The Effect of Exemestane, Anastrozole, and Tamoxifen on the Lipidemic Profile of Postmenopausal Early Breast Cancer Patients: Preliminary Results of National Surgical Adjuvant Study BC 04, the TEAM Japan Substudy

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Abstract

Introduction: **Long-term endocrine therapy for breast cancer may have clinical implications as drugs that potentially alter the lipid profile may increase the risk of developing cardiovascular diseases. In this study, a companion sub-protocol to the TEAM (Tamoxifen and Exemestane Adjuvant Multicenter) international trial, we compared the effect of exemestane on the lipid profile of postmenopausal women with early breast cancer in the adjuvant setting to that of anastrozole and tamoxifen.**

Patients and Methods: **In this open-label, randomized, parallel-group study, postmenopausal patients with estrogen- and/or progesterone receptor–positive early breast cancer were randomized to either adjuvant exemestane (25 mg/d; n=53), anastrozole (1 mg/d; n=51) or tamoxifen (20 mg/d; n=53). Assessments of total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), remnant-like particle cholesterol (RLP-C), lipoprotein(a), apolipoprotein A-I (apo A1), apolipoprotein B (apo B) and apolipoprotein C-II (apo C2) were performed at baseline and 3, 6, 12 months after surgery. All patients were confirmed to be within the normal range of TC and TG when they entered this study.**

Results: **In this study, TG levels consistently increased above baseline throughout the study in the tamoxifen arm and decreased after exemestane treatment, while there were no significant changes throughout the study in the anastrozole arm. TC levels decreased in both the exemestane and tamoxifen arms. There were no changes during anastrozole treatment to the contrary. LDL-cholesterol, Lp(a), apo B and apo C2 levels decreased and apo A1 levels increased significantly in the tamoxifen arms. Apo A1 and C2 levels decreased with exemestane treatment. There were, however, no significant differences among other parameters in the anastrozole arm.**

Conclusions: **In the present study, eligibility criteria for lipid parameters were strict. Tamoxifen is confirmed to have beneficial effects on lipid profiles, as many previous studies have indicated. Anastrozole appears to have few effects on all lipid parameters in postmenopausal normo-lipid patients. On the other hand, exemestane seems to have more beneficial effects on lipid profiles than anastrozole. Therefore, exemestane may have a beneficial effect for atherosclerosis. Although this study is small and the results are preliminary, these data offer additional information with regard to the safety and tolerability. Further study is mandatory.**

Introduction

- Third-generation aromatase inhibitors (AIs) are currently challenging tamoxifen as adjuvant endocrine therapy in postmenopausal women with hormone-responsive early breast cancer, both as initial therapy and as sequential therapy after treatment with tamoxifen.
- Tamoxifen has been shown to have favorable effects on lipid profiles, whereas the AIs appear to have differential effects on lipid profiles in patients with breast cancer.[1]
- National Surgical Adjuvant Study of Breast Cancer trial 04 (N-SAS BC 04) is a subprotocol of the ongoing phase III Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial and is designed to evaluate the relative impact of exemestane, tamoxifen, and anastrozole on lipid metabolism, bone mineral density (BMD), coagulation, and quality of life in postmenopausal women with hormone-responsive early breast cancer.
- Here we present interim results of the effects of these treatments on lipid metabolism.

Objective

- To evaluate the impact of adjuvant treatment with exemestane, tamoxifen, and anastrozole on lipid profiles in postmenopausal women with hormone-responsive early breast cancer

Methods

Study Design

- N-SAS BC 04 comprises a subprotocol (TEAM Japan) of a core protocol (TEAM international) of the phase III, randomized, open-label TEAM trial[2] and is being conducted at 31 sites in Japan.
- The original international TEAM protocol was designed to compare the efficacy and tolerability of 5 years of exemestane with a standard adjuvant regimen of 5 years of tamoxifen in postmenopausal women with early breast cancer.
  - The study design was subsequently amended to evaluate sequential therapy with 2.5–3 years of tamoxifen followed by exemestane for a total of 5 years compared with exemestane for 5 years.[2]
- The N-SAS BC 04 subprotocol compares 5 years of up front adjuvant therapy with exemestane or anastrozole with 2.5–3 years of tamoxifen followed by exemestane for a total of 5 years.
  - Primary end points: change from baseline in lipid parameters and BMD
  - Secondary end points: effects on measures of quality of life and coagulation

Inclusion Criteria

- Stage I–IIIA estrogen or progesterone receptor–positive breast cancer treated with surgery and meeting at least 1 of the following criteria:
  - Pathologic tumor size >3 cm
  - Node positive
  - Nuclear grade 3
  - Invasive lobular carcinoma or metaplastic carcinoma
- Eastern Cooperative Oncology Group performance status 0–1
- Postmenopausal, defined as
  - Age ≥60 years
  - Age ≥45 years with ≥1 year amenorrhea
  - Bilateral oopherectomy
- Adequate hematologic, hepatic, and biochemical function

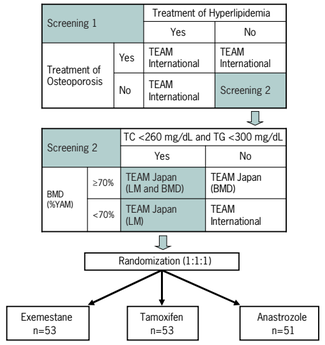
Exclusion Criteria

- History of invasive carcinoma within 5 years, deep vein thrombosis, ischemic heart disease, or congestive heart failure
- Current treatment for cerebral infarction, myocardial infarction, or valvular disease
- Bilateral breast cancer
- Hormone replacement therapy within 4 weeks of enrollment

Treatment Regimen

- Patients who met TEAM trial eligibility criteria were further stratified by baseline measures of lipid metabolism and BMD **(Figure 1)**.
  - Patients with elevated lipid levels and/or decreased BMD, or who were receiving treatment for hyperlipidemia or osteoporosis, were enrolled in the international TEAM trial.

Figure 1. Patient Enrollment and Distribution



BMD=bone mineral density; LM=lipid metabolism; TEAM=Tamoxifen Exemestane Adjuvant Multinational trial; TC=total cholesterol; TG=triglycerides; YAM=young adult mean.

- TEAM Japan eligible patients were randomly assigned to 1 of 3 treatment regimens.
  - Exemestane 25 mg/d PO
  - Tamoxifen 20 mg/d PO
  - Anastrozole 1 mg/d PO
- Patients were stratified according to chemotherapy, nodal metastases, radiation therapy, and institute.

Assessments

- Lipid parameters listed in **Table 1** were assessed at study entry (baseline) and after 3, 6, and 12 months of treatment.

Statistical Analyses

- Lipid measurements were analyzed by repeated-measures Analysis of Variance (ANOVA) and generalized estimating equations with the baseline value as a covariate.
- *P* values were calculated without adjustment for multiple comparisons.

Table 1. Lipid Parameters Assessed

Total cholesterol
Triglycerides
Low-density lipoprotein cholesterol
High-density lipoprotein cholesterol
Remnant-like particle cholesterol[3]
Lipoprotein (a)
Apolipoprotein A-I
Apolipoprotein B
Apolipoprotein C-II
Apolipoprotein B/ apolipoprotein A-I ratio

Results

Patients

- A total of 157 patients were enrolled in this lipid substudy **(Figure 1)**.
- Baseline characteristics were similar across treatment groups **(Table 2)**.
- Mean (standard deviation) duration of follow-up was 1.30 (0.68) years in the anastrozole group and 1.34 (0.66) years and 1.37 (0.59) years in the exemestane and tamoxifen groups, respectively.

Table 2. Demographic Characteristics

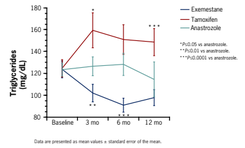
	Exemestane (n=53)	Tamoxifen (n=53)	Anastrozole (n=51)	Total (N=157)
Age, y				
Mean (SD)	63.2 (7.1)	63.1 (8.1)	63.0 (8.0)	63.1 (7.7)
Median (range)	64 (51–83)	61 (50–88)	63 (49–81)	63 (49–88)
Clinical stage, n (%)				
n	53	52	51	156
I	15 (28.3)	18 (34.6)	16 (31.4)	49 (31.4)
IIA	30 (56.6)	24 (46.2)	27 (52.9)	81 (51.9)
IIB	6 (11.3)	7 (13.5)	7 (13.7)	20 (12.8)
IIIA	2 (3.8)	3 (5.8)	1 (2.0)	6 (3.8)
Type of surgery, n (%)				
n	53	52	51	156
Breast conserving	39 (73.6)	34 (65.4)	36 (70.6)	109 (69.9)
Mastectomy	14 (26.4)	18 (34.6)	15 (29.4)	47 (30.1)
Tumor size, cm				
n	53	51	51	155
Mean (SD)	2.23 (1.26)	2.52 (1.96)	2.37 (2.22)	2.37 (1.84)
ER status, n (%)				
Positive	51 (96.2)	51 (96.2)	48 (94.1)	150 (95.5)
Negative	2 (3.8)	2 (3.8)	3 (5.9)	7 (4.5)
PR status, n (%)				
Positive	36 (67.9)	42 (79.2)	42 (82.4)	120 (76.4)
Negative	17 (32.1)	11 (20.8)	9 (17.6)	37 (23.6)
Chemotherapy, n (%)				
No	34 (64.2)	33 (62.3)	32 (62.7)	99 (63.1)
Yes	19 (35.8)	20 (37.7)	19 (37.3)	58 (36.9)
Lymph node metastases, n (%)				
No	20 (37.7)	19 (35.8)	18 (35.3)	57 (36.3)
Yes	33 (62.3)	34 (64.2)	33 (64.7)	100 (63.7)
Radiation therapy, n (%)				
No	19 (35.8)	20 (37.7)	18 (35.3)	57 (36.3)
Yes	34 (64.2)	33 (62.3)	33 (64.7)	100 (63.7)

ER=estrogen receptor; PR=progesterone receptor; SD=standard deviation.

Changes in Lipid Metabolism

- Only a few of the lipid parameters assessed were significantly altered by anastrozole treatment compared with baseline measurements.
- Mean triglyceride concentrations increased during treatment with tamoxifen and decreased during treatment with exemestane **(Figure 2)**.
  - Mean triglyceride concentrations were significantly lower in the exemestane group compared with the tamoxifen group at all time points (*P*≤0.0001) and compared with the anastrozole group at 3 months (*P*≤0.01) and 6 months (*P*≤0.0001).

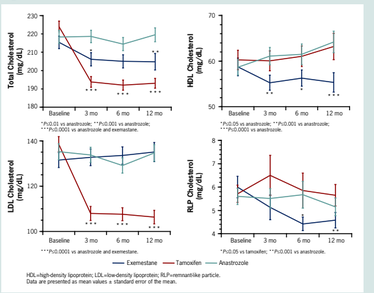
Figure 2. Serum Triglyceride Concentrations



Data are presented as mean values ± standard error of the mean.

- Mean total cholesterol concentrations decreased during treatment with tamoxifen, and concentrations were significantly lower than in the anastrozole and exemestane groups at all time points (*P*≤0.0001) **(Figure 3)**.
  - In the exemestane group, mean total cholesterol levels were significantly lower compared with the anastrozole group at 3 months (*P*≤0.01) and 12 months (*P*≤0.001).
  - Treatment with exemestane was associated with lower concentrations of high-density lipoprotein cholesterol compared with anastrozole at all time points (*P*≤0.05) and with lower levels of remnant-like particle (RLP) cholesterol compared with anastrozole at 6 months (*P*≤0.01).
  - Tamoxifen treatment was associated with significantly lower concentrations of low-density lipoprotein cholesterol at all time points (*P*≤0.0001) compared with both anastrozole and exemestane.

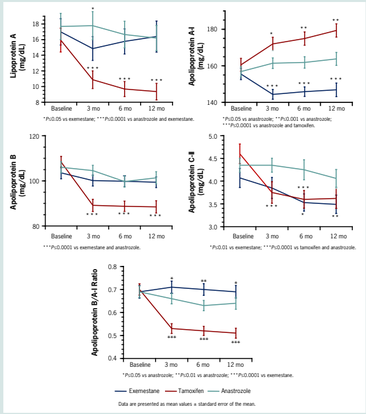
Figure 3. Serum Cholesterol Concentrations



HDL=high-density lipoprotein; LDL=low-density lipoprotein; RLP=remnant-like particle.
Data are presented as mean values ± standard error of the mean.

- Tamoxifen treatment was associated with reductions in serum concentrations of apolipoprotein A, apolipoprotein B, apolipoprotein C-II, and a reduced apolipoprotein B/A-I ratio **(Figure 4)**.
  - Exemestane treatment was associated with a decrease in levels of apolipoprotein A-I and C-II and a decreased apolipoprotein B/A-I ratio.

Figure 4. Lipoprotein Parameters



Data are presented as mean values ± standard error of the mean.

Conclusions

- **The beneficial effects of tamoxifen on lipid metabolism seen in previous studies have been confirmed in this study.**
- **The effects of third-generation AIs on lipid profiles in postmenopausal patients with normal lipids at baseline are variable.**
- **Whereas anastrozole appears to have minimal effects on lipids, exemestane treatment was associated with a decrease in serum concentrations of triglycerides, total cholesterol, RLP-cholesterol, apolipoproteins A-I and CII and a decrease in the apolipoprotein B/A-I ratio.**
- **Continued evaluation of the population in this substudy and further investigation into the relative effects of AIs on lipid metabolism in patients with breast cancer are warranted.**

References

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