pre-menopausal estrogen receptor-positive (ER+) breast cancer and is licensed worldwide for the palliative treatment of breast cancer in these patients [4–6]. Furthermore, the large-scale Zoladex Early Breast Cancer Research Association (ZEBRA) trial concluded that goserelin was equivalent to cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy in terms of disease-free survival (DFS) [7, 8].

Current guidelines indicate that tamoxifen alone or with ovarian function suppression is now considered standard treatment for pre-menopausal women with ER+ breast cancer [9]. Clinical trials examining goserelin 3.6 mg in combination with tamoxifen have shown that this combination was more efficacious than goserelin 3.6 mg alone [10, 11], and has greater [12] or at least equivalent efficacy to CMF [13]. Accordingly, an increasing number of pre-menopausal women with ER+ breast cancer have recently been treated with goserelin 3.6 mg and concomitant tamoxifen for 2–5 years in the adjuvant setting. Thus, it seems to be very important to develop a longer-acting goserelin formulation since such a formulation requires fewer clinic visits and could potentially increase convenience for the patient. In patients with prostate cancer, a long-acting goserelin formulation given once every 3 months (goserelin 10.8 mg) was shown to be equivalent to the 3.6 mg depot in terms of tolerability and pharmacodynamics [9, 14], and gained Food and Drug Administration approval for the treatment of prostate cancer in 1996 following Phase III trials which demonstrated non-inferiority between the two dose regimens [15, 16]. However, goserelin 10.8 mg is not currently indicated for use in breast cancer.

The purpose of this study was to compare the efficacy and safety of goserelin 10.8 mg every 3 months with monthly goserelin 3.6 mg in pre-menopausal women with ER+ early breast cancer.

Methods

Study design

This was a multicenter, open-label, randomized, parallel-group study (NCT00303524) in pre-menopausal Japanese women with ER+ early breast cancer recruited from 29 centers across Japan. Eligible patients were randomized 1:1 to receive a subcutaneous depot injection of either goserelin 10.8 mg once every 3 months (12 weeks) or goserelin 3.6 mg once every month (4 weeks). All the patients also received concomitant tamoxifen therapy (20 mg daily) from day 0. Treatment continued until any of the criteria for discontinuation were met [including recurrence or onset of secondary malignancy, death in the absence of recurrence, voluntary discontinuation, any adverse event (AE) leading to discontinuation of treatment, severe non-compliance, pregnancy, or the patient being lost to follow-up], or until patients completed a 96-week treatment period, whichever occurred first.

The primary objective of this study was to determine whether 3-monthly goserelin 10.8 mg was non-inferior to monthly goserelin 3.6 mg in terms of E_2 suppression from baseline to week 24 in pre-menopausal patients with ER+ early breast cancer. Secondary objectives were to compare goserelin 10.8 and 3.6 mg in terms of E_2 and follicle-stimulating hormone (FSH) serum levels, suppression of menstruation, and safety and tolerability. The pharmacokinetics (PK) of the 10.8 mg depot administration was also investigated.

The study was approved by the relevant ethics committees and institutional review boards, and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice, the applicable Japanese regulatory requirements and the AstraZeneca policy on Bioethics. All the patients gave written informed consent before entering the study.

Patients

The study population comprised pre-menopausal Japanese women aged ≥20 years with histologically or cytologically confirmed breast cancer and an ER+ primary tumor. All the patients had to have undergone prior radical surgery and have a World Health Organization performance status ≤2. Women were considered pre-menopausal if they met the following criteria: menses within 1 year, E_2 levels of ≥10 pg/ml, and FSH levels of ≤30 mIU/ml within 3 weeks before randomization.

Patients were excluded from the trial if they had any evidence of metastatic disease, if they had received prior bilateral oophorectomy or radiotherapy to the ovaries, or if breast surgery had been completed >12 weeks before starting randomized treatment. Further exclusion criteria were: prior chemotherapy (including neo-adjuvant chemotherapy) or hormone therapy for breast cancer; a history of systemic malignancy other than breast cancer within the last 3 years; laboratory values indicating impaired liver or renal function; or any other clinically relevant abnormal laboratory test result. Patients requiring anti-coagulant or anti-platelet therapy while receiving study treatments were treated at the discretion of the study investigator; concomitant hormone replacement therapy or oral contraceptives were not permitted.

Assessments

The primary endpoint was the area under the concentration–time curve (AUC) of E_2 serum concentration for the

first 24 weeks of treatment. Secondary endpoints included E_2 and FSH serum concentration, percentage of the patients with a mean E_2 concentration $\leq$30 pg/ml, menstruation, DFS and tolerability (AEs and clinical laboratory test values). In addition, PK assessment of goserelin was also conducted on a subset of evaluable patients who provided written informed consent for additional blood sample collection and received goserelin 10.8 mg every 3 months.

Patient visits took place at screening; on day 0; at weeks 4, 8, 10, 12, 16, 20, 22, 24, 48, 72, 96, and at time of withdrawal. An additional safety follow-up was also performed, if possible, at week 100.

The E_2 and FSH concentrations were evaluated from blood samples taken at each visit, before the administration of the study treatment. E_2 concentration was determined using a double antibody radioimmunoassay procedure (Covance Central Laboratory Services). FSH concentration was determined by chemiluminescent enzyme immunoassay (Mitsubishi Kagaku Bio-clinical Laboratories Incorporation). For patients in the 10.8 mg group, goserelin plasma concentrations were also assessed from blood samples taken at each visit using protein precipitation extraction followed by detection with high-performance liquid chromatography with tandem mass spectrometric detection. In addition, for a subgroup of 20 evaluable patients in the 10.8 mg group, plasma concentrations of goserelin were assessed 1, 2, 24, and 48 h post dose. Clinical chemistry and hematology tests were also conducted on blood samples taken at day 0, week 12 and 24 for all the patients.

The DFS, defined as the number of days from randomization to date of recurrence, second malignancy or death from any cause, was determined by clinical evaluation at baseline and weeks 4, 8, 12, 16, 20, 24, 48, 72, and 96. If signs of recurrence or second malignancy were noted, they were confirmed by imaging techniques (chest X-ray, liver echo, computed tomography scan, or bone scan). AEs and serious AEs (SAEs) were recorded throughout the study and the relationship between the AEs/SAEs and treatment was determined by the study investigator. AEs were classified by the Medical Dictionary for Regulatory Activities (Version 10.1) preferred terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTC). All AEs/SAEs were followed-up to resolution or until the condition stabilized.

Statistical analysis

The primary objective of this study was to establish whether the goserelin 10.8 mg depot was non-inferior to the goserelin 3.6 mg depot in terms of E_2 suppression. With 76 patients per group, this study had 80% power to establish non-inferiority at the 2.5% (one-sided) significance level, with the limit of non-inferiority defined as 1.25 (assuming AUC ratio of 1.06 and common standard deviation on log scale of 0.36). A sample size of 168 randomized patients was planned to recruit 152 evaluable patients.

For the primary endpoint, data cut-off was performed when evaluation of all patients' data from the first 24 weeks of study was completed. Non-inferiority was assessed using $AUC_{(4-24\ week)}$ of the E_2 concentration–time curve with AUC of E_2 values log-transformed before analysis and the results exponentiated. E_2 data were analyzed using analysis of covariance. Values below the limit of quantification (LOQ) (1.4 pg/ml) were recorded as 0.7 pg/ml. The 95% confidence interval (CI) was constructed around the AUCs with goserelin 3.6 mg as the reference treatment. Non-inferiority was demonstrated if the upper 95% CI limit of the E_2 AUC ratio (10.8/3.6 mg) was $\leq$1.25.

The E_2 and FSH concentrations observed throughout the study were summarized for each treatment group using descriptive statistics. The proportion of patients whose E_2 concentration was $\leq$30 pg/ml at any study visit was also calculated. The goserelin plasma concentration data were derived from the subgroup of 20 patients in the 10.8 mg group. Maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the curve at time t (AUC_t), and trough drug concentrations were determined. Median follow-up data are reported for DFS. The patients who discontinued due to an AE were treated as censored observations.

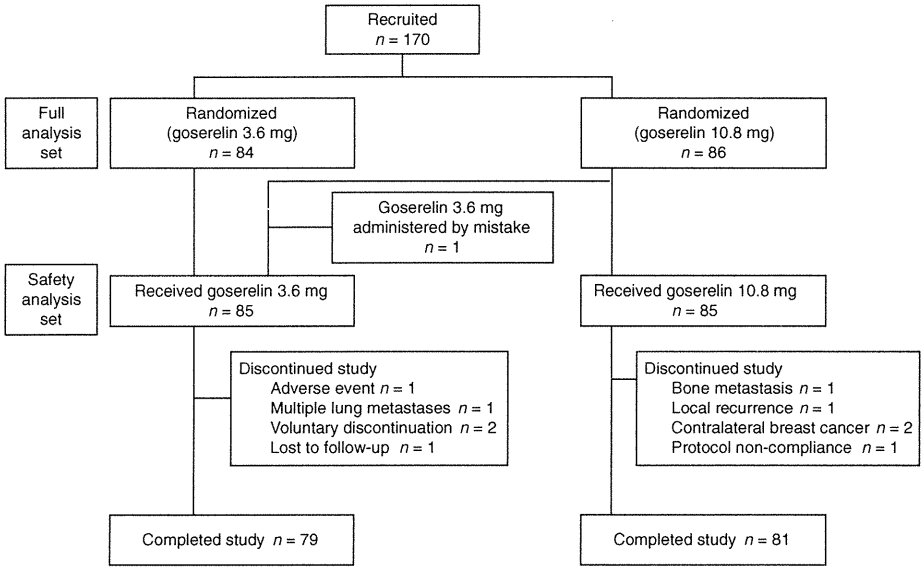
Statistical analysis sets included: full analysis set (FAS; all the patients randomized to study treatment regardless of actual treatment(s) received, with data available for any endpoint post randomization); safety analysis set (all the randomized patients who received at least one dose of study treatment); PK analysis set (20 patients randomized to goserelin 10.8 mg whose blood samples were collected for assessment of goserelin plasma concentrations).

Results

Patients

In total, 170 patients were randomly assigned to treatment; 86 to goserelin 10.8 mg and 84 to goserelin 3.6 mg (Fig. 1). The first patient entered the study in January 2006 and the last patient entered in February 2007. For evaluation of the primary endpoint of E_2 AUC for the first 24 weeks of treatment, the data cut-off was performed on August 31, 2007. For evaluation of safety and DFS, the last patient completed the 2-year study treatment in February 2009. All 170 randomized patients were included in the FAS. One patient randomized to receive goserelin 10.8 mg

Fig. 1 Patient disposition



The number of patients who completed the study equals the number of randomized patients minus the number of patients who discontinued

received goserelin 3.6 mg by mistake and so was included in the 10.8 mg group in the FAS and the 3.6 mg group in the safety analysis set (Fig. 1). Baseline and disease characteristics were generally similar for each treatment group. Most patients had invasive breast cancer that was progesterone-receptor positive; most tumors were classified as T1 or T2, with no regional lymph-node involvement (Table 1).

Efficacy

AUC of E_2 serum concentration during the first 24 weeks of treatment

The geometric mean E_2 AUC from weeks 4–24 of treatment was similar in both treatment groups, i.e., 18.32 and 18.95 pg/ml·week for the patients receiving goserelin 10.8 and 3.6 mg, respectively. The goserelin AUC ratio (10.8/3.6 mg), adjusted by baseline E_2 value, was 0.974 (95% CI, 0.80, 1.19). The 95% CI upper limit (1.188) was below the predefined non-inferiority margin of 1.25, indicating the non-inferiority of depot goserelin 10.8 mg versus goserelin 3.6 mg.

E_2 and FSH serum concentrations

Baseline mean E_2 serum concentrations were 69.87 and 60.19 pg/ml for the goserelin 10.8 and 3.6 mg group, respectively. After week 4, the mean E_2 serum concentrations in both groups had decreased to a range between 0.71 and 4.69 pg/ml (Fig. 2a), and ≥98.8% of the patients in both groups maintained E_2 serum concentrations of below 30 pg/ml, i.e., within a range regarded as the postmenopausal status. E_2 serum concentrations >30 pg/ml were only observed in one patient at week 22 in the 10.8 mg group and in four patients (once each) at weeks 4, 8, 12, and 20 in the goserelin 3.6 mg group.

Mean baseline FSH concentrations were 8.18 and 7.72 mIU/ml for the goserelin 10.8 and 3.6 mg group, respectively. After week 4, mean FSH concentrations were lower in both groups (range 1.28–1.89 mIU/ml) (Fig. 2b).

Goserelin concentrations

For the PK analysis set, the mean plasma concentration–time profile for goserelin 10.8 mg from baseline up to week 12 is shown in Fig. 3. Plasma concentrations of goserelin increased rapidly following administration, with C_{max} (geometric mean C_{max} of 4.5 ng/ml) occurring at a median T_{max} of 2.4 h. The goserelin plasma concentrations subsequently decreased rapidly up to 48 h and more steadily thereafter, with values approaching the LOQ (0.1 ng/ml) by weeks 10–12. Trough plasma concentrations of goserelin fell below the LOQ in most patients by week 12.

Menstruation

The proportion of patients experiencing menses fell from 67.4% (week 4) to 2.3% (week 8) and 72.6% (week 4) to 1.2% (week 8) for the 10.8 and 3.6 mg treatment groups, respectively. All the patients experienced amenorrhea by week 12 in the 10.8 mg group and by week 16 in the 3.6 mg group.

Table 1 Baseline patient demographics and disease characteristics (full analysis set)

	Goserelin 10.8 mg (n = 86) n(%)	Goserelin 3.6 mg (n = 84) n(%)
Age (years)		
Mean	43.2	43.8
Range	26–51	30–53
Weight (kg)		
Mean	54.3	53.9
Range	39–78	39–93
Body mass index (kg/m^2)		
Mean	21.4	21.9
Range	16.3–30.5	17.1–40.3
Histology		
Invasive	83 (96.5)	79 (94.0)
Non-invasive	3 (3.5)	5 (6.0)
TNM classification—primary tumor		
T1	49 (57.0)	54 (64.3)
T2	33 (38.4)	25 (29.8)
T3	1 (1.2)	2 (2.4)
Not applicable[a]	3 (3.5)	3 (3.6)
TNM classification—regional lymph nodes		
0	81 (94.2)	78 (92.9)
N1	5 (5.8)	6 (7.1)
TNM classification—distant metastases		
M0	86 (100)	84 (100)
PgR status		
Negative	5 (5.8)	4 (4.8)
Positive	81 (94.2)	80 (95.2)
Baseline E_2 concentration (pg/ml)		
Mean (SD)	69.87 (60.26)	60.19 (55.36)
Median	49.70	53.50
Range	0.7–275.4	0.7–327.0

[a] Carcinoma in situ, *E_2* estradiol; *PgR* progesterone receptor; *SD* standard deviation; *TNM* tumor, node, metastases

DFS

The median follow-up period for DFS was 675.0 days (range 142–687) and 675.5 days (range 160–685) for the 10.8 and 3.6 mg group, respectively. A total of five events were observed during the study: four in the 10.8 mg group (bone metastasis, local recurrence, and two contralateral breast cancers) and one in the 3.6 mg group (multiple lung metastases).

Safety

Overall, 97.6% of the patients in each group experienced an AE. Four CTC grade 3/4 AEs were observed in four patients in the 10.8 mg group and six grade 3/4 AEs were observed in four patients in the 3.6 mg group (Table 2). A total of seven patients had a SAE [four patients in the 10.8 mg group (breast cancer, contralateral breast cancer, dermoid cyst, and radiation pneumonitis) and three patients in the 3.6 mg group (cervix carcinoma, headache, and calculus ureteric)]; however, no SAE was considered related to study treatment and none led to death. Most drug-related AEs (as determined by the investigator) were CTC grade 1 or 2, with the most common being hot flash (69.4 and 63.5%), headache (16.5 and 15.3%), arthralgia (14.1 and 16.5%), and hyperhidrosis (11.8 and 17.6%) in the 10.8 and 3.6 mg groups, respectively (Table 3). One patient in the 3.6 mg group discontinued treatment due to a non-drug-related AE (cervix carcinoma). Overall, there was no apparent difference in the safety and tolerability profile for goserelin 10.8 mg compared with 3.6 mg.

Discussion

The primary objective of this study was to determine whether goserelin 10.8 mg was non-inferior to goserelin 3.6 mg in terms of E_2 suppression in pre-menopausal patients with ER+ early breast cancer. The AUC E_2 serum

concentrations reported here were similar between treatment groups. Moreover, the AUC ratio (10.8/3.6 mg) was 0.974 and the 95% CI upper limit of 1.188 was below the predefined non-inferiority margin of 1.25, thus demonstrating that goserelin 10.8 mg once every 3 months was indeed non-inferior to monthly administration of goserelin 3.6 mg in these patients.

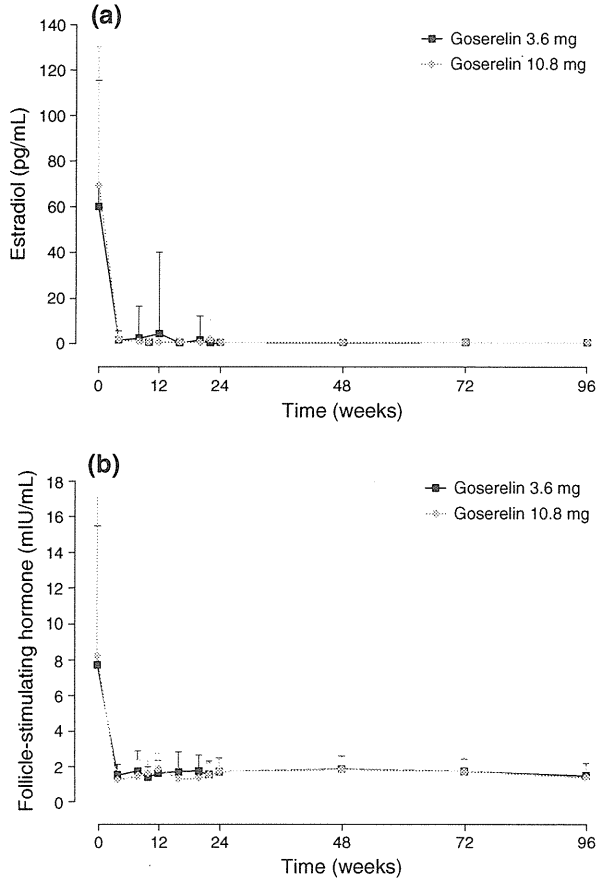


Fig. 2 Mean estradiol serum concentrations (**a**) and mean FSH serum concentrations (**b**) following administration of goserelin 10.8 or 3.6 mg depot (full analysis set)

The secondary variables, E_2 and FSH serum concentrations, were also suppressed in both treatment groups following an injection of goserelin, and this suppression was maintained throughout the study, suggesting no apparent difference between monthly and 3-monthly goserelin administration. Indeed, from week 4 onwards, E_2 serum concentrations were suppressed to postmenopausal levels ($\leq$30 pg/ml) in 98.8% of the patients across both treatment groups. In addition, after week 4, FSH serum concentrations were well suppressed in both treatment groups. Suppression of hormone levels was accompanied by a rapid decrease in the number of patients experiencing menstruation, with most patients experiencing amenorrhea by week 8. These findings show that goserelin 10.8 mg once every 3 months induces effective ovarian suppression that is maintained between doses.

Both goserelin 10.8 and 3.6 mg depots are sustained-release formulations containing a lactide/glycolide co-polymer. However, the lactide/glycolide ratios differ between the two formulations, with the 95:5 ratio of the 10.8 mg depot enabling a more gradual release of goserelin compared with the monthly formulation (1:1 ratio), leading to maintenance of drug levels associated with therapeutic efficacy for 3 months. Following administration of the 10.8 mg depot, maximum goserelin plasma concentrations were seen at around 2.4 h post injection, before decreasing rapidly up to 48 h, and more steadily to 12 weeks. Goserelin plasma concentrations then approached the LOQ by weeks 10–12 and actually fell below this limit in about half of the patients.

In females with breast cancer or benign gynecological conditions, the AUC values for goserelin after the first 10.8 mg depot were approximately 20% lower than those

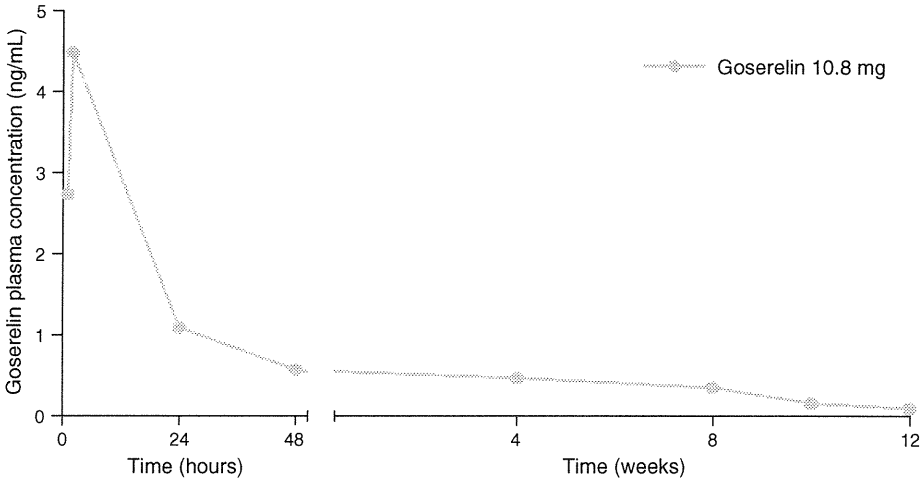


Fig. 3 Goserelin plasma concentrations following administration of 10.8 mg depot injection (pharmacokinetic analysis set)

Table 2 Summary of individual grade 3/4 adverse events

Treatment group	Adverse event (MedDRA preferred term)	Grade	Time from administration to onset of adverse event (days)	Discontinued study	Treatment-related[a] goserelin/tamoxifen/procedure
Goserelin 3.6 mg	Osteoarthritis	3	141	No	Yes/Yes/No
	Cervix carcinoma	4	224	Yes	No/No/No
	Hepatic function abnormal	3	86	No	No/Yes/No
	Calculus ureteric	3	397	No	No/No/No
	Leukopenia	3	673	No	No/No/No
	Neutropenia	4	673	No	No/No/No
Goserelin 10.8 mg	Breast cancer	3	590	No	No/No/No
	Labile blood pressure	3	153	No	No/No/No
	Hypertension	3	103	No	No/No/No
	Contralateral breast cancer	4	668	No	No/No/No

[a] Investigator opinion determined whether there was a reasonable possibility that the event may have been caused by either goserelin, tamoxifen, or the procedure, *MedDRA* medical dictionary for regulatory activities

Table 3 Incidence of drug-related adverse events occurring in more than 2% of patients in either treatment group (safety analysis set)

Adverse event (MedDRA preferred term)	Goserelin 10.8 mg ($n = 85$) n(%)	Goserelin 3.6 mg ($n = 85$) n(%)
Hot flash	59 (69.4)	54 (63.5)
Headache	14 (16.5)	13 (15.3)
Arthralgia	12 (14.1)	14 (16.5)
Hyperhidrosis	10 (11.8)	15 (17.6)
Musculoskeletal stiffness	7 (8.2)	10 (11.8)
Dizziness	6 (7.1)	8 (9.4)
Hepatic steatosis	5 (5.9)	4 (4.7)
Insomnia	4 (4.7)	3 (3.5)
Head discomfort	3 (3.5)	3 (3.5)
Edema peripheral	5 (5.9)	1 (1.2)
Back pain	2 (2.4)	3 (3.5)
Hypertension	3 (3.5)	2 (2.4)
Nausea	0	5 (5.9)
Anxiety	4 (4.7)	0
Constipation	3 (3.5)	1 (1.2)
Rash	2 (2.4)	2 (2.4)
Palpitations	2 (2.4)	2 (2.4)

Any patient with more than one event was counted separately for each event, *MedDRA* medical dictionary for regulatory activities

predicted from the 3.6 mg depot data [17]. Overall, these studies confirm that, as one might expect, goserelin serum concentrations rise sharply immediately after a 10.8 mg injection, and decrease gradually over time [16, 17]. The speed and extent to which blood goserelin levels decrease reflects inter-patient variability. However, the low goserelin plasma concentration seen in some patients 10–12 weeks post injection was not associated with increased E_2 or FSH concentrations.

The efficacy of goserelin 10.8 or 3.6 mg in controlling disease was measured by DFS, but with only five progression events, no formal comparison was conducted. Although these are not long-term survival data, the 2-year DFS data reported here are similar to those reported in other clinical studies of goserelin 3.6 mg. For example, similar survival data were reported in the Zoladex® in Premenopausal Patients (ZIPP) trial, which used goserelin 3.6 mg in combination with standard adjuvant therapy [18], and the Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 5, which compared goserelin 3.6 mg plus tamoxifen versus CMF in pre-menopausal women [7, 8]. In addition, a recent 15-year follow-up of data from the ZIPP trial has reported that 2 years of goserelin treatment is equivalent to 2 years of tamoxifen treatment, and also a large benefit for goserelin was observed on survival and recurrence [19].

There were no clinically important differences in the safety and tolerability profiles between the two dosing regimens of goserelin, suggesting that a 3-monthly dosing regimen is feasible. Indeed, consistent with previous reports of monthly goserelin 3.6 mg in ER+ early breast cancer, the most frequently observed AEs following treatment with 10.8 mg goserelin every 3 months were hot flash, headache, and hyperhidrosis [7, 20]. The current treatment recommendations for pre-menopausal women with ER+ early breast cancer are tamoxifen or tamoxifen plus ovarian suppression for 5 years [9]. As most patients will likely receive treatment for several years, a 3-monthly dosing regimen of goserelin 10.8 mg offers an alternative dosing schedule that may be more convenient for some patients, thus helping to improve compliance. Moreover, a 3-monthly dosing regimen with fewer clinic visits could help to reduce associated healthcare costs.

Possible limitations to this study include a lack of PK data for the goserelin 3.6 mg/month treatment group. In addition, a longer follow-up period would be required to fully determine the effect of the monthly versus 3-monthly dosing regimen on DFS. The results must also be considered within the limits of an open-label trial.

In conclusion, the findings reported here show that goserelin 10.8 mg given every 3 months is as effective as monthly goserelin 3.6 mg in achieving and maintaining ovarian suppression in pre-menopausal women with ER+ early-stage breast cancer. Goserelin 10.8 mg also has a similar tolerability profile to the monthly dosing regimen and, therefore, could offer these patients an alternative dosing regimen that could increase convenience and improve compliance.

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References

1. Debruyne FM, Dijkman GA (1995) Advances and trends in hormonal therapy for advanced prostate cancer. Eur Urol 28: 177–188
2. Soto AM, Sonnenschein C (1985) The role of estrogens on the proliferation of human breast tumor cells (MCF-7). J Steroid Biochem 23:87–94
3. Nicholson S, Halcrow R, Sainsbury J, Angus B, Chambers P, Farndon J, Harris A (1988) Epidermal growth factor receptor (EGFr) status associated with failure of primary endocrine therapy in elderly postmenopausal patients with breast cancer. Br J Cancer 58:810–814
4. AstraZeneca (2009) Zoladex prescribing information
5. AstraZeneca (2009) Zoladex 3.6 mg Implant–Summary of product characteristics (SPC)
6. Taylor CW, Green S, Dalton WS, Martino S, Rector D, Ingle JN, Robert NJ, Budd GT, Paradelo JC, Natale RB, Bearden JD, Mailliard JA, Osborne CK (1998) Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. J Clin Oncol 16:994–999
7. Jonat W, Kaufmann M, Sauerbrei W, Blamey R, Cuzick J, Namer M, Fogelman I, de Haes JC, De Matteis A, Stewart A, Eiermann W, Szakolczai I, Palmer M, Schumacher M, Geberth M, Lisboa B (2002) Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: The Zoladex Early Breast Cancer Research Association Study. J Clin Oncol 20:4628–4635
8. Kaufmann M, Jonat W, Blamey R, Cuzick J, Namer M, Fogelman I, de Haes JC, Schumacher M, Sauerbrei W, Zoladex Early Breast Cancer Research Association (ZEBRA) Trialists' Group (2003) Survival analyses from the ZEBRA study: goserelin (Zoladex^{TM}) versus CMF in premenopausal women with node-positive breast cancer. Eur J Cancer 39:1711–1717
9. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thurlimann B, Senn H-J (2009) Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009. Ann Oncol 20:1319–1329
10. Klijn JG, Beex LV, Mauriac L, van Zijl JA, Veyret C, Wildiers J, Jassem J, Piccart M, Burghouts J, Becquart D, Seynaeve C, Mignolet F, Duchateau L (2000) Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a randomized study. J Natl Cancer Inst 92:903–911
11. Klijn JG, Blamey RW, Boccardo F, Tominaga T, Duchateau L, Sylvester R, Combined Hormone Trialists' Group and the European Organization for Research and Treatment of Cancer (2001) Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol 19:343–353
12. Jakesz R, Hausmaninger H, Kubista E, Gnant M, Menzel C, Bauernhofer T, Seifert M, Haider K, Mlineritsch B, Steindorfer P, Kwasny W, Fridrik M, Steger G, Wette V, Samonigg H (2002) Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer–Austrian Breast and Colorectal Cancer Study Group Trial 5. J Clin Oncol 20:4621–4627

13. Boccardo F, Rubagotti A, Amoroso D, Mesiti M, Romeo D, Sismondi P, Giai M, Genta F, Pacini P, Distante V, Bolognesi A, Aldrighetti D, Farris A (2000) Cyclophosphamide, methotrexate, and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results of the Italian Breast Cancer Adjuvant Study Group 02 randomized trial. J Clin Oncol 18:2718–2727
14. Dijkman GA, del Moral PF, Plasman JW, Kums JJ, Delaere KP, Debruyne FM, Hutchinson FJ, Furr BJ (1990) A new extra long acting depot preparation of the LHRH analogue Zoladex. First endocrinological and pharmacokinetic data in patients with advanced prostate cancer. J Steroid Biochem Mol Biol 37:933–936
15. Dijkman GA, Debruyne FM, Fernandez del MP, Plasman JW, Hoefakker JW, Idema JG, Sykes M (1994) A phase III randomized trial comparing the efficacy and safety of the 3-monthly 10.8-mg depot of Zoladex with the monthly 3.6-mg depot in patients with advanced prostate cancer. Dutch South East Cooperative Urological Group. Eur Urol 26(Suppl 1):1–2
16. Dijkman GA, Debruyne FM, Fernandez del MP, Plasman JW, Hoefakker JW, Idema JG, Sykes M (1995) A randomised trial comparing the safety and efficacy of the Zoladex 10.8-mg depot, administered every 12 weeks, to that of the Zoladex 3.6-mg depot, administered every 4 weeks, in patients with advanced prostate cancer. The Dutch South East Cooperative Urological Group. Eur Urol 27:43–46
17. Cockshott ID (2000) Clinical pharmacokinetics of goserelin. Clin Pharmacokinet 39:27–48
18. Baum M, Hackshaw A, Houghton J, Rutqvist LE, Fornander T, Nordenskjold B, Nicolucci A, Sainsbury R (2006) Adjuvant goserelin in pre-menopausal patients with early breast cancer: results from the ZIPP study. Eur J Cancer 42:895–904
19. Hackshaw A, Baum M, Fornander T, Nordenskjold B, Nicolucci A, Monson K, Forsyth S, Reczko K, Johansson U, Fohlin H, Valentini M, Sainsbury R (2009) Long-term effectiveness of adjuvant goserelin in premenopausal women with early breast cancer. J Natl Cancer Inst 101:341–349
20. Nystedt M, Berglund G, Bolund C, Fornander T, Rutqvist LE (2003) Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: a prospective randomized study. J Clin Oncol 21:1836–1844

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Ki67 index changes, pathological response and clinical benefits in primary breast cancer patients treated with 24 weeks of aromatase inhibition

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Aromatase inhibitor shows efficacy for hormone receptor positive postmenopausal breast cancer. We evaluated the activity of 24 weeks of aromatase inhibition with exemestane for primary breast cancer in a neoadjuvant setting. Patients with stage II/IIIA invasive breast cancer with estrogen receptor (ER) and/or progesterone receptor (PgR)-positive status were eligible. Primary endpoints were objective response rate (ORR) and safety. A steroidal aromatase inhibitor exemestane of 25 mg/day was administered for 16 weeks with an 8-week extension. Secondary endpoints were rates of breast-conserving surgery (BCS), and change of Ki67 index and ER/PgR expression in central laboratory analyses. Between March 2006 and December 2007, 116 patients were enrolled. Among those, 102 patients completed 24 weeks of administration. The ORR was 47% (55/116) at Week 16 and 51% (59/116) at Week 24, respectively. No serious toxicity was seen. ORR was associated with ER Allred scores but not with PgR scores. The significant reduction in Ki67 index was confirmed. No progression was experienced in tumors with less than 15% Ki67 index. Pathological response was observed in 28 (30%) of 94 evaluated cases. No statistical correlation between pre-treatment Ki67 index and pathological response was detected; however, a trend of correlation was found between the post-treatment preoperative endocrine prognostic index (PEPI), a prognostic score and the pathological response. At diagnosis, 59 patients (51%) would have required mastectomy but 40 patients were converted to BCS, showing an increase in the rate of BCS (77%). The 24-week aromatase inhibition provided preferable clinical benefits with significant reduction in Ki67 index. More precise mechanisms of the response need to be investigated. (*Cancer Sci* 2011; 102: 858–865)

Many studies of neoadjuvant chemotherapy for breast cancer have been conducted. These studies have revealed that neoadjuvant chemotherapy allows more women to undergo breast-conserving surgery (BCS) rather than total mastectomy, and prolongs the survival of patients who achieved pathological complete response (pCR).[1–3] However, it has been described that neoadjuvant chemotherapy has a limited effect in hormone receptor-positive patients in terms of pCR rates, and raises safety concerns for elderly patients.[4–7] Therefore, as a treatment strategy, the efficacy and safety of neoadjuvant hormone therapy using aromatase inhibitors (AI) is being assessed in several trials in postmenopausal breast cancer patients.[8–11]

In a phase II randomized study in which neoadjuvant hormone therapy and neoadjuvant chemotherapy were compared in hormone receptor-positive patients, no significant difference in the clinical response rate was observed between these two groups. Notably, the rate of BCS tended to be higher, and the incidence of adverse events was generally lower in the neoadjuvant hormone therapy group than in the neoadjuvant chemotherapy group.[12] These results suggest the benefit of neoadjuvant hormone therapy in hormone-sensitive postmenopausal breast cancer patients.[13] Therefore, it seems that neoadjuvant hormone therapy offers an alternative to neoadjuvant chemotherapy.

However, there are some concerns surrounding the use of neoadjuvant hormone therapy that need to be addressed. First, tumor regression is slower with neoadjuvant hormone therapy than with chemotherapy. In fact, a study investigating the response rate to 6-month neoadjuvant hormone therapy using exemestane reported that the objective response rate (ORR: complete response [CR] + partial response [PR]) continued to increase even after 4 months of treatment.[14] Another concern is that there is no established index for evaluating the efficacy of neoadjuvant hormone therapy. In neoadjuvant chemotherapy, the pCR rate can be used as a surrogate marker for the prognosis of patients.[2] However, it has been reported that, in estrogen receptor (ER)-positive patients, the proportion of patients who achieved a pCR was not significantly correlated with overall survival (OS) or disease-free survival (DFS).[15] In addition, several Phase II studies of neoadjuvant hormone therapy reported that pCR rates were from 0 to about 3%, which were remarkably lower than those expected from the benefit observed in adjuvant hormone therapy.[8,11,12] Therefore, in hormone receptor-positive breast cancer patients, pCR is unlikely to be a useful marker for assessing efficacy or prognosis. A possible alternative marker for neoadjuvant hormone therapy is the percentage of MIB1/Ki67-positive cells (MIB-1/Ki67 labeling index), a cell proliferative index. The Ki67 index after neoadjuvant hormone therapy was shown to correlate with the recurrence rate.[16,17] However, the usefulness of the Ki67 index has not been fully evaluated.

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Table 1. Patient characteristics

Factor	*n* (%)
Age, years (median, range)	64 (55–79)
Prior treatment	None
Tumor stage	
T2	110 (95)
T3	6 (5)
Nodal status	
N0	91 (78)
N1	23 (20)
Unknown	3 (2)
Clinical stage	
IIA	89 (77)
IIB	23 (20)
IIIA	4 (3)
Tumor diameter, mm (median, range)	
Caliper	32 (12–74)
Ultrasound	27.3 (15–102)
ER status	
ER+	116 (100)
ER–	0
PgR status	
PgR+	80 (69)
PgR–	36 (31)
HER2 status	
HER2+	3 (3)
HER2–	101 (87)
Not evaluated	12 (10)

ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

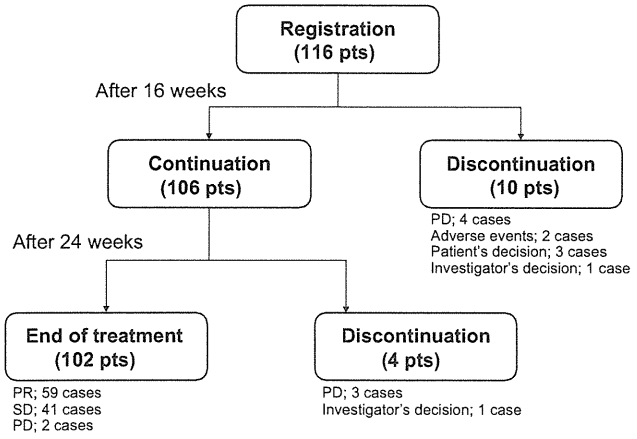

Fig. 1. Patient registration and the treatment flow of 24 weeks. PD, progressive disease; pts, patients; PR, partial response; SD, stable disease.

From these circumstances, we conducted the present study in Japanese patients with hormone receptor-positive postmenopausal breast cancer who received neoadjuvant hormone therapy using exemestane for 24 weeks to assess tumor response and safety of the treatment. We also evaluated the Ki67 index and expression of hormone receptors to determine its potential use as a marker to predict clinical and histopathological response in a central laboratory. Preoperative endocrine prognostic index (PEPI),[16] a prognostic index, was determined in each individual and the relationship with clinical and pathological responses was investigated.

Table 2. Clinical response after 16 weeks and 24 weeks of treatment

After 16 weeks evaluation (number of patients)		After 24 weeks evaluation (number of patients)	
PR	45	PR	59
SD	14		
PR	7	SD	41
SD	34		
PR	1	PD	4
SD	3		
PR	2	Not evaluated	12
SD	3		
PD	4		
Not evaluated	3		
Total		116	

PR, partial response; SD, stable disease; PD, progressive disease.

Patients and Methods

Patients. Postmenopausal women aged 55–75 years with operable, Stage II or IIIA, histologically confirmed invasive breast cancers were enrolled. Patients were confirmed positive for ER or progesterone receptor (PgR) by immunohistochemical staining (≥10% nuclear staining was defined as positive). Expression of human epidermal growth factor receptor 2 (HER2) was determined immunohistologically with the Herceptest (Dako, Glostrup, Denmark). Positive in HER2 status was defined as either 3+ or 2+ with confirmed *c-erbB2* gene amplification by the FISH test. All patients were judged by their primary physicians as having a good performance status (PS; 0–1) and an indication for neoadjuvant hormone therapy after consideration of other treatment options such as surgical therapy and neoadjuvant chemotherapy.

This study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research of the Ministry of Health, Labour and Welfare of Japan. Approval was obtained from the institutional review board at each study center. Written informed consent was obtained from all patients before enrolment.

Treatment scheme. The patients' lesions were measured by palpation, ultrasound and computed tomography or magnetic resonance imaging. Surgical procedures were determined based on the initial examination; axillary lymph node metastasis was also assessed.

Patients were initially treated with 25 mg of exemestane (Aromasin®; Pfizer Inc. Tokyo, Japan) once daily, orally, for 16 weeks. Clinical response was assessed by comparing the longest diameter of the target lesions with the baseline measurement based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Patients with progressive disease (PD) were withdrawn from the study and the remainder continued to receive exemestane for a further 8 weeks, for a total treatment period of 24 weeks. At Week 24, the clinical response was re-evaluated using the same criteria as at Week 16. Patients classified as showing CR, PR or stable disease (SD) at Week 24 underwent surgery as appropriate; patients classified as PD either underwent surgery or commenced another treatment. After surgery, patients classified as CR, PR or SD continued to receive exemestane for postoperative adjuvant hormone therapy for ≥5 years, including the neoadjuvant treatment period. Radiotherapy and drug therapy other than hormone therapy could be given concomitantly at the investigator's discretion. Postoperative treatment was not pre-specified for patients with PD.

Study end points. The primary end points were objective response rates (ORR) and safety after 16 and 24 weeks of

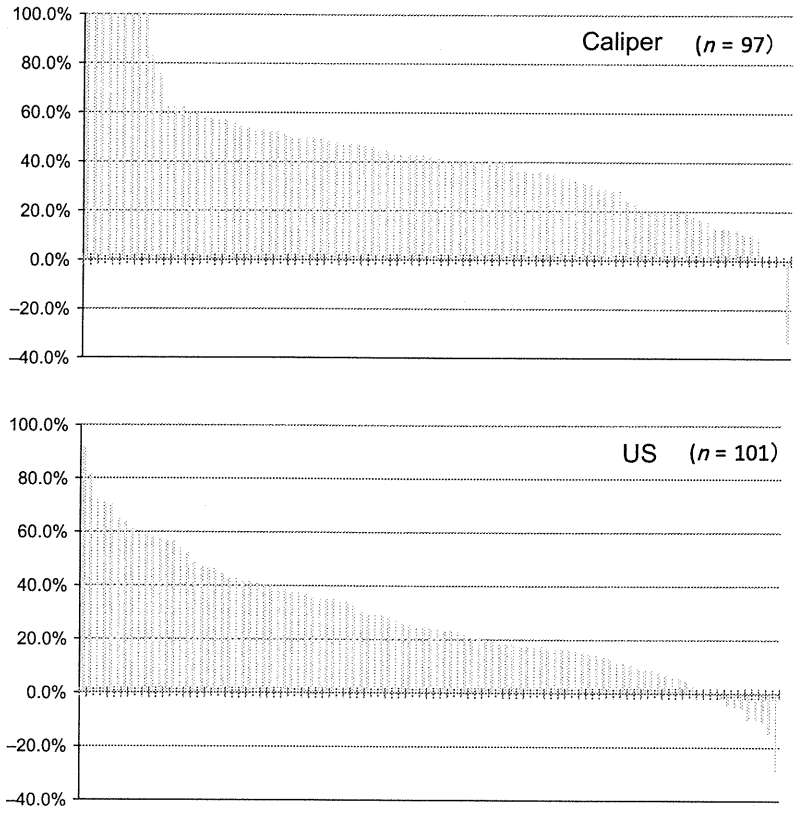

Fig. 2. Waterfall plot analysis of clinical response at 24 weeks evaluated by caliper and ultra sound (US). Horizontal axis indicates data from each patient and vertical axis, the reduction rate of tumor size evaluated by indicated modality. Negative values on vertical axis indicates tumor progression.

Table 3. Rates of breast conserving surgery in pre-treatment estimation and surgery undergone after treatment

		Post treatment (underwent)			Total
		Mastectomy	BCS	Without surgery	
Estimation pre-treatment	Mastectomy	14	40	5	59 (50.9%)
	BCS	5	49	3	57 (49.1%)
Total		19 (16.4%)	89 (76.7%)	8 (6.9%)	116

BCS, breast conserving surgery.

treatment in intent to treatment analysis. Secondary end points were rates of breast-conserving surgery and mastectomy, nodal status, biomarker changes, pathological response and Allred score. Correlations between the pre-treatment Ki67 labeling index and its changes by treatment and therapeutic effects were also investigated.

Safety assessments. Adverse events (defined as the development of a new medical condition or the deterioration of a pre-existing medical condition) were recorded every 4 weeks, and were graded according to the National Cancer Institute, Common Toxicity Criteria version 3.0. Pre-specified adverse events were hot flushes, sweating, headache, dizziness, fatigue, nausea/vomiting, appetite loss, weight gain, hypertension, vaginal bleeding, joint pain and bone fracture.

Central biomarker analysis. In order to determine the suitability for further immunohistochemical (IHC) analyses and then for the evaluation of pathological response, initially, one 4-μm section of each submitted paraffin blocks of pre- and post-treatment specimens of 107 patients who underwent surgery were stained with H&E to verify an adequate number of invasive breast carcinoma cells and the quality of fixation for this study. Serial tissue sections were then prepared from selected blocks and immunohistochemistry was performed to immunolocalize ER, PgR, HER2 and Ki67 as described previously.[18–20] In brief, IHC staining was performed by streptavidin–biotin amplification method using a Histofine Kit (Nichirei, Tokyo, Japan). The Ki67 was stained after overnight preparation using the following antibody dilution: 1:100 (Dako). The ER, PgR and HER2 were stained automatically (Ventana, Tucson, Arizona, USA). The immunostained slides were independently evaluated by three of the authors (NC, TS, HS) who were blinded to clinical outcome of individual patients. The immunoreactivity of ER and PgR was scored by assigning proportion and intensity scores according to Allred's procedure.[18] The membrane staining pattern was estimated in HER2 immunostaining and scored on a scale of 0–3.[19] Evaluation of Ki67 was performed by counting 1000 carcinoma cells or more from each patient and the percentage of immunoreactivity was subsequently determined by a labeling index.[20]

Pre-operative endocrine prognostic index (PEPI). According to an algorithm proposed by Ellis's group, we calculated the total PEPI score for each patient. Briefly, the PEPI score is the sum of the risk points derived from the pathological T stage, pathological nodal stage, Ki67 level and ER Allred score status of the surgical specimen.[16] High PEPI scores correlate with high risk of relapse.

Statistical analysis. The target sample size of this study (110 patients) was calculated based on clinical data obtained in previous studies of aromatase inhibitors and assumptions regarding the expected number of dropouts. Tumor response was evaluated by summary statistics and calculated together with 95% confidence intervals. The distribution of adverse events was summarized and their incidence rates calculated for each grade of severity (grades 1–4). Univariate and multivariate analyses

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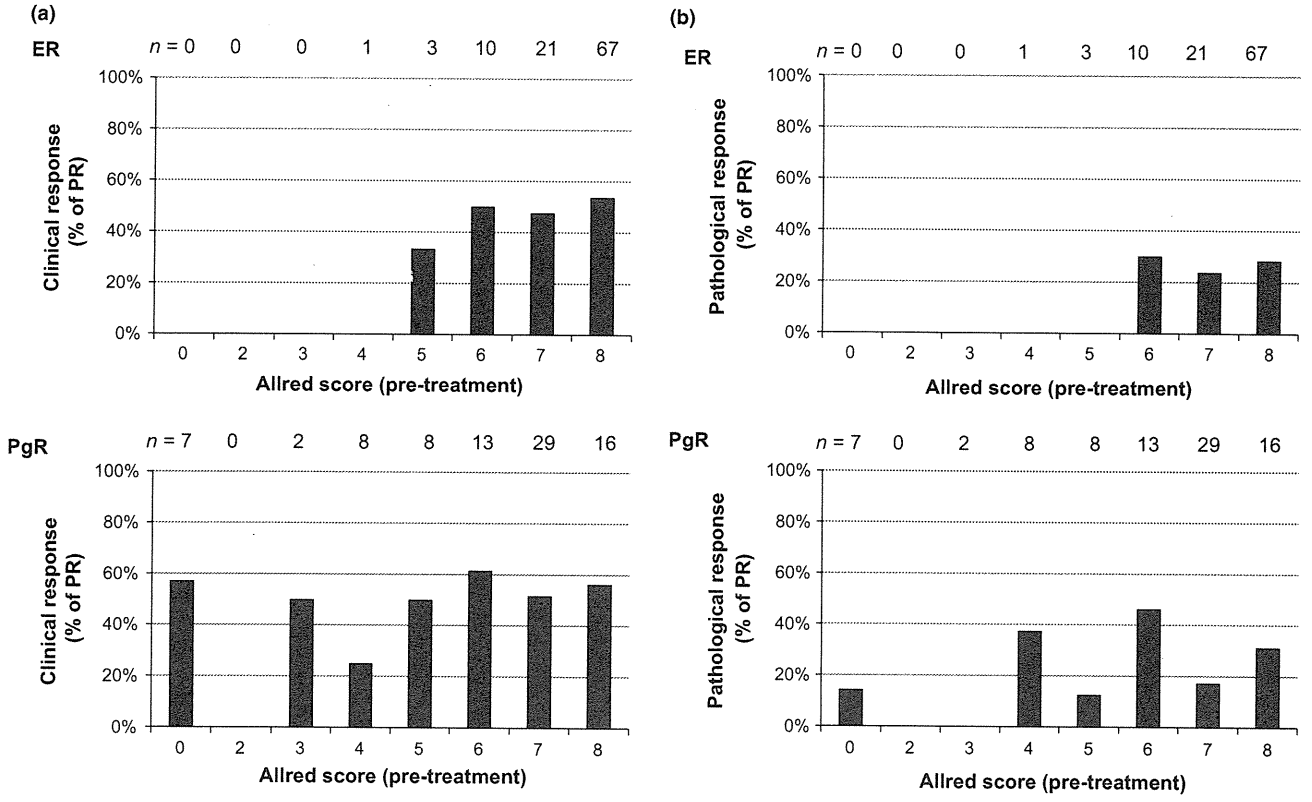

Fig. 3. (a) Clinical response rates and centrally evaluated ER and PgR Allred scores. Numbers above the graph indicate total patient counts in each Allred score group. (b) Pathological response rates and centrally evaluated ER and PgR Allred scores. Numbers above the graph indicate total patient counts in each Allred score group.

were performed with a logistic regression model, Pearson's chi-squared test and multiple logistic regression models, respectively.

Results

Patients. Between March 2006 and December 2007, 116 patients were enrolled; their baseline characteristics are displayed in Table 1. All patients were defined as ER-positive; 80 (68.9%) were PgR-positive and 3(2.5%) were HER2-positive by investigator evaluation. During the first 16 weeks, ten patients discontinued neoadjuvant exemestane treatment because of PD (four patients), investigator decision (one patient), adverse events (two patients, one of whom was not evaluable at Week 16), or the patient's decision (three patients, two of whom were not evaluable at Week 16) (Fig. 1). A total of 106 patients were included in the 8-week extension and 102 patients completed 24 weeks of exemestane neoadjuvant treatment. Of 102 patients who completed the extension study, 99 underwent surgery.

Clinical response. The clinical response was determined by the investigators evaluation based on the combination of caliper measurement and other image modalities such as ultrasound (US), computed tomography (CT) and MRI as defined by protocol. In intent to treat (ITT) analysis with 116 patients, at Week 16, 55 patients (47.4%) achieved PR and 54 patients (46.6%) showed SD. Four patients (3.4%) were considered to have PD (Table 2). The ORR at Week 24 analysis was 50.9%. In detail, no patient achieved CR, 59 (50.9%) achieved PR, 41 (35.3%) had SD and PD was noted in eight patients (6.9%), including four PD cases at Week 16. There was no significant difference in ORR between Weeks 16 and 24 (P = 0.54, McNemar's test). As a reference, ORR in patients who could complete the 24-week exemestane course was 57.8% (59/102). Although ORR at 24 weeks treatment was about 50%, most patients experienced shrinkage of the tumor with no regard to the evaluation with caliper or ultrasound as shown in the Waterfall plot analysis (Fig. 2).

Rate of conversion to breast conserving surgery (BCS). Based on assessments before neoadjuvant hormone therapy, 59 (50.9%) and 57 (49.1%) of 116 patients were indicated for total mastectomy and BCS, respectively (Table 3). At Week 24, 19 (16.4%) and 89 (76.7%) patients underwent total mastectomy and BCS, showing an increase in the rate of BCS. Of the 59 patients originally indicated for total mastectomy, 14 underwent total mastectomy, 40 were converted to BCS and five received no surgical treatment because of multiple reasons as already described. Of the 57 patients originally indicated for BCS, 49 underwent BCS, five underwent total mastectomy and three received no surgical treatment, respectively. Among five patients whose surgery were converted from BCS to mastectomy after neoadjuvant treatment, four were due to the patient's preference for mastectomy rather than BCS, and one patient showed progression of the primary tumor.

Safety. The most frequently seen adverse events were an abnormal increase in liver enzyme levels (SGOT, SGPT, ALP), hot flushes, joint pain, hypoalbuminuria and elevated creatinine and bilirubin levels. None of these adverse events was deemed to be severe in intensity. The only Grade 3 adverse events were elevated liver enzymes in four cases. No other adverse events of Grade 3 or 4 were noted in this study. Overall, two patients discontinued the study during the initial 16-week phase because

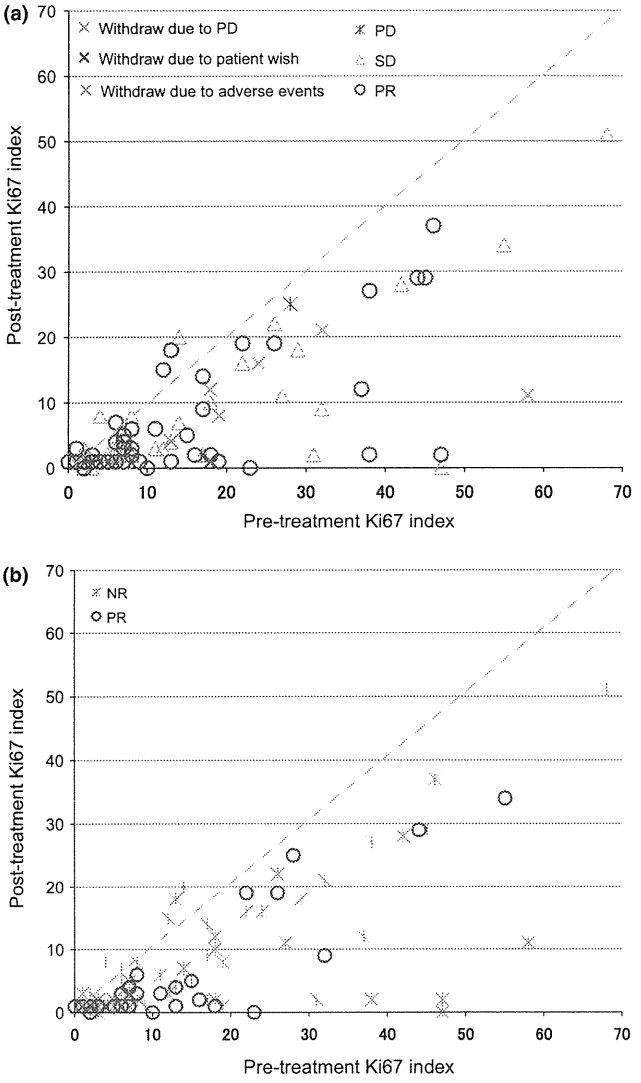

Fig. 4. (a) Correlation between pre- and post-treatment Ki67 index and clinical response. PD, progressive disease; PR, partial response; SD, stable disease (n = 93). (b) Correlation between pre-and post-treatment Ki67 index and pathological response. NR, non-response; PR, Partial response (n = 90).

of adverse events. One patient had Grade 3 AST and ALT elevations, and the other patient had Grade 2 AST and Grade 3 ALT elevations. No patient discontinued the study during the 8-week extension because of adverse events. Details are described in a Data S1.

Centrally evaluated pathological response. Tissue sections from 94 patients among 107 surgical specimens, from pretreatment core needle biopsies and final surgical specimens, were available to be assessed for changes in cellularity and degree of fibrosis in H&E stained slides. Pathological response was categorized using the modified criteria previously described by Miller *et al.*,[21] and assessed as follows: complete when there was no evidence of malignant cell at the original tumor site, partial response when histological decrement in cellularity and/or increment in fibrosis was detected, or no change/non-response. All of the pathological responders were partial response 28 cases (29.8%) while non-responders comprised 66 cases (70.2%).

Centrally evaluated ER/PgR Allred scores and Ki67 labeling index. Paraffin embedded slides for biomarker studies were submitted to the Department of Pathology, Tohoku University School of Medicine, which served as the central laboratory as described in Patients and Methods. Allred scores of ER and PgR staining before treatment (102 samples and 83 samples, respectively, were available from 116 enrolled patients) were analyzed for evaluating the correlation to clinical response. Clinical objective response was observed in patients with score 5 or greater in ER expression, and had a tendency to increase in higher score group (Fig. 3a). However, it was shown that in any PgR score patients could have a favorable clinical response.

Allred scores of ER and PgR staining of the same population were also assessed for correlation to pathological response (Fig. 3b). For ER, there was the same tendency that pathological responses were observed in higher Allred score group such as 6 or more. In PgR evaluation, there was no obvious correlation of pathological response to PgR score. Ninety-three pairs of core needle biopsies before treatment and tumor tissues after surgery were applied to Ki67 index evaluation.

Figure 4a shows the scatter plot of pre-treatment and post-treatment Ki67 indices with information of clinical response. Plots located under the curve of $y = x$ indicate the tumors that Ki67 decreased by neo-adjuvant exemestane treatment. At first, there was no correlation between the pre-treatment Ki67 index and clinical responses (PR versus others, P = 0.52). Overall, significant reduction in the Ki67 index was observed at Week 24 compared to the baseline (Median [range]: pre, 11 [0–68]; post, 3 [0–51], $P < 0.0001$, paired Student's t-test). Analysis of the Ki67 index according to clinical response revealed that the Ki67 index was significantly decreased in patients with both PR and SD ($P < 0.0001$ for both). In patients who achieved PR, the median Ki67 index decreased from 9 (range 0–47) to 2 (range 0–37) after neoadjuvant treatment with exemestane, while that in patients with SD decreased from 8 (range 1–68) to 3 (range 0–51). No association was observed between changes in Ki67 index and clinical responses. A noteworthy observation in Figure 4a was that there were no PD patients during the 24-week treatment period, if pretreatment tumor expressed a Ki67 index of 15% or less.

Correlation of Ki67 index to pathological response was also evaluated in the same manner (Fig. 4b). In patients who achieved pathological partial response (PR), the median Ki67 index decreased from 10 (range 0–55) to 2 (range 0–34) after neoadjuvant treatment, while that in patients with NR decreased from 12 (range 1–68) to 4 (range 0–51). Statistically, the Ki67 index dropped significantly in both pathological responders and non-responders ($P < 0.0001$). There was no statistical correlation between pre-treatment Ki67 index and pathological response. Nevertheless, all cases that showed increases of Ki67 index after the treatment were evaluated as pathological non-responders.

The results of univariate and multivariate analysis with respect to clinical and pathological response are summarized in Table 4. Young age, small tumor size and high ER score were associated with clinical response: PR + SD versus PD.

The relationship between the PEPI score and responses is described in Table 5. There was no correlation between PEPI score and clinical response (P = 0.99, chi-squared test). Nevertheless, a trend was found that that patients with PEPI score of 4 or more unlikely to have pathological response (P = 0.053, chi-squared test).

Discussion

The objectives of neoadjuvant hormone therapy for breast cancer are to increase the likelihood for patients to undergo

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Table 4. Univariate and multivariate analysis with respect to clinical and pathological response

(a) Outcome = clinical response (PR versus SD + PD)

Variables	Univariate analysis				Multivariate analysis (full model)				Multivariate analysis (stepwise)			
	P-value	Odds	95%CI		*P*-value	Odds	95%CI		*P*-value	Odds	95%CI	
Age	0.233	0.963	0.904	1.024	0.295	0.959	0.884	1.037	0.233	0.963	0.904	1.024
T	0.516	0.550	0.088	3.428	0.726	0.683	0.071	6.507				
N (N2–3 *vs* N0)	0.892	0.944	0.413	2.159	0.308	1.726	0.609	5.166				
ER (score)	0.356	1.253	0.777	2.071	0.269	1.360	0.790	2.422				
PR (score)	0.769	1.030	0.842	1.261	0.901	0.986	0.783	1.232				
HER2 (positive versus negative)*	0.189				0.200	5553.597	0.000	0.000				
Ki67 index	0.254	0.984	0.956	1.011	0.358	0.983	0.000	0.000				
Model *P*-value					0.617				0.233			
Model R2					0.050				0.009			

(b) Outcome = clinical response (PR + SD versus PD)

Variables	Univariate analysis				Multivariate analysis (full model)				Multivariate analysis (stepwise)			
	P-value	Odds	95%CI		*P*-value	Odds	95%CI		*P*-value	Odds	95%CI	
Age	0.067	0.900	0.794	1.007	0.227	0.903	0.741	1.063	0.072	0.867	0.717	1.012
T	0.008	0.108	0.015	0.758	0.023	0.032	0.001	0.608	0.006	0.019	0.001	0.306
N (N2–3 *vs* N0)	0.010	0.176	0.041	0.754	0.389	0.436	0.056	2.935				
ER (score)	0.024	2.227	1.117	4.558	0.009	3.318	1.339	11.136	0.002	4.046	1.674	12.841
PR (score)	0.161	1.225	0.915	1.603	0.649	1.095	0.708	1.579				
HER2 (positive versus negative)*	0.668				0.699	2242.634	0.000	0.000				
Ki67 index	0.050	0.959	0.920	1.000	0.085	0.952	0.000	0.000	0.102	0.958	0.905	1.009
Model *P*-value					0.008				0.001			
Model R2					0.367				0.353			

(c) Outcome = pathological response

Variables	Univariate analysis				Multivariate analysis (full model)				Multivariate analysis (stepwise)			
	P-value	Odds	95%CI		*P*-value	Odds	95%CI		*P*-value	Odds	95%CI	
Age	0.337	0.965	0.893	1.038	0.498	0.969	0.879	1.062				
T	0.252	0.000			0.206	0.000	0.000	3.280				
N (N2–3 *vs* N0)	0.058	0.297	0.080	1.101	0.274	0.466	0.000	0.000	0.046	0.297	0.065	0.979
ER (score)	0.329	1.325	0.767	2.545	0.282	1.453	0.000	0.000				
PR (score)	0.510	1.081	0.864	1.409	0.771	1.040	0.000	0.000				
HER2 (positive versus negative)	0.156	5.000	0.434	57.547	0.581	2.447	0.000	0.000				
Ki67 index	0.555	0.991	0.957	1.021	0.428	0.982	0.000	0.000				
Model *P*-value					0.379				0.046			
Model R2					0.087				0.035			

PR, partial response; SD, stable disease; PD, progressive disease. *All HER2 positive cases (n = 2) were PR, so that odds calculation could be unstable.

Table 5. Association between tumor response and preoperative endocrine prognostic index

Response	PEPI			*P* value (chi-squared test)
	0	1–3	4–	
Pathological responder	9	11	3	$P = 0.112$
Pathological non-responder	14	26	21	(0–3 *vs* 4–:0.053)
Clinical PR	13	22	12	$P = 0.988$
Clinical SD	10	17	10	(0–3 *vs* 4–: 0.88)

PEPI, preoperative endocrine prognostic index; PR, partial response; SD, stable disease.

BCS rather than mastectomy, and to expect benefits from a drug that is used in adjuvant therapy. With the introduction of third-generation AI such as anastrozole, exemestane and letrozole, the response rate in hormone-sensitive breast cancer patients has increased. In addition, several clinical studies have reported that neoadjuvant hormone therapy using AI improves the rate of BCS. For example, in the P024 study,[9] 4 months of neoadjuvant hormone therapy using letrozole was compared with tamoxifen in 337 postmenopausal patients with hormone receptor-positive early breast cancer. The ORR and the rate of BCS were significantly higher in the letrozole group (55% and 45%, respectively) than in the tamoxifen group (36% and 35%, respectively). Similarly, in the large-scale PROACT study, 314 patients received only neoadjuvant hormone therapy with anastrozole or tamoxifen for 3 months, and the ORR and rate of BCS were significantly higher in the anastrozole group (49.7% and 43.0%, respectively) than in the tamoxifen group (39.7% and 30.8%, respectively).[10] In the ABCSG-17 study, which used exemestane,[8] the ORR was 34% in hormone receptor-positive breast cancer patients who received 4 months of neoadjuvant treatment with exemestane, and the rate of BCS was 76%.

In the present study, the ORR for exemestane was 47.4% at Week 16 and 50.9% at Week 24 in ITT analysis, which were comparable with the results of the previous studies. Although the response rate at Week 24 was slightly higher than that at Week 16, this difference was not significant. Notably, of the 55 patients with PR at Week 16, 45 patients maintained PR at Week 24 and, of the 54 patients with SD at Week 16, 14 had PR at Week 24 and 35 had SD. These results suggest that 24 weeks of continuous treatment with exemestane induces sustained tumor regression. The response rate in patients who could complete 24 weeks of exemestane was 57.8%.

The proportion of patients suitable for BCS was 49.1% in the evaluation performed before treatment, but improved to 76.7% after 24 weeks of neoadjuvant hormone therapy. Notably, among 59 patients who are initially candidates for mastectomy, 40 patients (67.8%) could undergo BCS. This observation is almost identical to the recent phase II study in which 30 (65%) of 46 patients who were initially marginal for BCS underwent BCS after 16–24 weeks of treatment with letrozole.[22] These improvements seem to be due to universal tumor shrinkage in the majority of the patients, as shown in the Waterfall plot analysis. Toxicity was acceptable. Therefore, treatment with exemestane for 24 weeks was effective in promoting tumor regression and improving BCS rates, with an acceptable tolerability. It has also been reported that continuing letrozole in responding patients beyond 3–4 months achieves further clinical reduction in tumor size.[23] A treatment period of 24 weeks is considered to achieve the efficacy and safety levels required for neoadjuvant therapy.

The ER status is an established predictive factor for the response to endocrine therapy. In the central laboratory evaluation of ER IHC, there was a tendency for higher ER Allred scores in a tumor to correlate with preferable response both for clinical and pathological outcomes. Limitation of this finding was all patients enrolled to this study were above score 4 in the ER evaluation and 65.7% were at score 8. Progesterone receptor expression before treatment predicted neither clinical response nor pathological response. Although further studies are required with a central laboratory determination, this result indicates that tumors with lower or absent expression of PgR should not be excluded from neoadjuvant AI treatment.

The percentage of MIB1/Ki67-positive cells (Ki67 index) is considered to be a prognostic factor for breast cancer patients. In the P024 study, although no correlation was observed between the Ki67 index before neoadjuvant hormone therapy and the recurrence rate, the Ki67 index after neoadjuvant hormone therapy (at surgery) was correlated with the recurrence rate.[16] The Ki67 index and progression free survival (PFS) has also been studied in patients receiving neoadjuvant hormone therapy with anastrozole, with reported similar findings.[17] Miller *et al.*[21] evaluated 63 postmenopausal breast cancer patients after 3 months of neoadjuvant hormone therapy with letrozole and reported that the clinical response rate was 85% (41 of 48) in patients with a ≥40% decrease in the Ki67 index, and that a ≥40% decrease in Ki67 index was observed in 11 (70%) of 15 patients with SD.

In the present study, the Ki67 index decreased significantly between baseline and endpoint but the change ratio showed no significant correlation with clinical objective response. As in previous reports, the pretreatment Ki67 index had no predictive value for the probability of clinical objective response and pathological response, indicating that patients who have higher Ki67 tumors still may achieve clinical and/or pathological responses with neoadjuvant exemestane treatment. On the other hand, there were no clinical PD patients during the 24-week treatment period (patients withdraw due to PD and PD, Fig. 4a), if a primary tumor expressed a Ki67 index of 15% or less. In addition, an increase of Ki67 index after treatment, even among tumors with of Ki67 index less than 15%, meant no chance of pathological response. The prognostic impact of clinical non-responders and of pathological non-responders is not fully understood yet, and these are crucial issues to be investigated with a long-term follow-up.[24,25] In this study, a PEPI score[16] was used as a prognostic indicator, and correlation to clinical and pathological responses was investigated. The results implied that pathological non-response might correlate to the poor prognosis, which was shown as a PEPI score of 4 or higher. In future studies, the relationship between pathological response and biomarker changes will be assessed on survival outcomes.

From our investigation of the Ki67 index, monitoring of changes in Ki67 index during treatment, as well as primary treatment stratification with the initial Ki67 index, is essentially important to identify a more appropriate combination of neoadjuvant hormone therapy and chemotherapy, and also to realize the selection of an optimal regimen for each individual patient. For the future, it is warranted to analyze hormone receptor associations and crosstalks with other growth axes such as the HER family in further depth.

In conclusion, this study revealed that 24 weeks of neoadjuvant treatment with exemestane is safe and effective in patients with postmenopausal, hormone receptor-positive breast cancer, achieving ORR values of 50.9%. Furthermore, the number of patients considered candidates for BCS was increased by neoadjuvant treatment. The Ki67 index decreased significantly in patients with PR and SD after treatment. The treatment of hormone responsive breast cancer patients will be personalized with clinical and/or pathological response and biomarker determinations for greater efficacy.

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References

1 Fisher B, Bryant J, Wolmark N *et al.* Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998; **16**: 2672–85.
2 Wolmark N, Wang J, Mamounas E *et al.* Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr* 2001; (30): 96–102.
3 van der Hage JA, van de Velde CJ. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol* 2001; **19**: 4224–37.
4 Bear HD, Anderson S, Brown A *et al.* The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2003; **21**: 4165–74.
5 Bear HD, Anderson S, Smith RE *et al.* Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2006; **24**: 2019–27.
6 Guarneri V, Broglio K, Kau SW *et al.* Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. *J Clin Oncol* 2006; **24**: 1037–44.
7 Aapro M, Monfardini S, Jirillo A, Basso U. Management of primary and advanced breast cancer in older unfit patients (medical treatment). *Cancer Treat Rev* 2009; **35**: 503–8.
8 Mlineritsch B, Tausch C, Singer C *et al.* Exemestane as primary systemic treatment for hormone receptor positive post-menopausal breast cancer patients: a phase II trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG-17). *Breast Cancer Res Treat* 2008; **112**: 203–13.
9 Eiermann W, Paepke S, Appfelstaedt J *et al.* Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. *Ann Oncol* 2001; **12**: 1527–32.
10 Cataliotti L, Buzdar AU, Noguchi S *et al.* Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial. *Cancer* 2006; **106**: 2095–103.
11 Takei H, Suemasu K, Inoue K *et al.* Multicenter phase II trial of neoadjuvant exemestane for postmenopausal patients with hormone receptor-positive, operable breast cancer: Saitama Breast Cancer Clinical Study Group (SBCCSG-03). *Breast Cancer Res Treat* 2008; **107**: 87–94.
12 Semiglazov VF, Semiglazov VV, Dashyan GA *et al.* Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. *Cancer* 2007; **110**: 244–54.
13 NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. [Cited September 2010.] Available from URL: http://www.nccn.org/index.asp.
14 Barnadas A, Gil M, González S, *et al.* Exemestane as primary treatment of oestrogen receptor-positive breast cancer in postmenopausal women: a phase II trial. *Br J Cancer* 2009; **100**: 442–9.
15 Ring AE, Smith IE, Ashley S *et al.* Oestrogen receptor status, pathological complete response and prognosis in patients receiving neoadjuvant chemotherapy for early breast cancer. *Br J Cancer* 2004; **91**: 2012–7.
16 Ellis MJ, Tao Y, Luo J *et al.* Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst* 2008; **100**: 1380–8.
17 Dowsett M, Smith IE, Ebbs S *et al.* Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. *J Natl Cancer Inst* 2007; **99**: 167–70.
18 Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol* 1999; **17**: 1474–81.
19 Wolff AC, Hammond ME, Schwartz JN *et al.* American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol* 2007; **25**: 118–45.
20 Bouzubar N, Walker KJ, Griffiths K *et al.* Ki67 immunostaining in primary breast cancer: pathological and clinical associations. *Br J Cancer* 1989; **59**: 943–7.
21 Miller WR, White S, Dixon JM *et al.* Proliferation, steroid receptors and clinical/pathological response in breast cancer treated with letrozole. *Br J Cancer* 2006; **94**: 1051–6.
22 Olson JA Jr, Budd GT, Carey LA *et al.* Improved surgical outcomes for breast cancer patients receiving neoadjuvant aromatase inhibitor therapy: results from a multicenter phase II trial. *J Am Coll Surg* 2009; **208**: 906–14.
23 Dixon JM, Renshaw L, Macaskill EJ *et al.* Increase in response rate by prolonged treatment with neoadjuvant letrozole. *Breast Cancer Res Treat* 2009; **113**: 145–51.
24 Burstein HJ, Prestrud AA, Seidenfeld J *et al.* American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol* 2010; **28**: 3784–96.
25 Miller WR. Clinical, pathological, proliferative and molecular responses associated with neoadjuvant aromatase inhibitor treatment in breast cancer. *J Steroid Biochem Mol Biol* 2010; **118**: 273–6.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Adverse events (number of patients).

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Luminal A乳癌に対する術前内分泌療法

増田慎三*・山村 順*・水谷麻紀子*

abstract

閉経後Luminal A乳癌に対する術前内分泌療法はいくつかの臨床試験結果をベースに，アロマターゼ阻害剤（aromatase inhibitor：AI剤）を中心に，その概念と臨床応用が広まってきた．しかし，適正な術前の治療期間や効果判定法の適応などまだ解決すべき点は多い．また，個別化治療の実践への期待が高まってきた背景や，薬剤の治療効果は，単に癌細胞と薬剤のパワーで決まるものではなく，宿主のさまざまな健康要因が交絡していることを考えると，まさに，その術前治療の概念を上手に応用することがより最適な個別化治療法の開発の第一歩にもつながると期待できる．したがってtranslational researchを組み入れた臨床試験というプラットフォームで，経験とデータを蓄積していくことが急務である．

はじめに

乳癌治療では薬物療法を中心に，個別化治療の実践が積極的に進められている．遺伝子プロファイリングによる乳癌の分類も研究が進んでいるが，現時点では乳癌を，免疫組織学的手法により，①ホルモン感受性乳癌（エストロゲン受容体〔ER〕陽性），②HER2陽性乳癌（HER2陽性），③triple-negative乳癌（ER陰性，HER2陰性）に大別してアプローチするのが一般的である．本稿では，遺伝子プロファイリング分類によるLuminal Aタイプ乳癌とほぼ合致すると考えられるER陽性，HER2陰性乳癌における薬物療法，特に術前薬物療法の考え方を中心に概説する．

ER陽性，HER2陰性乳癌に対する薬物療法の考え方

手術可能なホルモン感受性乳癌の場合，まず根治手術を行い，その病理組織診断の結果，再発リスクが高いと判断されると，化学療法が実施され，その後，内分泌療法を実施するというのが標準的な治療である（図1）．その化学療法の選択の基準として，わが国の乳腺専門医の多くが参考にするのは，St. Gallen会議（St. Gallen international breast cancer conference. primary therapy of early breast cancer with treatment consensus update）で提唱された基準である（表1）[1]．

各項目のなかで，すべてが「内分泌療法単独の相対的適応」にあてはまれば，化学療法は絶対に不要，ひとつでも「化学・内分泌療法単独の相対的適応」にあてはまると，化学療法の実施を積極的に考慮するという基準と理解される．ただし，多くの症例が，その中間に分類され，実際の診療の場では，化学療法の選択に悩むことになる．

化学療法の選択においては，2つのポイントが考えられる．つまり，第一に，早期の再発高リスク群の選別であり，第二に，化学療法の感受性である．

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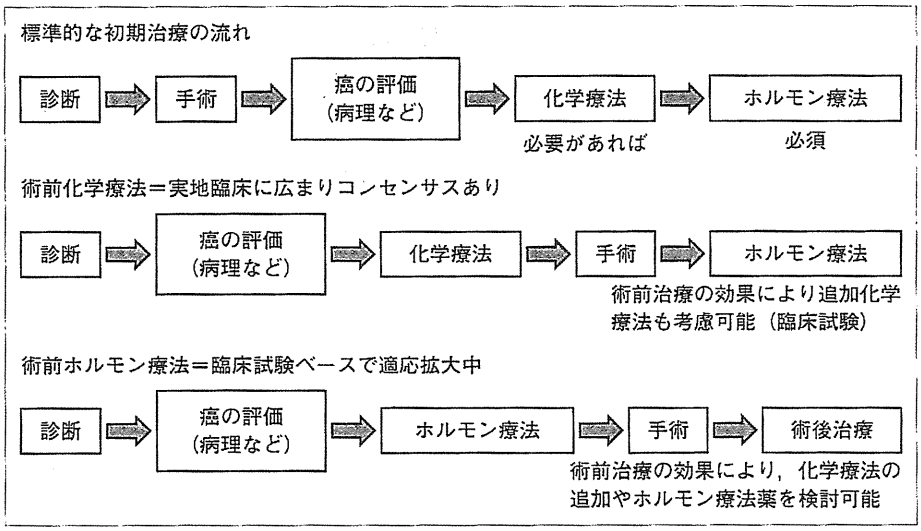

図1
Luminal A乳癌の初期治療

	化学・内分泌療法の相対的適応	決定には役立たない因子	内分泌療法単独の相対的適応
ERとPgR	より低いERとPgRレベル	—	より高いERとPgRレベル
組織学的グレード	グレード3	グレード2	グレード1
増殖マーカー	高い	中間	低い
腋窩リンパ節転移	4個以上	1〜3個	陰性
腫瘍周囲の脈管侵襲(PVI)	広汎なPVIがある	—	広汎なPVIがない
病理学的浸潤径（pT）	＞5cm	2.1〜5cm	≦2cm
患者の選好	使用可能なすべての治療を希望	—	化学療法に伴う副作用はさけたい
遺伝子シグニチャ	高スコア	中スコア	低スコア

表1
ER陽性・HER2陰性患者に対する化学療法と内分泌療法の選択基準

その観点から表1に示された，8個の判断項目を分析すると，腋窩リンパ節転移の有無，腫瘍周囲の脈管侵襲の有無，病理学的な浸潤径の3つはいわゆる癌の進行度を示し，再発リスクの予想に関係する．また一方，ER/プロゲステロン受容体（PgR）発現，組織学的グレード，Ki-67に代表される増殖マーカー，Oncotype DX®などの遺伝子シグニチャは，予後因子になると同時に，薬物療法，特に化学療法の感受性を示唆する因子である．手術後にこれらの病理組織診断の各項目のバランスを考慮して，化学療法の適応可否が決定されるが，そのなかの優先順位（重みづけ）は担当医の経験によるところが大きいのが現状であろう．

Luminal Aタイプ乳癌は，一般的には，ER陽性乳癌のなかでも，内分泌療法が優先して適応されるタイプに相当すると考えられる．その意味では，表1で化学療法感受性が高い，つまり，内分泌療法感受性が低い性質を示唆する，組織学的悪性度（histological grade：HG）＝3，Ki-67＝Highを除いたER陽性乳癌の集合におおよそ合致すると考えるのが，多くの乳腺専門医のコンセンサスであろう．病理診断基準の施設間の不安定さを指摘されることもあるが，この基準については，再現性の高い指標と考える．

内分泌療法を考えるとき，宿主の女性ホルモン環境の把握もポイントで，卵巣から女性ホルモンが供給される閉経前と，卵巣機能が終焉し，脂肪組織に存在するアロマターゼにより副腎由来の男性ホルモンが変化をうけ，女性ホルモンが供給される閉経後で使用できる薬剤は異なる．閉経前の内分泌療法の基本は，タモキシフェン（TAM）5年間に卵巣機能を抑える黄体形成ホルモン・放出ホルモン（luteinizing hormone-releasing hormone analog：LH-RH

analog）を追加するかどうかを検討する．閉経後の場合は，アロマターゼ阻害剤（aromatase inhibitor：AI剤）が第一選択で，基本は5年間，近年は再発リスクに応じて10年の長期投与も検討されている．卵巣機能は連続的に低下し消失するため，特にその閉経期の治療選択は難しくなる．

Luminal A乳癌に対する術前化学療法と術前内分泌療法

術後薬物療法から術前薬物療法の概念が浸透してきた．術前化学療法の当初の目的は，腫瘍のダウンステージングにより，局所コントロールをより安全にすることであったが，薬物療法に高感受性癌であること，また，一連の治療の流れのなかで，局所療法よりも全身療法である薬物療法のウエイトが高くなったことから，術前化学療法の目的は，腫瘍の抗癌剤感受性の把握に重点が移行した．**図1**に示すように，術後に化学療法が必要と考えられる症例に対する術前化学療法はおおよそのコンセンサスを得て，実地臨床で広く行われるようになってきた．

しかし，術前化学療法の経験から，われわれは，luminal Aタイプ乳癌の場合，臨床的な腫瘍縮小効果は十分に得られるものの，組織学的完全奏効（pathological complete response：pCR）が得られる確率は5%以下と，他のHER2タイプやtriple negativeタイプと全く異なる抗癌剤感受性を示す知見を得ている[2]．また，luminal Aタイプの乳癌薬物療法の基本は，ホルモン療法であることの再認識から，化学療法を必須としない症例における術前内分泌療法の概念が，その術前化学療法の経験から発展しいくつかの臨床試験ベースでわが国でも適応の拡大がみられる（**図1**）．その目的は，大きく2点考えられる．まず第一は，腫瘍縮小効果による乳房温存術と腋窩センチネルリンパ節生検（sentinel lymph node biopsy：SLNB）といった縮小手術であり，第二は，薬剤感受性の把握による個別化治療の実践である．日本乳癌学会編集の薬物療法ガイドライン[3]でも，閉経後患者を対象に，乳房温存手術目的での術前ホルモン療法は推奨グレードC1として実地臨床での使用は可能との判断であるが，まだまだ解決すべき課題もあり，十分な計画下で行うべき治療戦略といえる．閉経前の場合は，グレードC2で臨床試験での実施が求められている．

閉経後Luminal A乳癌に対する術前内分泌療法

閉経後のluminal A乳癌で選択されるホルモン療法剤として，TAM，AI剤（アナストロゾール：ANA，レトロゾール：LET，エキセメスタン：EXE）がありうる．薬剤開発の経緯から，TAMを標準治療として各AI剤を比較する形で臨床試験が行われ（ATAC試験：TAM vs. ANA，TEAM：TAM vs. EXE，BIG1-98：TAM vs. LET），再発抑制の予後改善の面からはTAMよりもAI剤が第一選択薬として好んで使用されるようになった．同様の比較試験は，術前治療においても報告されており，IMPACT試験[4]とPROACT試験[5]ではTAM，ANA，TAM＋ANAの比較，P024試験[6]ではTAMとLETの比較がなされ，臨床効果や乳房温存率の観点から検討されている．EXEについては大規模な比較研究がなされていないが，単アームの試験結果として，ABCSG-17試験[7]などで他のAI剤と同等の臨床効果が確認されている．わが国でも多施設共同前向き試験が実施され（JFMC34-0601），24週投与の臨床効果として54%の奏効率，76.7%の乳房温存率の成績が得られている[8]．

AI剤の3剤（ANA，LET，EXE）の比較は，術前治療としては，ACOSOG Z1031試験が行われその結果が2010年のサンアントニオ乳癌シンポジウムで報告された．臨床効果や乳房温存率の評価項目では3剤間で有意差を認めなかった．また，translational researchとして，ホルモン療法の効果と相関するとされるKi-67の低下率も，各治療群で有意差を認めなかった．術後療法における再発抑制効果の面からは，MA27試験（ANA vs. EXE）の結果も同時期に公表され，両群とも有意な差を認めなかった．今後，FACE試験（ANA vs. LET）の結果がまとまってくる見込みであるが，現在までのエビデンスから考察すると，この3剤間に特に大きな相違を見出すことは，臨床レベルでの可能性は少なく，実臨床での使い分け議論は別次元への移行が予想される．**表2**に術後ならびに術前の3剤比較試験のサマリーを記すが，Ki-67低下率の結果と術後再発抑制効果の結

術後治療	術後再発抑制効果	術前治療	臨床効果	乳房温存率	Ki-67低下率
ATAC	ANA＞TAM＝ANA＋TAM	IMPACT(3カ月)	ANA＝TAM＝ANA＋TAM	ANA＝TAM＝ANA＋TAM	ANA＞TAM＝ANA＋TAM
		PROACT(3カ月)	ANA＝TAM＝ANA＋TAM	ANA＞TAM＝ANA＋TAM	
BIG1-98	LET＞TAM	P024(4カ月)	LET＞TAM	LET＞TAM	LET＞TAM
TEAM	EXE＝TAM (→EXE switch)	ABCSG-17(4カ月)	34%	76%	—
		JFMC34(日本：6カ月)	54%	76.7%	Ki-67高値例は効果低い
MA27	EXE＝ANA	ACOSOG Z1031	EXE＝ANA＝LET(60～70%)	EXE＝ANA＝LET(60～70%)	EXE＝ANA＝LET(～80%)
FACE	LET?ANA				

表2
AI剤の比較

果とはparallelなようで，いまだ結果を得ていないFACE試験も同様の傾向かどうか興味深いところである．このことは，今後薬剤の比較を，大規模な症例数を要する術後治療のphaseではなく，術前治療のphaseで実現可能であることを示唆しており，術前薬物療法の第三の意義は，つまり，今後の新規治療法の評価が可能という点にあるかもしれない．

今後，個別化治療を展開するにあたり，適正な術前ホルモン療法の期間，客観的な効果判定法の確立など解決すべき課題は多い．

術前内分泌療法の効果判定

Luminal A乳癌の術前治療の効果判定基準が重要な課題である．一般的に，術前化学療法ではpCR(癌の完全消失）が予後予測因子になる．しかし，luminal A乳癌におけるpCR率は数%以下と非常に少なく，術前ホルモン療法でpCRはさらに期待できない．術前化学療法の効果判定基準が作成され，その予後予測因子としての有用性は認知されているが，その基準をそのまま術前ホルモン療法の効果判定に応用できるかどうか，いまだその結論は出ていない．治療有効例をgrade 1b以上とするか，grade 2以上とするかのせめぎ合いかと考える．

治療経過中の効果判定方法として，触診径，マンモグラフィやエコー，MRIやCTによる変化，PETなどの応用が検討されるが，さまざまな縮小パターンをとること，検査方法の各施設間の多様性などから客観的指標とは言い難い．今後は，腫瘍量とその機能をいかに画像診断という非侵襲的な手法で，正確に再現性をもって表現できるか期待したいところである．

P024試験（術前LET vs. TAM）の結果から，提唱された「preoperative endocrine prognostic index (PEPI) スコア」が現時点では，luminal A乳癌の術前ホルモン療法の効果基準として標準化され，今後のさまざまな検討の基本となると考えられている[9]．PEPIスコアは，治療後の腫瘍径，腋窩リンパ節転移，ER (Allred score)，Ki-67の4項目の評価から点数化され，各々，T2以下，n0，3点以上，2.7%以下の場合，0点となり，その場合，術後の再発リスクは非常に低く，予後良好であることが推測される．各因子のポイントの和で，術後経過の再発リスクを分類できる．Ki-67標識率が指数（log）で5段階に分類されており，その重要性が示唆される．

臨床試験と今後の展望

Luminal A乳癌の個別化治療を考える際，その治療効果は癌細胞と薬剤感受性のみならず宿主側の要因も交絡している複雑な系の結果であることから，「術前内分泌療法」という手段は最も適正な正攻法であると思われる．しかし，前述のように，その施行期間，効果判定基準なども確立していない状況では，臨床試験というプラットフォーム上で実際の患者に適応されるべきである．

Luminal A乳癌を大きく治療の側面から考察すると，①化学療法が必須のケース，②化学療法が必要な否か悩むケース，③化学療法は不要でホルモン療法のみで大丈夫なケースの3つに分類されよう．