausal early breast cancer patients: final results of National Surgical Adjuvant Study BC 04, the TEAM Japan sub-study


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Background: In this Tamoxifen Exemestane Adjuvant Multinational Japan sub-study, we evaluated the time course of changes in serum lipids in postmenopausal women with hormone-sensitive early breast cancer treated with exemestane, anastrozole, or tamoxifen for postoperative adjuvant therapy.

Patients and methods: A total of 154 breast cancer patients were assigned to receive exemestane, anastrozole, or tamoxifen in this randomized open-label study. Serum lipid parameters including triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured during 1 year of treatment.

Results: TC and LDL-C rapidly decreased in patients treated with tamoxifen at 3 months. Compared with anastrozole and exemestane patients, TC and LDL-C were significantly lower at all assessment time points in tamoxifen patients (P < 0.05). TG increased in tamoxifen patients; it was significantly higher compared with exemestane patients at all assessment time points (P < 0.05). HDL-C slightly decreased in exemestane patients; it was significantly lower compared with anastrozole patients at 3 months and 1 year (P = 0.0179 and 0.0013, respectively).

Conclusion: Changes of lipid profiles in Japanese postmenopausal women treated with tamoxifen were relatively favorable, while exemestane and anastrozole had no clinically significant effect on the serum lipids.

Key words: adjuvant therapy, early breast cancer, exemestane, lipid profile

Introduction

Breast cancer is the major malignancy affecting a large number of postmenopausal women in Japan as in the Western countries [1]. Hormone therapy to block estrogen stimulation is useful for treatment of hormone receptor-positive breast cancer, which takes up a large proportion of all breast cancer. The third-generation aromatase inhibitors (AIs), e.g. exemestane (steroidal AI), anastrozole and letrozole (nonsteroidal AIs), are now widely used for the treatment of early and advanced hormone-sensitive breast cancer in postmenopausal women [2]. Postoperative adjuvant therapy with AIs is a promising treatment for early breast cancer; it prevents recurrence more compared with the standard treatment tamoxifen [3–6] and is associated with less frequent serious adverse drug reactions such as thromboembolism and venous thrombosis that commonly occur in patients treated with tamoxifen [3, 5, 7, 8].

However, adverse drug reactions associated with long-term treatment with AIs, namely, changes in serum lipids and subsequent cardiovascular damage, remain a problem since AIs strongly inhibit blood estrogen levels in postmenopausal breast cancer patients [9]. Considering that the primary purpose of postoperative adjuvant therapy for early breast cancer is recurrence prevention, information about lipid profiles in patients treated with AIs will be useful for evaluation of risks and benefits of adjuvant therapies with AIs. Accumulation of clinical data of Japanese patients is required for development of a more suitable treatment strategy since the effect of AIs on serum lipids may vary among ethnicities.

Tamoxifen is a selective estrogen receptor modulator and known to favorably affect lipid profiles [10]. On the other hand, steroidal AIs may affect the serum lipids differently from nonsteroidal AIs because the former irreversibly bind to...
aromatase and have a potential androgenic effect [11]. Data from existing studies are inconsistent. For example, exemestane was shown to have little effect on the serum lipids in some studies [12, 13], while one study reported the drug adversely affected the high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) [14]. As for nonsteroidal AIs, the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA-17 lipid sub-study showed no remarkable changes in total cholesterol (TC), HDL-C, LDL-C, and triglyceride (TG) in patients treated with letrozole [15], while the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial showed that the frequency of hypercholesterolemia in patients treated with anastrozole was about three times higher compared with patients treated with tamoxifen [8]. The clinical significance of exemestane in terms of changes in serum lipids has not been established because no study has directly compared the effect of exemestane and nonsteroidal AIs in postoperative adjuvant therapy for early breast cancer.

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) Japan is a sub-study of an ongoing phase III TEAM trial conducted as part of the National Surgical Adjuvant Study of Breast Cancer trial (N-SAS BC) 04. TEAM Japan was designed to evaluate serum lipids, bone mineral density and, health-related quality of life (HRQOL) in postmenopausal women with hormone-sensitive early breast cancer receiving postoperative adjuvant therapy with exemestane, anastrozole, or tamoxifen. This paper reports the final analysis of changes in serum lipids over time in early breast cancer patients participated in TEAM Japan.

patients and methods

study design

N-SAS BC 04 comprises a core protocol (TEAM international) and a sub-protocol (TEAM Japan, Figure 1). TEAM Japan was a randomized, open-label multicenter study designed to compare tamoxifen (treatment duration, 2.5–3 years) followed by exemestane (2.5–3 years), anastrozole alone (5 years), and exemestane alone (5 years). The primary end points were serum lipids and bone mineral density, and the secondary end point was HRQOL.

TEAM trial, the original study, was a randomized, open-label multinational study designed to evaluate disease-free survival in postmenopausal women receiving postoperative adjuvant therapy with tamoxifen (2.5–3 years) followed by exemestane (2.5–3 years) or exemestane alone (5 years) for hormone-sensitive breast cancer. Patient recruitment for TEAM trial started in 2001, and 9775 patients from nine countries including Japan were registered. Nineteen sub-studies that primarily evaluate long-term safety (e.g. serum lipids and bone mineral density) and quality of life, including TEAM Japan, are either ongoing or have been completed in the participating countries.

patients and procedures

Postmenopausal women who had undergone surgery for stage I, II, or IIIA estrogen receptor-positive and/or progesterone receptor-positive breast cancer with performance status of zero or one and adequate organ function, had satisfied the lipid criteria (TC < 260 mg/dl and TG < 300 mg/dl) and had never been treated for lipid metabolism disorder were enrolled in the TEAM Japan lipid sub-study. Eligible patients were dynamically allocated to receive oral exemestane 25 mg/day, anastrozole 1 mg/day or tamoxifen 20 mg/day, adjusted for chemotherapy, lymph node metastasis, radiation therapy, and institution. Use of statins and fibrates were allowed in patients who became hyperlipidemic during the protocol treatment. Hormone replacement therapy was not allowed. This study was conducted in compliance with the Declaration of Helsinki after its protocol had been approved by the ethical review board of the respective participating institutions. Written consent was obtained from all participating patients before their enrollment.

measurements

Ten serum lipid parameters used in this study included TC, HDL-C, LDL-C, TG, remnant-like particles cholesterol (RLP-C), lipoprotein (a) [Lp(a)], apolipoprotein A1 (Apo-A1), Apo-B, Apo-C2, and Apo-B/Apo-A1 ratio. They were measured at baseline, 3 months, 6 months, and 1 year. Blood
samples collected at the participating institutions were delivered to a single testing laboratory for analysis.

statistical analysis

Our analysis included patients who satisfied the lipid criteria before randomization and in whom the protocol treatment was appropriately started. This study evaluated whether exemestane, anastrozole, and tamoxifen would affect the serum lipids differently, whether exemestane and anastrozole would have more adverse effects compared with tamoxifen, and whether the efficacy of steroidal and nonsteroidal AIs would be different. One study arm required 21–82 patients to reject the null hypothesis that mean TC would increase by >5% at 2 years of treatment in patients treated with exemestane or anastrozole compared with tamoxifen at a 0.05 significance level (two sided) and 80% power.

Means and standard deviations were calculated for all the lipid parameters at all assessment time points to describe their changes over time. Least square means and 95% confidence intervals were calculated using a generalized estimating equation model including study arm, assessment time point, and interaction term as covariates to compare differences of the study drugs. Tukey–Kramer multiple comparison was used to compare intergroup differences at the assessment time points. Intergroup differences were tested at a 0.05 significance level (two sided); SAS (version 9.1.3) was used for all analyses.

results

One hundred fifty-four patients from 31 institutions were registered for the TEAM Japan lipid sub-study from 2003 to 2005. Fifty-two patients were assigned to receive tamoxifen, 52 to exemestane, and 50 to anastrozole. The baseline patient demographics were similar among the three arms (Table 1). Means and standard deviations for lipid parameters measured at the assessment time points are shown in Figure 2 and Table 2. Results of intergroup tests using least-square means are described in the text.

TG was significantly higher in tamoxifen patients compared with exemestane patients at all the assessment time points ($P < 0.05$).

TC rapidly decreased in tamoxifen patients and slightly decreased in exemestane patients at 3 months. TC was significantly lower in tamoxifen patients compared with anastrozole and exemestane patients at all the assessment time points ($P < 0.05$). Compared with anastrozole patients, TC was significantly lower in tamoxifen patients at 3 months and 1 year ($P = 0.0361$ and 0.0076, respectively).

HDL-C did not change significantly in tamoxifen patients and slightly decreased in exemestane patients. Compared with anastrozole patients, HDL-C was significantly lower in exemestane patients at 3 months and 1 year ($P = 0.0179$ and 0.0013, respectively).

LDL-C rapidly decreased at 3 months in tamoxifen patients. Compared with anastrozole and exemestane patients, LDL-C was significantly lower in tamoxifen patients at all the assessment time points ($P < 0.0001$).

RLP-C did not change significantly in tamoxifen patients. RLP-C slightly decreased in exemestane patients; however, the difference between exemestane and tamoxifen patients and between exemestane and anastrozole patients was not significant.

Lp(a) decreased at 3 months in tamoxifen patients. Compared with anastrozole and exemestane patients, Lp(a) was significantly lower in tamoxifen patients at all the assessment time points ($P < 0.05$).

Apo-A1 slightly increased in tamoxifen patients and slightly decreased in exemestane patients. Compared with tamoxifen and anastrozole patients, Apo-A1 was significantly lower in exemestane patients at all the assessment time points ($P < 0.05$).

Apo-B was significantly lower in tamoxifen patients compared with anastrozole and exemestane patients at all the assessment time points ($P < 0.0001$).

Apo-C2 was significantly lower in tamoxifen patients compared with anastrozole patients at all the assessment time points ($P < 0.05$).

Apo-B/Apo-A1 ratio was significantly lower in tamoxifen patients at all the assessment time points ($P < 0.0001$).

discussion

TEAM Japan evaluated the changes of lipid profiles in postmenopausal women with hormone-sensitive early breast
Cancer receiving postoperative adjuvant therapy with exemestane, anastrozole or tamoxifen. Being the first study to directly compare steroidal and nonsteroidal AIs in postoperative adjuvant therapy for early breast cancer, TEAM Japan provided physicians and patients with useful information to help understand the difference in effects on serum lipids between the two types of AIs and valuable data of Japanese patients in whom few studies had been conducted.

TEAM Japan showed that changes of lipid profiles differed among patients treated with tamoxifen, anastrozole, or exemestane. Specifically, the beneficial effect of tamoxifen to lower TC, LDL-C, and Lp(a) shown in TEAM Japan was

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**Table 2.** Summary statistics of lipidemic parameters over time

<table>
<thead>
<tr>
<th>Lipid parameter</th>
<th>Treatment</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLP cholesterol (mg/dl)</td>
<td>Tamoxifen</td>
<td>5.7 (2.7)</td>
<td>6.5 (6.0)</td>
<td>5.9 (5.3)</td>
<td>5.3 (2.8)</td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td>6.0 (3.3)</td>
<td>5.1 (3.6)</td>
<td>4.7 (3.0)</td>
<td>4.8 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Anastrozole</td>
<td>5.6 (2.5)</td>
<td>5.5 (3.0)</td>
<td>5.9 (4.1)</td>
<td>5.2 (2.2)</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/dl)</td>
<td>Tamoxifen</td>
<td>16.1 (11.1)</td>
<td>10.9 (7.9)</td>
<td>9.7 (6.8)</td>
<td>9.5 (6.6)</td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td>17.3 (12.4)</td>
<td>15.4 (11.0)</td>
<td>15.8 (10.8)</td>
<td>15.6 (11.4)</td>
</tr>
<tr>
<td></td>
<td>Anastrozole</td>
<td>17.9 (12.0)</td>
<td>18.0 (12.9)</td>
<td>16.6 (11.3)</td>
<td>15.6 (10.0)</td>
</tr>
<tr>
<td>Apolipoprotein A1 (mg/dl)</td>
<td>Tamoxifen</td>
<td>160.7 (25.9)</td>
<td>171.9 (25.6)</td>
<td>174.9 (25.9)</td>
<td>178.4 (21.5)</td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td>155.5 (22.5)</td>
<td>145.2 (18.1)</td>
<td>146.0 (17.7)</td>
<td>148.1 (22.5)</td>
</tr>
<tr>
<td></td>
<td>Anastrozole</td>
<td>156.2 (19.7)</td>
<td>161.1 (20.7)</td>
<td>161.8 (20.8)</td>
<td>163.8 (21.0)</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dl)</td>
<td>Tamoxifen</td>
<td>108.4 (18.5)</td>
<td>89.1 (19.0)</td>
<td>88.8 (16.2)</td>
<td>89.4 (16.7)</td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td>103.3 (18.9)</td>
<td>100.3 (16.3)</td>
<td>99.3 (16.2)</td>
<td>99.2 (14.5)</td>
</tr>
<tr>
<td></td>
<td>Anastrozole</td>
<td>106.0 (17.8)</td>
<td>104.6 (17.0)</td>
<td>100.0 (16.8)</td>
<td>103.3 (16.2)</td>
</tr>
<tr>
<td>Apolipoprotein C2 (mg/dl)</td>
<td>Tamoxifen</td>
<td>4.6 (1.6)</td>
<td>3.8 (1.6)</td>
<td>3.6 (1.4)</td>
<td>3.5 (1.4)</td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td>4.1 (1.6)</td>
<td>3.9 (1.6)</td>
<td>3.6 (1.4)</td>
<td>3.6 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Anastrozole</td>
<td>4.4 (1.1)</td>
<td>4.4 (1.1)</td>
<td>4.3 (1.5)</td>
<td>4.0 (1.2)</td>
</tr>
<tr>
<td>Apolipoprotein B/A1 ratio</td>
<td>Tamoxifen</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Anastrozole</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.2)</td>
<td>0.6 (0.2)</td>
<td>0.7 (0.2)</td>
</tr>
</tbody>
</table>

Values are represented as mean (SD) unless otherwise.

RLP, remnant-like particles; SD, standard deviation.
consistent with an existing study [16]. While Sawada et al. [17] reported that anastrozole favorably affected HDL-C and TG, TEAM Japan showed that the effect of anastrozole on serum lipids might be insignificant. Exemestane was shown to favorably affect TG in TEAM Japan. According to the final report from TEAM Greek lipid sub-study [13], however, the favorable effect of exemestane was shown at 1 year as in TEAM Japan but was absent at 2 years.

Tamoxifen favorably affected LDL-C, one of the important risk factors for atherosclerotic disease, as expected. TEAM Japan newly showed that anastrozole might favorably affect HDL-C compared with exemestane. Specifically, changes of LDL-C were comparable between exemestane and anastrozole but HDL-C showed a decreasing trend in patients treated with exemestane and an increasing trend in those treated with anastrozole. Favorable changes of TC in patients treated with tamoxifen or exemestane may be attributable to the decrease in LDL-C in the former and the decrease in HDL-C and RLP-C in the latter. Based on the slight decrease in HDL-C and Apo-A1 in exemestane patients, decreased Apo-A1 synthesis due to the androgenic action of exemestane may be responsible for the untoward change of HDL-C.

Inconsistency between previous studies [13, 17] and this study may be explained by small sample sizes used in many of the former. Other possible reason for the inconsistency is that this study could precisely evaluate the drug efficacy due to homogeneity of participating patients who had satisfied the rigid lipid criteria.

Further discussion will be needed to evaluate the results of existing studies, including TEAM Japan, since some studies showed a beneficial effect of exemestane on serum lipids while others reported otherwise. Adjuvant post-Tamoxifen Exemestane versus Nothing Applied trial evaluated changes of HDL-C in early breast cancer patients treated with exemestane and reported that HDL-C had significantly decreased in exemestane patients at 24 months [18]. While similar results were reported by Lonning et al. [19], TEAM Greek lipid sub-study showed that the adverse effect of exemestane on HDL-C and LDL-C was insignificant [13]. As for an arteriosclerotic risk indicator Apo-B/Apo-A1 ratio, no significant change was seen in exemestane and anastrozole patients in TEAM Japan. However, Letrozole, Exemestane and Anastrozole Pharmacodynamics Study in healthy postmenopausal women showed that Apo-B/Apo-A1 ratio significantly increased at 24 weeks in women treated with exemestane compared with those treated with anastrozole [20].

No consensus has been reached on the effect of long-term AI therapy on serum lipids and cardiovascular diseases. According to the Intergroup Exemestane Study [5], the frequency of cardiovascular diseases was comparable between patients treated with tamoxifen and those treated with exemestane. ATAC showed comparable frequencies of cardiovascular diseases between patients treated with tamoxifen and those treated with anastrozole [8]; however, Italian Tamoxifen Anastrozole trial reported that lipid metabolism disorders had occurred more frequently in patients treated with anastrozole compared with those treated with tamoxifen [21]. According to NCIC CTG MA-17 [7], the frequency of hypercholesterolemia was comparable between patients treated with letrozole and those treated with placebo. Further evidence will be accumulated after the final efficacy and safety analyses for TEAM trial are completed. In the meantime, physicians are encouraged to develop treatment strategies based on evaluation of risk factors for lipid metabolism disorder, various laboratory tests, lifestyle counseling, and appropriate drug therapy when using AIs.

TEAM Japan used rigid lipid criteria for patient inclusion, resulting in enrollment of patients at a low risk of having serious conditions due to the protocol treatment. Although no information was obtained about patients who had received concurrent treatment for lipid metabolism disorder during the protocol treatment, such patients were few and hardly affected the analyses.

In conclusion, relatively favorable changes of lipid profiles were seen in patients treated with tamoxifen in TEAM Japan, which evaluated serum lipids in postmenopausal women with hormone-sensitive early breast cancer treated with exemestane, anastrozole or tamoxifen. The two types of AIs had no clinically significant effect on serum lipids. Tamoxifen may be a treatment choice for patients at high risk of cardiovascular events such as hyperlipidemia.

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**disclosure**

The authors have declared no conflicts of interest.

**references**


