Health-related quality of life and psychological distress in Japanese patients with breast cancer treated with tamoxifen, exemestane or anastrozole for adjuvant therapy: A phase III randomized study of National Surgical Adjuvant Study of Breast Cancer (N-SAS BC) 04

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Introduction

•Third-generation aromatase inhibitors (AIs) are challenging tamoxifen as adjuvant endocrine therapy in postmenopausal women with hormone-responsive early breast cancer, both as initial therapy and as sequential therapy following treatment with tamoxifen.
•Previous studies have indicated that adjuvant AIs and tamoxifen have similar effects on overall health-related quality of life (HRQOL) in patients with breast cancer[1,2].
•The ongoing phase III Tamoxifen (TAM) and Exemestane (EXE) Adjuvant Multicenter (TEAM) trial compares adjuvant 5 years of EXE with 2.5 to 3 years of TAM followed by EXE for a total of 5 years.
•National Surgical Adjuvant Study of Breast Cancer (N-SAS BC) 04 trial is a subprotocol of the TEAM trial and designed to evaluate the relative impact of three drugs of EXE, anastrozole (ANA) and TAM, on lipid metabolism, bone mineral density (BMD), coagulation, and HRQOL in postmenopausal women with hormone-responsive early breast cancer.
•Final HRQOL results are presented.

Objective

•To evaluate the impact of adjuvant treatment with EXE, TAM, and ANA on HRQOL in postmenopausal women with hormone-responsive early breast cancer.

Methods

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

Inclusion Criteria
•Stage I-IIIA estrogen receptor-positive and/or progesterone receptor-positive breast cancer treated with surgery and meeting at least 1 of the following criteria:
Pathological tumor size > 3cm, 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, or 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 the eligibility criteria were stratified by baseline measures of lipid metabolism and BMD **(Figure 1).**
Patients who were receiving treatment for hyperlipidemia or osteoporosis, or who exhibited elevated lipid levels and/or decreased BMD, were enrolled in the international TEAM trial and randomly assigned to EXE or TAM **(Figure 1).**
• N-SAS BC 04 eligible patients were randomly assigned to 1 of 3 treatment regimens **(Figure 1).**
EXE 25mg/d PO, TAM 20mg/d PO, ANA 1mg/d PO
• Stratification was according to chemotherapy, nodal metastasis, radiation therapy, and institute.

Assessment
• HRQOL was monitored using the Functional Assessment of Cancer Therapy-General (FACT-G) scale plus following subscales:
Functional Assessment of Cancer Therapy-Breast (FACT-B): FACT-G + breast cancer subscale (BCS)
Functional Assessment of Cancer Therapy-Endocrine Symptoms (FACT-ES): FACT-G + endocrine symptom subscale (ESS)
Higher scores correspond to improved HRQOL
• The 20-items Center for Epidemiologic Studies Depression Scale (CES-D)[4]
Lower scores indicate fewer depressive symptoms.
• Patients were asked to complete all HRQOL scales at baseline and at 3 months and 12 months after the start of treatment.

Statistical analyses
• Baseline characteristics: Descriptive statistics were calculated by the groups and ANOVA or chi-square tests were performed to determine imbalance among the groups.
• HRQOL scores were compared between groups using the mixed effect model with the baseline value as a covariant.

Results

Patients
•A total of 169 patients were screened and enrolled in N-SAS BC 04 **(Figure1)**.
•Baseline characteristics were similar across 3 treatment groups **(Table1)**.
•HRQOL questionnaire response rates – measured as the percentage of patients who completed the required assessment questionnaires at each time point – were consistently high (90%-98%) in each group throughout the study period **(Table2)**.

HRQOL Outcomes
•There were no significant between-group differences in baseline scores for any of the scales used to assess HRQOL **(Table3)**.
•The scores of FACT-G, FACT-B, FACT-ES and BCS seemed to increase at 3 and 12 months from baseline in the patients of the TAM group, whereas, the scores of FACT-G, FACT-B and FACT-ES did not increase in the patients of the EXE and ANA groups. The total scores of FACT-B were statistically different among the treatment groups over the period of the study (repeated measures ANOVA: P=0.045) **(Figure 2-5)**.
•The score of BCS seemed to increase at 3 and 12 months from baseline in patients in the EXE or ANA group **(Figure 4)**.
•The scores of ESS and CES-D did not differ over the time period from baseline to 12 months and did not show any between-group differences in patients in the three treatment groups **(Figure 6, 7)**.

Figure 1. Patients Enrollment and Distribution

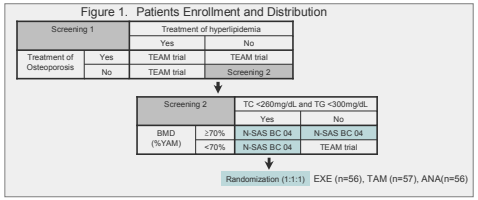

Figure 2. FACT-G

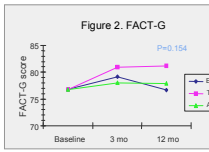

Figure 3. FACT-B

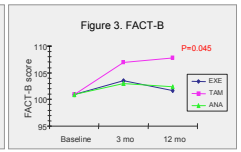

Figure 4. Breast Cancer Subscale (BCS)

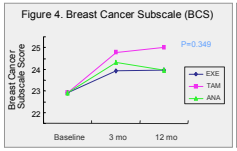

Figure 5. FACT-ES

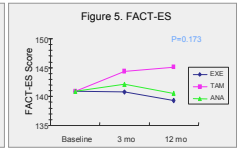

Figure 6. Endocrine Symptoms Subscale (ESS)

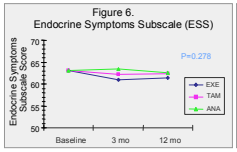

Figure 7. CES-D

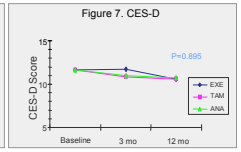

Table1. Baseline Characteristics

		EXE (n=56)	TAM (n=57)	ANA (n=56)	P Value
Age,y	Mean (SD)	63.3(7.9)	62.9(8.0)	62.9(7.9)	0.9421
Disease stage, n(%)	I	19(34.0)	20(35.1)	17(30.4)	
	IIA	31(55.4)	29(45.6)	30(53.6)	
	IIB	7(12.5)	8(14.0)	8(14.3)	0.7252
	IIIA	3(5.4)	3(5.3)	1(1.8)	
	Unknown	0(0.0)	0(0.0)	0(0.0)	
Pathologic tumor size, cm	Mean (SD)	2.30(1.30)	2.52(1.88)	2.39(2.14)	0.8159
	Unknown	0	0	1	
Number of metastatic nodes, n(%)	0	9(16.1)	6(10.5)	6(10.7)	
	1-3	29(46.4)	30(52.6)	25(44.6)	
	4-9	4(7.1)	8(14.0)	8(14.3)	0.4874
	≥10	3(5.4)	0(0.0)	2(3.6)	
	Not dissected	14(25.0)	13(22.8)	15(26.8)	
ER status, n(%)	Positive	34(66.4)	35(66.0)	33(64.6)	0.8557
	Negative	2(3.8)	2(3.8)	3(5.4)	
PR status, n(%)	Positive	38(67.9)	40(80.7)	44(78.6)	0.2346
	Negative	18(32.1)	11(19.3)	12(21.4)	
Nuclear grade, n(%)	1	6(10.7)	5(8.8)	7(12.5)	0.1868
	2	27(48.2)	40(70.2)	27(48.2)	
	3	20(35.7)	11(19.3)	17(30.4)	
	Unknown	3(5.4)	1(1.8)	5(8.9)	
Mitotic index, n(%)	1	19(33.9)	21(36.8)	20(35.7)	0.8051
	2	12(21.4)	8(14.0)	11(19.6)	
	3	21(37.5)	25(43.9)	19(33.9)	
	Unknown	4(7.1)	3(5.3)	6(10.7)	
Adjuvant chemotherapy	No	35(62.5)	34(59.6)	37(66.1)	0.5372
	Yes	21(37.5)	23(40.4)	21(37.5)	
Radiation therapy	No	23(35.7)	27(36.8)	21(37.5)	0.9835
	Yes	36(64.3)	36(63.2)	35(62.5)	

Table 2. QOL Questionnaire Response Rate

	Responders at Each Time Point, n/N (%)		
	Baseline	3 Months	1 Year
EXE	52/56 (92.9)	51/54(94.4)	43/45(95.6)
TAM	56/57 (98.2)	52/55 (94.5)	46/51 (90.2)
ANA	54/56 (96.4)	54/56 (96.4)	45/49 (91.8)

Table 3. QOL Assessment at Baseline

	Treatment Group		
Scale, MEAN±SD	EXE	TAM	ANA
FACT-G	77.1±16.2	75.4±18.0	77.9±13.4
Physical well-being	22.8±4.5	22.1±5.1	21.8±4.6
Social well-being	19.2±6.9	20.4±6.2	20.5±5.5
Emotional well-being	17.3±4.6	16.1±5.6	16.8±4.1
Functional well-being	19.6±5.9	18.6±6.5	19.2±4.5
FACT-B	102.9±15.3	99.4±21.1	100.4±16.5
Breast cancer subscale	23.7±4.2	22.6±5.8	22.5±5.3
FACT-ES	143.3±17.5	139.5±21.5	140.3±19.1
Endocrine symptom subscale	64.4±6.9	62.6±9.3	62.2±8.4
CES-D	10.2±7.5	12.4±7.3	12.2±6.5

Conclusions

•The HRQOL assessed by FACT-B was better in Japanese postmenopausal women with breast cancer treated with adjuvant TAM than AIs (EXE or ANA).
•The psychological distress was similar in the 3 treatment groups.

Discussion

•Although the HRQOL has been reported to be similar between patients treated with adjuvant TAM and AIs[1,2], the better HRQOL was shown in Japanese patients treated with adjuvant TAM than EXE or ANA in this study. Similarly, the HRQOL was better in Japanese women with breast cancer treated with continued TAM than ANA after 1-4 years of TAM in NSAS BC 03 study[5].
•From these studies, we hypothesize that the HRQOL may be better by adjuvant TAM than EXE or ANA in Japanese women with breast cancer.
•Some menopausal symptoms or adverse events were reported to be different between ethnic minority women and Caucasians with breast cancer treated with letrozole[6]. The difference of the results in HRQOL between the previously reported randomized clinical trials and our trial might be caused by the ethnic difference.
•We need to evaluate the effects of these agents on individual symptoms, and how they may affect the HRQOL. This will help to confirm our hypothesis.

References

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