San Antonio Breast Cancer Symposium
December 9 – 13, 2014

P1-14-1

The first report of clinicopathological analysis at neoadjuvant treatment phase in NEOS, a randomized study of adjuvant endocrine therapy with or without chemotherapy for postmenopausal breast cancer patients who responded to neoadjuvant letrozole.

Takehiko Sakai[1], Hiroji Iwata[2], Yoshie Hasegawa[3], Rikiya Nakamura[4], Hiromitsu Akabane[5], Shoichiro Ohtani[6], Masahiro Kashiwaba[7], Naruto Taira[8], Tatsuya Toyama[9], Yutaka Yamamoto[10] ,Tomomi Fujisawa[11], Norikazu Masuda[12], Takuhiro Yamaguchi[13], Hirofumi Mukai[14], Yasuo Ohashi[15];

[1] Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; [2]Aichi Cancer Center, Nagoya, Japan; [3]Hirosaki Municipal Hospital, Hirosaki, Japan; [4]Chiba Cancer Center, Chiba, Japan; [5]Hokkaido P.W.F.A.C Asahikawa-Kosei General Hospital, Asahikawa, Japan; [6]Hiroshima City Hospital, Hiroshima, Japan; [7]Iwate Medical University School of Medicine, Morioka, Japan; [8] Okayama University Hospital, Okayama, Japan; [9]Nagoya City University Hospital, Nagoya, Japan; [10]Kumamoto University Hospital, Kumamoto, Japan; [11]Gunma Prefectural Cancer Center, Ohta, Japan; [12]NHO Osaka National Hospital, Osaka, Japan; [13]Tohoku University Graduate School of Medicine, Sendai, Japan; [14] National Cancer Center Hospital East, Kashiwa, Japan; [15] Chuo University, Tokyo, Japan

Comprehensive Support Project

Background

- Neoadjuvant aromatase inhibitor (AI) therapy is an effective approach for improving the breast-conserving surgery (BCS) rate in postmenopausal patients with estrogen receptor (ER)-rich breast cancers. However, it has not yet been established whether adjuvant chemotherapy is required for patients with intermediate-risk endocrine-responsive postmenopausal breast cancer.
- The New primary Endocrine-therapy Origination Study [1](NEOS: N-SAS BC06 study) was a randomized controlled trial that was conducted to verify the necessity of adjuvant chemotherapy for patients with clinically node-negative, ER-positive, and HER2-negative postmenopausal breast cancer who did not progress during neoadjuvant endocrine therapy.
- Primary registration was completed in July 2013 and the primary treatment of neoadjuvant letrozole (LET) for 24-28 weeks was finished. QOL by neoadjuvant LET has already been assessed[2]. This first report evaluates the clinical responses and radiological findings in the neoadjuvant LET treatment phase over 6 months.

Methods

- Patients who complied with the eligibility criteria were administered LET preoperatively in weeks 24-28 after primary enrollment. Patients evaluated as achieving a complete response (CR), partial response (PR) or stable disease (SD) by each investigator underwent a secondary enrollment .
- Secondary enrollment patients will be divided at random into two arms after surgery, an arm given LET for 4.5-5 years after chemotherapy and another arm given only LET for 4.5-5 years. Patients evaluated as having progressive disease during the LET treatment will receive discretionary treatment.
- Primary endpoint: disease-free survival (DS)
- Secondary endpoint: overall survival (OS), clinical response rates at the neoadjuvant treatment phase, pathological responses, breast-conserving surgery rated, DFS/OS in subgroups of patients according to clinical responses (CR,PR,SD, or PD), safety, HRQOL, and cost-effectiveness.
- Statistical analysis: The Mantel-Haenszel test and risk ratio regression were used to investigate relationships between baseline characteristics and clinical responses. Relationships between pathological and measured tumor sizes were analyzed by Pearson's correlation coefficient.

References

1. Iwata H. Neoadjuvant endocrine therapy for postmenopausal patients with hormone receptor-positive early breast cancer: a new concept. Breast Cancer 18:92-7,2011
2. Taira N, et al. Health-related quality of life and psychological distress during neoadjuvant endocrine therapy with letrozole to determine endocrine responsiveness in postmenopausal breast cancer. Breast Cancer Res Treat 145:155-64, 2014

Results

- Between May 2008 and June 2013, 905 patients at 100 sites entered, primary registration and completed neoadjuvant LET. We used data from 869 patients and excluded 36 patients who did not obtain the confirmed data. Patient characteristics at baseline are presented in **Table 1.**
- Clinical responses are presented in **Table 2**, and were evaluated using calipers, ultrasound, and MRI (or CT) at baseline and the end of the treatment before surgery.
- Since patients who could not enroll in the second registration were excluded according to the rules of the protocol, 83 (55.3%) out of 150 patients scheduled for total mastectomy were converted to BCS according to the final radiological evaluation before surgery (**Table 3**.).
- A univariate analysis revealed that a PgR-positive status, HER2:1+,2+(vs 0), and a high BMI at baseline correlated with clinical responses (**Table 4**). However, no correlation was observed between performance status, nuclear grade at baseline, and the negative conversion of PgR from before to after neoadjuvant LET (**Table 6**).
- A multivariate analysis showed that a PgR-positive status (Risk ratio 1.76 95%CI:1.39-2.22, *P*<0.0001) at baseline was a significant independent predictive factor of clinical responses by neoadjuvant LET (**Table 5**).
- The correlation between tumor size measured by MRI (r=0.87) after neoadjuvant LET and pathological invasive tumor size was stronger than that of other modalities (r=0.68, 0.57, 0.33 by CT, US, and calipers, respectively) (**Fig. 1**).

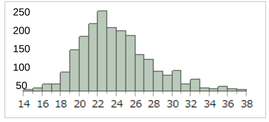
Table 1. Baseline characteristics

Factor		n	%
Age Median (SD)		63.2	(5.9)
BMI Mean (SD)		23.9	(3.7)
PS	0	868	>99%
	1	1	<1%
T	T1c	322	37%
	T2	546	63%
Histological type	IDC	803	93%
	ILC	34	4%
	Other types	30	3%
ER	Positive	869	100%
	Negative	0	0%
PgR	Positive	683	79%
	Negative	186	21%
HER2	0	283	34%
	1+	424	51%
	2+	136	16%
Planned operation	BCS	640	74%
	Mastectomy	228	26%

IDC Invasive ductal carcinoma
ILC Invasive lobular carcinoma
BCS Breast-conserving surgery

- A total of 869 patients at 100 sites had completed neoadjuvant LET by June 2013. Data cleaning of 36 patients is ongoing.

Fig. 2. Distribution of BMI in this study.



- The mean BMI in this study was 23.9.
- No significant difference was observed between BMI and clinical responses; however, a univariate analysis revealed an association between a high BMI and clinical responses (Table 4).

Table 2. Clinical responses

	n	%
CR	16	2%
PR	417	48%
SD	397	46%
PD	39	4%
CR+PR	433	50%
CR+PR+SD	830	96%
Total	869	

Table 3. Rates of breast-conserving surgery in pre-treatment estimations and surgery performed after the treatment.

		Post treatment (underwent)		
		BCS	Mastectomy	Total
Estimation Pre-treatment	BCS	403	26	429(74.1%)
	Mastectomy	83	67	150(25.9%)
	Total	486(83.9%)	93(16.1%)	579

BCS Breast-conserving surgery

Table 4. Univariate analysis of clinical responses.

		CR	PR	SD	PD	CR+PR	*P*
Body mass index	18.5>	0(0%)	14(39%)	21(57%)	2(5%)	14(39%)	0.006
	18.5-25	9(2%)	248(46%)	248(46%)	30(6%)	257(48%)	
	25<=	7(2%)	155(52%)	128 (43%)	7(2%)	162(54%)	
T	T1c	9 (3%)	162 (50%)	139 (43%)	12 (4%)	171 (53%)	0.062
	T2	7 (1%)	254 (47%)	258 (47%)	27 (5%)	261 (48%)	
Histological type	IDC	15 (2%)	393 (49%)	360 (45%)	35 (4%)	408 (51%)	0.206
	ILC	1 (3%)	12 (35%)	18 (53%)	3 (9%)	13 (38%)	
	Other	0 (0%)	11 (37%)	19 (63%)	0 (0%)	11 (37%)	
PS	0	16 (2%)	410 (48%)	396 (46%)	35 (4%)	426 (50%)	0.062
	1	0 (0%)	7 (88%)	7 (13%)	3 (9%)	7 (88%)	
PgR	Positive	15 (2%)	361 (53%)	289 (42%)	18 (3%)	376 (55%)	<0.001
	Negative	1 (1%)	56 (30%)	108 (58%)	21(11%)	57 (31%)	
HER2	0	4 (1%)	122 (43%)	137 (48%)	20 (7%)	126 (44%)	0.015
	1+	7 (2%)	211 (50%)	194 (46%)	12 (3%)	218 (52%)	
	2+	5 (4%)	68 (50%)	56 (41%)	7 (5%)	73 (54%)	
Nuclear grade	1	11 (2%)	259 (48%)	256 (47%)	18 (3%)	270 (50%)	0.351
	2	4 (2%)	99 (51%)	83 (43%)	9 (5%)	103 (53%)	
	3	1 (1%)	37 (48%)	29 (38%)	10(13%)	38 (49%)	

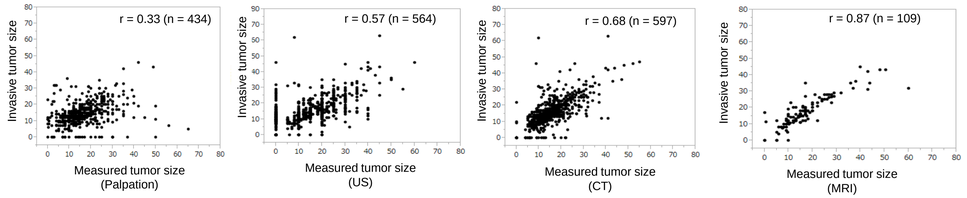
Table 5. Multivariate analysis of clinical responses.

		Reference	Risk ratio	95%CI		*P*
Age	65<=	65>	1.12	0.98	1.28	0.085
Body mass index	18.5>	18.5-25	0.76	0.49	1.17	0.213
	25<=		1.07	0.93	1.22	0.358
T	T2	T1c	0.93	0.81	1.06	0.266
PgR	Positive	negative	1.76	1.39	2.22	<0.0001
HER2	1+	0	1.07	0.92	1.25	0.379
	2+		1.18	0.97	1.43	0.095

Table 6. Relationship between PgR and clinical responses.

	Clinical response (CR+PR) (%)			Clinical response (CR+PR) (%)	
PgR-positive n=421	251 (59.6%)	*P*<0.001	positive→negative n=238	144 (61%)	*P*=0.847
			positive→positive n=183	107 (59%)	
PgR-negative n=98	38 (38.8%)		negative→positive n=10	5 (50%)	*P*=0.188
			negative→negative n=88	33 (38%)	

Fig. 1. Relationship between pathological invasive tumor size and measured tumor size.



Conclusions and Perspectives

- This is the first large-scale clinical study on neoadjuvant hormone therapy for early breast cancer.
- Neoadjuvant LET therapy improved BCS rates.
- MRI was useful for predicting residual pathological invasive tumor sizes.
- The PgR-positive status was a significant independent predictive factor of clinical responses.
- However, the negative conversion of PgR positivity was not a predictive marker of clinical responses.
- A central biomarker analysis is being scheduled in order to evaluate ER/PgR Allred scores and Ki67.

Acknowledgements

- We are deeply grateful to all the 900+ patients who generously volunteered to participate in this study.
- We would like to express our gratitude to all the NEOS investigators as well as to the clinical research coordinators and data managers of the CSPOR data center for their efforts.

Conflict 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).

Takehiko Sakai, M.D. email: takehiko.sakai@jfcr.or.jp

Clinical Trial Registration Information: UMIN (http://www.umin.ac.jp/), Study ID: 000001090