American Society of Clinical Oncology
May 31 – June 4, 2013
6588
Comprehensive Support Project

Analysis of health-related quality of life during neoadjuvant endocrine therapy with letrozole in postmenopausal breast cancer patients: N-SAS BC06 trial

Shoichiro Ohtani[1], Naruto Taira[2], Kiyohiro Kihara[3], Yoshie Hasegawa[4], Takehiko Sakai[5], Takuji Iwase[5], Norikazu Masuda[6], Tomomi Fujisawa[7], Yasuhiro Yanagita[7], Shozo Ohsumi[8], Kenji Higaki[1], Takuhiro Yamaguchi[9], Hiroji Iwata[10]

[1] Division of Breast Surgery, Hiroshima City Hospital, Hiroshima, Japan; [2] Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan; [3] Department of Biostatistics, The University of Tokyo, Tokyo, Japan; [4]Department of Breast Surgery, Hirosaki Municipal Hospital, Hirosaki, Japan; [5]Breast Oncology Center, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; [6]Department of Surgery, Breast Oncology, NHO Osaka National Hospital, Osaka, Japan; [7]Department of Breast Oncology, Gunma Prefectural Cancer Center, Ohta, Japan; [8]Department of Breast Oncology, NHO Shikoku Cancer Center, Matusyama, Japan; [9]Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Japan; [10]Department of Breast Oncology, Aichi Cancer Center, Nagoya, Japan

Background

In most postmenopausal breast cancer patients, aromatase inhibitors (AIs) are commonly used in the adjuvant setting rather than tamoxifen, based on the findings of randomized clinical trials (RCTs)[1]. Health-related quality of life (HRQoL) is an important consideration in the long-term use of an anticancer therapy, and the impact of AIs on HRQoL has been evaluated in these RCTs[2-4]. In general, AIs and tamoxifen have a similar impacts on HRQoL, but there are differences between the treatment groups in the patient-reported side effects, i.e., vaginal dryness, painful intercourse, diminished libido, and insomnia occur significantly more often with AIs than tamoxifen. At present, there are few published reports on the HRQoL effects or psychological aspects associated with the neoadjuvant administration of AIs.

Methods

Study Design

- The National Surgical Adjuvant Study of Breast Cancer (N-SAS BC) 06 is a multicenter, phase III RCT in postmenopausal patients with hormone-sensitive primary breast cancer, with two-stage (preoperative and postoperative) enrollment, and intervention. The primary aim of this study was to evaluate the necessity of adjuvant chemotherapy in the treatment of postmenopausal breast cancer patients with clinical T1c-T2N0M0, ER-positive and HER2-negative tumors that responded to neoadjuvant treatment with Letrozole (LET). Neoadjuvant LET was administered for 24-28 weeks before surgery, and responders (CR, PR or SD) were then randomized into two arms receiving either chemotherapy plus LET for 4.5-5 years, or LET alone for 4.5-5 years after surgery.
- The primary endpoint was disease-free survival, and the secondary endpoints included adverse events, HRQoL and health economic evaluation. The target sample size was 850 patients of whom the first 500 enrolled patients were included in the HRQoL sub-protocol evaluation. This report presents the planned analysis of HRQoL during the 24-28 weeks of neoadjuvant LET (UMIN000001090).

HRQoL and psychological assessment during neoadjuvant LET

- Subjects were assessed at the time of enrollment, i.e., baseline, and at 4 and 16 weeks after starting neoadjuvant LET, using FACT-G (General), B (Breast), ES (Endocrine Symptoms), EQ-5D and HADS (Hospital Anxiety and Depression Scale).

Results

- A total of 503 patients were recruited for the HRQoL sub-protocol, 5 patients did not meet the inclusion criteria, and ultimately data from 498 patients were used in this analysis. The baseline characteristics are presented in **Table 1**. The results of clinical efficacy with neoadjuvant LET were as follows: CR: 2%; PR: 44.3%; SD: 48%; and PD: 5.7%. The questionnaire response rates at enrollment and at 4 and 16 weeks were 94%, 90% and 86%, respectively, which were quite high.
- The mean scores at enrollment and at 4 and 16 weeks after starting neoadjuvant LET are presented in **Table 2**. There were no significant changes in the FACT-G, FACT-B, Breast-trial outcome index (TOI), or FACT-ES over time, while the Social-Family Well-Being scale score and the ES subscale, decreased significantly (i.e., worse Social-Family Well-Being and ES). In the ES analysis by item, symptoms such as hot flashes showed a greater decrease (data not shown). The EQ-5D score increased significantly at 4 weeks after starting neoadjuvant LET (better HRQoL). HADS scores decreased significantly (improved anxiety and depression), and Emotional Well-Being scale scores increased significantly (better Emotional Well-Being) at 4 and 16 weeks after starting neoadjuvant LET (**Figure 1**).
- Multivariate regression model analysis using a generalized estimating equation showed that age at enrollment, baseline B-TOI score and baseline HADS score were independent predictors of B-TOI at 4 and 16 weeks after starting neoadjuvant LET. B-TOI scores at 4 and 16 weeks after starting neoadjuvant LET correlated positively with the baseline B-TOI score, and negatively with the age and the HADS score at enrollment, respectively (**Table 3**).

Table 1. Baseline characteristics

Age (years)		**Histologic type**	
Mean (range)	63 (46-75)	Ductal	455 (91%)
Body mass index		Lobular	18 (4%)
Mean (range)	23.9 (14.3-37.7)	Other	22 (4%)
Tumor size (cm)		Unknown	3 (<1%)
>1.0, ≤2.0	174 (35%)	**Planned type of surgery**	
>2.0, ≤5.0	321 (65%)	Breast conserving surgery	361 (73%)
Unknown	3 (<1%)	Mastectomy	134 (27%)
Nodal status		Unknown	3 (<1%)
Negative	495 (99%)	**ECOG performance status**	
Positive	0	0	494 (99%)
Unknown	3 (<1%)	1	1 (<1%)
		Unknown	3 (<1%)

Data represent n (%) unless otherwise stated.
ECOG=Eastern Cooperative Oncology Group.

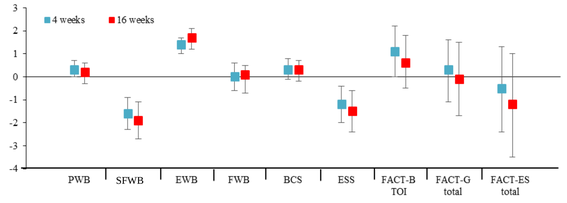
Table 2. HRQoL, anxiety and depression scores at the evaluation points

	Baseline	After 4 weeks of neoadjuvant LET		After 16 weeks of neoadjuvant LET	
	Mean (SD)	Mean (SD)	p value*	Mean (SD)	p value*
FACT-G total score	82.9 (16.5)	83.4 (18.0)	0.719	82.7 (17.6)	0.089
PWB	24.6 (3.8)	25.0 (4.1)	0.075	24.8 (3.9)	0.474
SFWB	22.2 (8.4)	20.7 (8.4)	<.0001	20.2 (8.5)	<.0001
EWB	16.2 (5.0)	17.6 (4.8)	<.0001	17.9 (4.8)	<.0001
FWB	20.1 (6.2)	20.2 (6.4)	0.936	20.0 (6.7)	0.662
FACT-B TOI	68.3 (11.9)	69.5 (12.4)	0.053	68.9 (12.2)	0.293
Breast cancer subscale	24.0 (4.8)	24.4 (5.0)	0.124	24.2 (4.7)	0.284
FACT-ES total score	143.6 (21.5)	143.5 (24.3)	0.567	142.3 (23.0)	0.268
ESS	61.2 (7.8)	60.1 (10.0)	0.002	59.7 (9.6)	0.001
EQ-5D	0.90 (0.13)	0.92 (0.12)	0.046	0.91 (0.13)	0.228
HADS Total score	10.4 (6.0)	8.9 (5.9)	<.0001	8.8 (6.0)	<.0001
Anxiety score	6.1 (3.4)	5.1 (3.4)	<.0001	5.0 (3.4)	<.0001
Depression score	4.3 (3.2)	3.9 (3.1)	<.001	3.9 (3.2)	0.004

* paired t-test, compared with the baseline score

SD= Standard deviation. FACT-G=Functional Assessment of Cancer Treatment- General.
PWB= Physical Well-Being. SWB=Social-Family Well-Being. EWB=Emotional Well-Being.
FWB=Functional Well-Being. FACT-B TOI= FACT- Breast Trial Outcome Index.
BCS= Breast cancer subscale. FACT-ES= FACT-Endocrine Symptom(s).
ESS= Endocrine symptom subscale. HADS= Hospital anxiety and depression scale.

Figure 1. Mean score change value



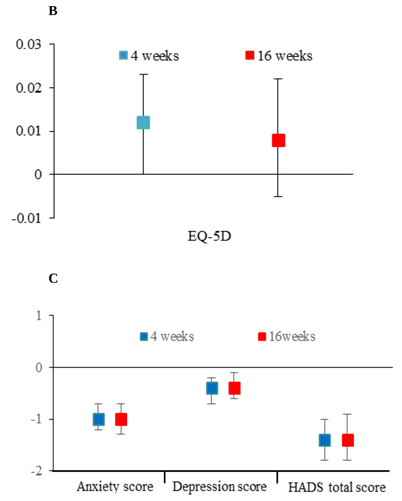
95%CI= 95% confidence interval.
HADS= Hospital anxiety and depression scale.

Mean score change value of, A: FACT-G, B, B-TOI, ES and sub-scale, B: EQ-5D, C: HADS, 4 and 16 weeks after starting neoadjuvant letrozole compared with each of the respective scores at enrollment. Error bars indicate 95% confidence intervals.

Table 3. Estimated impact value of factors on Breast-trial outcome index 4 and 16 weeks after starting neoadjuvant LET

variable	estimated value	95%CI	p value
Age at enrollment	-0.19	(-0.33, -0.05)	0.01
Body mass index	-0.1	(-0.32, 0.12)	0.38
Time point (4 weeks)	reference		
Time point (16 weeks)	-0.72	(-1.81, 0.36)	0.19
Nuclear grade 1	reference		
Nuclear grade 2	-0.19	(-2.15, 1.78)	0.85
Nuclear grade 3	-1.99	(-5.27, 1.29)	0.23
Baseline tumor size	-0.07	(-0.18, 0.03)	0.17
Baseline B-TOI score	0.39	(0.30, 0.48)	<.0001
Baseline HADS score	-0.64	(-0.81, -0.48)	<.0001

95%CI= 95% confidence interval.
HADS= Hospital anxiety and depression scale.



Discussion and Conclusions

1. The anxiety and depression observed at enrollment rapidly improved by 4 weeks after therapy, and the score of Emotional Well-Being increased significantly improved over time. Women are at increased risk of developing both physical and psychological disorders after the diagnosis; however, the majority use various strategies to cope with the disease[5].

   Neoadjuvant endocrine treatment with low toxicity, and that does not require an invasive initial approach, did not interfere with the way they coped with the disease, which is considered an appropriate approach in terms of HRQoL.
2. Neoadjuvant endocrine treatment with LET had no impact on the overall HRQoL scores; although it did influence endocrine-related symptoms, i.e., hot flashes and cold sweat.
3. To the best of our knowledge, this is the first report of HRQoL during neoadjuvant endocrine treatment with AIs.

References

1. Dowsett M, et al. Meta-analysis of breast cancer outcomes In adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 2010; 28: 509-18.
2. Fallowfield L, et al. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. J Clin Oncol 2004; 22: 4261-71.
3. Ohsumi S, et al. Health-related quality of life and psychological distress of breast cancer patients after surgery during a phase III randomized trial comparing continuation of tamoxifen with switching to anastrozole after adjuvant tamoxifen for 1-4 years: N-SAS BC 03. Breast Cancer Res Treat 2011; 127: 143-52.
4. Van Nes JG, et al. Quality of life in relation to tamoxifen or exemestane treatment in postmenopausal breast cancer patients: a Tamoxifen Exemestane Adjuvant Multinational (TEAM) Trial side study. Breast Cancer Res Treat 2012; 134: 267-76.
5. Al-Azri M, et al. Coping with a diagnosis of breast cancer-literature review and implications for developing countries. Breast J 2009; 15: 615-22.

Conflicts of Interest

This study was funded by the Comprehensive Support Project (CSP) of the Public Health Research Foundation. The corporate and individual sponsors of this study are listed on the CSPOR website (http://www.csp.or.jp/cspor/kyousan_e.html). The pharmaceutical manufacturer/distributor who had provided financial contributions as a corporate sponsor took no part in this study other than providing information relevant to the proper use of the study drug(s).

Shoichiro Ohtani, M.D. email: sho_ohtani@hotmail.com Clinical Trial Registration Information: UMIN (http://www.umin.ac.jp/), Study ID: 000001090