Comprehensive Support Project

Health-Related Quality Of Life and Psychological Distress of Breast Cancer Patients After Surgery During Phase III Randomized Trial Comparing Tamoxifen, Exemestane, and Anastrozole: N-SAS BC 04

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Abstract

Background: **Large randomized trials have shown the superior efficacy of aromatase inhibitors (AIs) to tamoxifen (TAM) in the adjuvant setting for patients (pts) with breast cancer; however, limited data have been reported regarding health-related quality of life (HRQOL) outcomes between pts treated with AIs and TAM.**

Patients and Methods: **A randomized, multicenter study; the National Surgical Adjuvant Study of Breast Cancer (N-SAS BC) 04 was designed as a subprotocol study of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial, which is comparing 5 years of exemestane (EXE) with 5 years of TAM. The N-SAS BC 04 trial compared 5 years of EXE, anastrozole (ANA), and TAM. Primary end points of the NSAS BC 04 trial were lipid metabolism (LM) and bone mineral density (BMD). Secondary end points were coagulation and HRQOL. Eligible pts were postmenopausal women with stage I to IIIA hormone receptor–positive breast cancer treated surgically with pathological tumor size of 3 cm or larger, pathologically positive nodes, or nuclear grade of 3. Eligible pts with normal LM and BMD at the entry were randomly assigned to one of the 3 treatment arms, while pts with abnormal lipid levels and/or BMD at the entry were randomized to one of the 2 arms of TEAM trial. Pts were asked to answer the patient-based instruments to assess HRQOL (FACT-B and FACT-ES [endocrine symptom scale]) and psychological distress (CES-D) at baseline, 3 months, and 1 year after the randomization. Statistical significance was analyzed by ANOVA and the mixed effect model.**

Results: **At baseline the response rate was 94%, and 232 pts (89 in EXE group, 54 in ANA, and 89 in TAM) answered the questionnaires. FACT-G, -B, -ES and CES-D scores did not statistically differ over the 1-year period among the 3 arms. Moreover, the scores of all the FACT domains were similar among the groups at any time point. On the other hand, the mean scores of all the pts became significantly better over the period in FACT-G total, FACT-B total, and breast cancer subscale of FACT-B ($P \leq 0.01$ for all), whereas the mean scores of all the pts became significantly worse in the endocrine subscale of FACT-ES ($P=0.04$) but did not change in CES-D after the randomization.**

Conclusions: **The HRQOL was not significantly different among the 3 treatment groups. However, all agents had similar negative effects on endocrine symptoms assessed by FACT-ES.**

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 (QOL) 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 QOL in postmenopausal women with hormone-responsive early breast cancer.
- Interim QOL results are presented.

Objective

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

Methods

Study Design

- N-SAS BC 04 comprises a subprotocol (TEAM Japan) and 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 up front adjuvant therapy with exemestane or anastrozole for 5 years, vs 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: change from baseline in measures of QOL 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 >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 stratified by baseline measures of lipid metabolism and BMD **(Figure 1)**.
  - Patients who exhibited elevated lipid levels and/or decreased BMD, or who were receiving treatment for hyperlipidemia or osteoporosis, were enrolled in TEAM international and randomly assigned to exemestane or tamoxifen **(Figure 1)**.
- TEAM Japan eligible patients were randomly assigned to 1 of 3 treatment regimens **(Figure 1)**.
  - Exemestane 25 mg/d PO
  - Tamoxifen 20 mg/d PO
  - Anastrozole 1 mg/d PO
- Patients were further stratified according to chemotherapy, nodal metastasis, radiation therapy, and institute.

Assessments

- Health-related QOL was monitored using the Functional Assessment of Cancer Therapy–General (FACT-G) scale plus the following secondary scales:
  - 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 QOL
- The 20-item Center for Epidemiologic Studies Depression Scale (CES-D)[3]; lower scores indicate fewer depressive symptoms.
- Patients were asked to complete all QOL scales at baseline and at 3 months and 12 months after the start of treatment.

Statistical Analyses

- Baseline characteristics of each group were evaluated using descriptive statistics. Analysis of variance (ANOVA) or chi-square tests were performed to determine imbalance among the groups.
- QOL scores were compared between groups using the repeated-measures ANOVA with the baseline value as a covariant.

Results

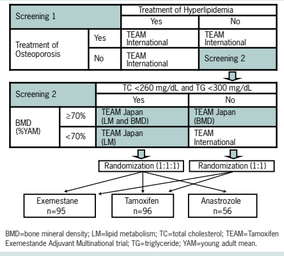
Patients

- A total of 247 patients were screened and enrolled in N-SAS BC 04 **(Figure 1)**.
- Baseline characteristics were similar across treatment groups **(Table 1)**.
- Mean (standard deviation) duration of follow-up was 1.28 (0.72) years in the anastrozole group, and 1.51 (0.64) years and 1.49 (0.59) years in the exemestane and tamoxifen groups, respectively.
- QOL questionaire response rates—measured as the percentage of patients who completed the required assessment questionnaires at each time point—were consistently high (89%–97%) throughout the study period **(Table 2)**.

Quality-of-Life Outcomes

- There were no significant between-group differences in baseline scores for any of the scales used to assess QOL **(Table 3)**.
- Mean scores on the FACT-G and FACT-B increased significantly from baseline for all of the 3 treatment groups combined ($P \leq 0.01$) **(Figures 2** and **3)**.
  - Scores on the FACT-G and FACT-B appeared to decrease in the anastrozole group between 3 months and 12 months, and this decrease from baseline to 12 months was statistically significant compared with the tamoxifen group ($P=0.04$ for FACT-G and FACT-B).
- All 3 treatment groups showed improvement in the FACT-B breast subscale at both 3 and 12 months ($P<0.01$) **(Figure 4)**.
- In contrast, scores on the FACT-ES endocrine subscale **(Figure 5)** had declined in all 3 groups at 12 months ($P=0.04$), indicating an increase in (or worsening of) endocrine symptoms.
- Scores on the FACT-ES **(Figure 6)** and CES-D **(Figure 7)** did not differ over the time period from baseline to 12 months ($P=0.64$ and $P=0.32$, respectively) for all groups combined.
- There were no between-group differences for any outcome at 3 or 12 months ($P>0.05$ for all scales at both time points).

Figure 1. Patient Enrollment and Distribution



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

Table 1. Baseline Characteristics

Characteristic	Exemestane (n=95)	Tamoxifen (n=96)	Anastrozole (n=56)	*P* Value*
	Treatment Group			
Age, y				
Mean (SD)	64.1 (7.2)	64.2 (8.4)	62.9 (7.9)	0.60
Disease stage, n (%)				
I	23 (24.2)	37 (38.9)	17 (30.4)	
IIA	46 (48.4)	40 (42.1)	30 (53.6)	
IIB	20 (21.1)	14 (14.7)	8 (14.3)	0.28
IIIA	6 (6.3)	4 (4.2)	1 (1.8)	
Unknown	0 (0.0)	1 (1.0)	0 (0.0)	
Pathologic tumor size, cm				
Mean (SD)	2.49 (1.31)	2.33 (1.61)	2.39 (2.14)	0.79
Unknown	0 (0.0)	2 (2.1)	1 (1.8)	
Number of metastatic nodes, n (%)				
0	13 (17.3)	14 (17.3)	6 (14.6)	
1–3	47 (62.7)	51 (63.0)	25 (61.0)	
4–9	11 (14.7)	12 (14.8)	8 (19.5)	0.10
≥10	4 (5.3)	4 (4.9)	2 (4.9)	
Not dissected	20 (21.1)	15 (15.6)	15 (26.8)	
ER status, n (%)				
Positive	93 (97.9)	94 (97.9)	53 (94.6)	0.43
Negative	2 (2.1)	2 (2.1)	3 (5.4)	
PR status, n (%)				
Positive	65 (68.4)	73 (76.0)	44 (78.6)	0.31
Negative	30 (31.6)	23 (24.0)	12 (21.4)	
Nuclear grade, n (%)				
1	9 (10.2)	8 (8.6)	7 (13.7)	
2	53 (60.2)	58 (62.4)	27 (52.9)	0.82
3	26 (29.5)	27 (29.0)	17 (33.3)	
Unknown	7 (7.4)	3 (3.1)	5 (8.9)	
Mitotic index, n (%)				
1	34 (40.0)	36 (40.0)	20 (40.0)	
2	21 (24.7)	14 (15.6)	11 (22.0)	0.59
3	30 (35.3)	40 (44.4)	19 (38.0)	
Unknown	10 (10.5)	6 (6.3)	6 (10.7)	
Type of surgery, n (%)				
Breast conserving	60 (63.2)	61 (64.2)	38 (67.9)	
Mastectomy	35 (36.8)	34 (35.8)	18 (32.1)	0.84
Unknown	0 (0.0)	1 (1.0)	0 (0.0)	
Adjuvant chemotherapy, n (%)				
No	61 (64.2)	61 (63.5)	35 (62.5)	0.98
Yes	34 (35.8)	35 (36.5)	21 (37.5)	
Radiation therapy, n (%)				
No	37 (38.9)	36 (37.5)	21 (37.5)	0.97
Yes	58 (61.1)	60 (62.5)	35 (62.5)	

ER=estrogen receptor; PR=progesterone receptor; SD=standard deviation.
*Difference between treatment groups.

Table 2. QOL Questionnaire Response Rates

Treatment Group	Responders at Each Time Point, n/N (%)		
	Baseline	3 Months	12 Months
Exemestane	89/95 (93.7)	73/78 (93.6)	52/54 (96.3)
Tamoxifen	89/96 (92.7)	77/83 (92.8)	48/54 (88.9)
Anastrozole	54/56 (96.4)	38/39 (97.4)	14/15 (93.3)

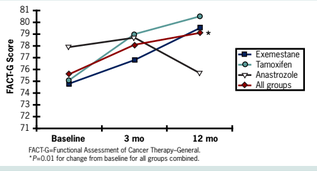
N=number of patients in treatment arm at specified time point; n=number of responders; QOL=quality of life.

Table 3. QOL Assessment Scores at Baseline

Scale, Mean ± SD	Exemestane (n=89)	Tamoxifen (n=89)	Anastrozole (n=54)
	Treatment Group		
FACT-G total	74.8±17.2	75.1±18.0	77.9±13.4
FACT-G subscales			
Physical well-being	22.2±4.7	22.3±5.1	21.8±4.6
Social well-being	19.5±6.9	20.4±5.9	20.5±5.5
Emotional well-being	16.6±4.5	15.9±5.6	16.8±4.1
Functional well-being	18.8±6.0	18.2±6.5	19.2±4.5
FACT-B total	97.8±17.6	97.8±20.5	99.2±16.0
FACT-B, breast subscale	21.3±5.2	21.4±5.5	21.3±4.7
FACT-ES total	141.1±18.4	140.3±21.3	140.3±19.1
FACT-ES endocrine subscale	63.9±7.6	63.6±8.4	62.2±8.4
CES-D	10.9±7.4	12.8±8.9	12.2±6.5

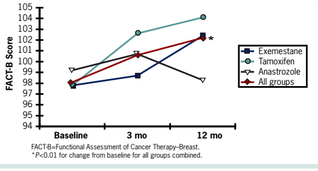
CES-D=Center for Epidemiologic Studies Depression Scale; FACT-B=Functional Assessment of Cancer Therapy–Breast; FACT-ES=Functional Assessment of Cancer Therapy–Endocrine Symptoms; FACT-G=Functional Assessment of Cancer Therapy–General; QOL=quality of life; SD=standard deviation.

Figure 2. FACT-G Total Scores



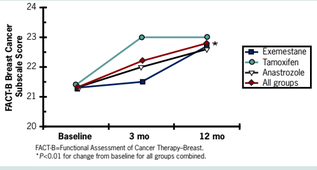
FACT-G=Functional Assessment of Cancer Therapy–General.
*$P<0.01$ for change from baseline for all groups combined.

Figure 3. FACT-B Total Scores



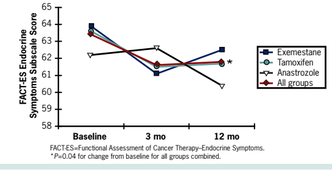
FACT-B=Functional Assessment of Cancer Therapy–Breast.
*$P<0.01$ for change from baseline for all groups combined.

Figure 4. FACT-B Breast Cancer Subscale Scores



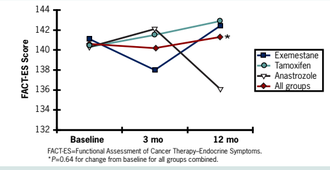
FACT-B=Functional Assessment of Cancer Therapy–Breast.
*$P<0.01$ for change from baseline for all groups combined.

Figure 5. FACT-ES Endocrine Symptoms Subscale Scores



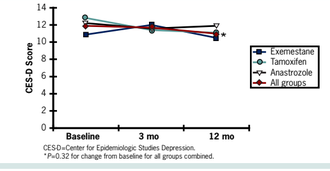
FACT-ES=Functional Assessment of Cancer Therapy–Endocrine Symptoms.
*$P=0.04$ for change from baseline for all groups combined.

Figure 6. FACT-ES Scores



FACT-ES=Functional Assessment of Cancer Therapy–Endocrine Symptoms.
*$P=0.64$ for change from baseline for all groups combined.

Figure 7. Change From Baseline in CES-D Scores



CES-D=Center for Epidemiologic Studies Depression.
*$P=0.32$ for change from baseline for all groups combined.

Conclusions

- **AIs and tamoxifen have similar effects on general measures of QOL and psychological distress in postmenopausal patients with hormone-responsive early breast cancer.**
- **There was a slight deterioration in overall endocrine symptoms in all treatment groups at 12 months; further studies are required to evaluate the effects of these agents on individual endocrine symptoms.**

References

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