Therefore, this tumor was considered negative for LOH on 16q. On the other hand, case 15 (Fig. 2) was histologically diagnosed as low-grade DCIS or intraductal papillary carcinoma in the surgically resected specimen. Figure 2b, c shows a difference in the allele 2 peak heights between the normal and tumor DNA, and the ratio of allele 2 peak height to allele 1 peak height in the tumor DNA divided by the ratio in the normal DNA was 0.18. Therefore, this tumor was considered positive for LOH on 16q.

As shown in Table 3, 6 of the 11 (55%) informative malignant tumors showed LOH on 16q, whereas LOH was not detected in benign tumors. The incidence of 16q LOH in CNB specimens of intraductal papillary tumors was significantly different between benign and malignant tumors (P=0.007). Of three malignant tumors which were negative for LOH on 16q, two were histologically diagnosed as intraductal papillary carcinoma associated with papilloma in the surgically resected specimens.

Discussion

The aim of this study was to evaluate the use of LOH on chromosome 16q to make a final diagnosis in case of an indeterminate or suspicous intraductal papillary tumor in a CNB specimen. We found a statistically significant difference in the incidence of 16q LOH between of benign and malignant intraductal papillary tumors on CNB specimens. The results of the present study suggest that analysis of LOH on 16q may be helpful for making a definitive diagnosis of an indeterminate or suspicious papillary breast lesion in CNB and surgically resected specimens.

In our previous studies, we examined LOH on 16q in intracystic papillary tumors by Southern blot analysis using frozen tissue samples [3, 5] and determined that the incidence of LOH on 16q is strikingly different between cases of DCIS and papilloma [1, 7]. In the present study, we performed PCR-based LOH analysis using DNA isolated from formalin-fixed, paraffin-embedded samples from CNB specimens of intraductal papillary tumors. Although we used a different technique and different type of samples than in previous studies, we show that the incidence of 16q LOH is significantly different between CNB specimens of benign and malignant intraductal papillary tumors.

In the present study, LOH was detected at either16q12.2 or 16q21 in 6 of 11 malignant tumors (55%), whereas LOH was not detected in histologically benign tumors. Similarly, our previous data on intracystic papillary breast tumors showed that 12 of 17 intracystic papillary adenocarcinomas (71%) had LOH on 16q, whereas none of 11 intraductal papillomas had this genetic alteration [1]. Di Cristofano et al. [5] documented LOH at locus 16q23.1–16q24.1 in 7 of 11 malignant samples (63.6%), whereas none of the four informative benign samples appeared to be altered. Taken together, LOH on 16q has high specificity and positive predictive value for the diagnosis of malignancy in intraductal papillary tumors of the breast.

None of the benign papillary lesions we examined in any of our studies, including the eight papillomas in the present study, revealed LOH on 16q. In contrast, Di Cristofano et al. [5] found LOH on 16q in benign papillary lesions, with LOH at locus 16q21.1–16q22.2 detected in both malignant and benign lesions, and at 16q23.3–16q24.1 detected only in malignant lesions. Based on these results, the authors concluded that these differences might be due to the use of the novel molecular marker D16S310 which targets 16q21.1–16q22.2, which putatively contains a tumor suppressor gene involved in the genesis/progression of breast carcinomas.

We propose that the differences between results can be explained by the cellular heterogeneity of the intraductal papillary lesions. Atypical proliferative breast lesions are thought to be precursors of breast carcinomas and have frequently been shown to have LOH on 16q [18, 19].

Table 3 Incidence of loss of heterozygosity (LOH) on 16q in core needle biopsy (CNB) specimens of papillary breast lesions

Final histological diagnosis	Number of cases (%)					P-value
	Chromosome 16q				Total	
	LOH		Constitutional heterozygosity		(Informative)	
Benign	0	(0)	8	(100)	8	0.007
Malignant	4	(57)	3	(43)	7	
Malignant (positive control)	2	(100)	0	(0)	2	

Atypical proliferative lesions and carcinomas are considered to be clones and probably originated from a field within these clones [19]. "Atypical papilloma" or "papilloma with atypia" is defined as papilloma with a proliferation of epithelial cells that have cytological and architectural features consistent with atypical ductal hyperplasia (ADH). Page et al. [15] further refined these terms and used atypical papilloma when the ADH focus involved 3 mm or less of the papillary lesion and the term minor DCIS lesion when the atypical focus involved more than 3 mm of the papillary lesion. These definitions were applied to the surgically resected specimens in the present study. In contrast, Tavassoli [20] suggested using the term atypical papilloma if the area of ADH occupies less than 33% of the papillary lesion, and the term carcinoma arising in a papilloma when the area of ADH occupies 33–90% of the papillary lesion. The ratio of atypical epithelial cells to total epithelial cells may have influenced the LOH analysis results.

Papillary lesions in CNB specimens are diagnosed as benign, atypical (indeterminate), suspicious for malignancy, or definitely malignant based on their pathologic features. Papillary lesions which are histologically diagnosed as definitely malignant must be treated as breast carcinomas. Papillary lesions with atypia, i.e., lesions that are histologically diagnosed as indeterminate or suspicious for malignancy in CNB specimens, need to be resected to determine if there is a more significant lesion [21]. Based on the results of our study, we propose that papillary lesions in CNB specimens that are histologically diagnosed as indeterminate or suspicious for malignancy and show LOH on 16q should also be treated as carcinoma. However, absence of LOH on 16q occurred in both papillomas and papillary carcinomas, and the predictive value of absence of LOH for a benign lesion was only 73%. In lesions in CNB judged as indeterminate or suspicious for malignancy, absence of LOH on 16q therefore has no diagnostic significance.

It is still controversial whether lesions diagnosed as papilloma without atypia by CNB need to be resected. From a pathological review of 19 papillary lesions with postoperative conversion from nonmalignant to malignant, Cheng et al. [22] concluded that the causes of diagnostic conversion were borderline atypical lesions (47%), sampling problems (32%), interpretation errors (16%), and an inadequate sample (5%). Based on the results of the present study, we cannot give clear guidelines for the management of papillomas without atypia based on LOH on 16q, but we consider that analysis of LOH on 16q in CNB specimens with an adequate amount of tumor tissue could reduce interpretation errors and be helpful in determining whether a papilloma without atypia needs to be resected.

The following limitations of the present study are worth discussing. First, results of analysis of LOH on 16q are not sufficiently sensitive for detection of malignancy. Absence of LOH cannot guarantee a benign lesion. Second, the number of cases examined in the present study is small. Third, we did not consider the possibility of intratumor heterogeneity, e.g., cases of carcinoma arising within papilloma. To our knowledge, this is nevertheless the first report which confirms that the incidence of LOH on 16q is significantly different between CNB specimens of benign and malignant intraductal papillary tumors. In conclusion, analysis of LOH on 16q may be helpful in making a definitive diagnosis in cases of papillary breast lesions, in both excised and CNB specimens.

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Conflict of interest The authors declare that they have no conflicts of interest.

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Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial

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Summary

Background Aromatase inhibitors have shown increased efficacy compared with tamoxifen in postmenopausal early breast cancer. We aimed to assess the efficacy and safety of anastrozole versus tamoxifen in premenopausal women receiving goserelin for early breast cancer in the neoadjuvant setting.

Methods In this phase 3, randomised, double-blind, parallel-group, multicentre study, we enrolled premenopausal women with oestrogen receptor (ER)-positive, HER2-negative, operable breast cancer with WHO performance status of 2 or lower. Patients were randomly assigned (1:1) to receive goserelin 3·6 mg/month plus either anastrozole 1 mg per day and tamoxifen placebo or tamoxifen 20 mg per day and anastrozole placebo for 24 weeks before surgery. Patients were randomised sequentially, stratified by centre, with randomisation codes. All study personnel were masked to study treatment. The primary endpoint was best overall tumour response (complete response or partial response), assessed by callipers, during the 24-week neoadjuvant treatment period for the intention-to-treat population. The primary endpoint was analysed for non-inferiority (with non-inferiority defined as the lower limit of the 95% CI for the difference in overall response rates between groups being 10% or less); in the event of non-inferiority, we assessed the superiority of the anastrozole group versus the tamoxifen group. We included all patients who received study medication at least once in the safety analysis set. We report the primary analysis; treatment will also continue in the adjuvant setting for 5 years. This trial is registered with ClinicalTrials.gov, number NCT00605267.

Findings Between Oct 2, 2007, and May 29, 2009, 204 patients were enrolled. 197 patients were randomly assigned to anastrozole (n=98) or tamoxifen (n=99), and 185 patients completed the 24-week neoadjuvant treatment period and had breast surgery (95 in the anastrazole group, 90 in the tamoxifen group). More patients in the anastrozole group had a complete or partial response than did those in the tamoxifen group during 24 weeks of neoadjuvant treatment (anastrozole 70·4% [69 of 98 patients] *vs* tamoxifen 50·5% [50 of 99 patients]; estimated difference between groups 19·9%, 95% CI 6·5–33·3; p=0·004). Two patients in the anastrozole group had treatment-related grade 3 adverse events (arthralgia and syncope) and so did one patient in the tamoxifen group (depression). One serious adverse event was reported in the anastrozole group (benign neoplasm, not related to treatment), compared with none in the tamoxifen group.

Interpretation Given its favourable risk–benefit profile, the combination of anastrozole plus goserelin could represent an alternative neoadjuvant treatment option for premenopausal women with early-stage breast cancer.

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Introduction

For premenopausal women with oestrogen receptor (ER)-positive or progesterone receptor (PgR)-positive breast cancer, treatment options include ablative surgery, radiotherapy, or cytotoxic chemotherapy. Endocrine treatments include the ER antagonist tamoxifen, and luteinising hormone releasing hormone (LHRH) agonists such as goserelin, which offer the potential for reversible ovarian ablation. Goserelin has shown efficacy for the treatment of premenopausal breast cancer, with equivalent disease-free survival to cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy in those patients with ER-positive disease.[1] Although extended goserelin treatment is associated with a known reduction in bone mineral density,[2] it offers a more favourable safety profile than does cytotoxic chemotherapy.[3] The combination of tamoxifen plus goserelin has shown improved progression-free survival compared with goserelin alone;[4] however, a report[5] suggested that the combination of tamoxifen with goserelin was not better than either drug alone (although patients also received concomitant cytotoxic chemotherapy). Present guidelines suggest that tamoxifen alone or with ovarian function suppression are standard treatment options for premenopausal women with ER-positive breast cancer.[6]

Based on the efficacy shown in postmenopausal women with early breast cancer,[7–9] aromatase inhibitors in combination with ovarian suppression are now being assessed for the treatment of premenopausal women with early-stage breast cancer.

Early clinical data in premenopausal women have suggested that the combination of anastrozole and

goserelin results in a greater reduction in mean oestradiol concentrations than does the combination of tamoxifen plus goserelin,[10] and data from the Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG-12)[11] have shown that 3-year adjuvant therapy with anastrozole plus goserelin is associated with similar disease-free survival to that associated with adjuvant tamoxifen plus goserelin therapy.[11]

The period before surgery offers an important treatment window to downstage breast tumours, which might allow for breast-conserving surgery rather than mastectomy.[12] This window provides the potential for an improved cosmetic outcome together with a reduction of surgical morbidity.[13,14] Aromatase inhibitors have shown to be effective and well tolerated neoadjuvant treatments in postmenopausal women with early breast cancer.[15] Therefore, the role of aromatase inhibitors plus goserelin for premenopausal breast cancer is of interest.

In this Study of Tamoxifen or Arimidex, combined with Goserelin acetate, to compare Efficacy and safety (STAGE), we aimed to compare anastrozole plus goserelin versus tamoxifen plus goserelin in the neoadjuvant setting (24 weeks of presurgical therapy) in premenopausal Japanese women with ER-positive early breast cancer.

Methods

Study design and patients

This phase 3, double-blind, randomised, parallel-group, multicentre study compared the efficacy and safety of anastrozole with that of tamoxifen in the neoadjuvant setting in premenopausal women with operable breast cancer receiving concomitant goserelin treatment.

We enrolled premenopausal women aged 20 years or older with ER-positive and HER2-negative breast cancer (ER-positive defined by ≥10% nuclear staining by immunohistochemistry; HER2-positive defined by immunohistochemistry 3 positivity or fluorescence in-situ hybridisation positivity, determined by each individual site) and with histologically confirmed operable and measurable lesions (T [2–5 cm], N0, M0). Locally advanced, with palpable supraclavicular nodes, or inflammatory breast cancers were deemed inoperable. Patients had to have a WHO performance status of 2 or lower. Patients were excluded if they had: necessity for concomitant chemotherapy; previous radiotherapy, chemotherapy, or hormone therapy for breast cancer; or history of systemic malignancy within 3 years. All patients provided written informed consent. The study was approved by the institutional review board for every trial centre and was done in accordance with the Declaration of Helsinki and Good Clinical Practice, the applicable local regulatory requirements, and the AstraZeneca policy on bioethics.

Randomisation and masking

Participants were enrolled by the study investigators, and eligible patients were assigned to treatment groups at random, stratified by centre, with computer-generated randomisation codes (permuted block method) that were generated sequentially at a central patient registration centre. All study personnel were masked to the randomised treatment until all data had been obtained and the primary analysis carried out. The study was of a double-dummy design, whereby the placebo tablets of anastrozole and tamoxifen were indistinguishable in their appearance and packaging from the corresponding active tablets. Breaking of the randomisation code was only to be allowed in medical emergencies that necessitated knowledge of the treatment randomisation, although this did not happen.

Procedures

Patients were randomly assigned (1:1) to receive either anastrozole 1 mg daily orally with a tamoxifen placebo plus a subcutaneous depot injection of goserelin 3·6 mg every 28 days or tamoxifen 20 mg daily orally with anastrozole placebo plus a subcutaneous injection of goserelin 3·6 mg every 28 days. Treatment continued for 24 weeks before surgery or until any criterion for discontinuation was met. Treatment will also continue in the adjuvant setting for both treatment groups for a period of 5 years.

We did tumour measurements using calliper and ultrasound every 4 weeks, and MRI or CT at day 0, week 12, and week 24. We determined objective tumour response with every measurement method and assessed according to modified Response Evaluation Criteria In Solid Tumors criteria (RECIST).[16] We measured serum concentrations of oestrone and oestradiol from blood samples taken every 4 weeks. We measured breast-tumour tissue concentrations of oestrone and oestradiol from core needle biopsy samples taken at day 0 and from samples obtained from excised tumours at surgery.

We measured bone mineral density using dual-energy X-ray absorptiometry at day 0 and at week 24 and the bone turnover markers serum bone-alkaline phosphatase (BAP) and serum crosslinked N-telopeptide of type 1 collagen (NTX) at day 0, week 12, and week 24. We identified BAP using either an enzyme immunoassay (EIA) or a chemiluminescent EIA (CLEIA). We measured NTX by EIA.

We defined histopathological response as the proportion of patients whose tumours were classified as grade 1b, 2, or 3, where grade 0 corresponds to no response; grade 1a to mild changes in cancer cells regardless of the area, or marked changes seen in less than a third of cancer cells; grade 1b to marked changes in a third or more cancer cells but less than two-thirds of cancer cells; grade 2 to marked changes in two-thirds or more of cancer cells; grade 3 to necrosis or disappearance of all cancer cells, and replacement of all cancer cells by granuloma-like or fibrous tissue, or both.[17] The pathologist at each individual site assessed histopathological effects by comparing of histopathological samples obtained at baseline and surgery.

Ki67 was stained with an antibody for MIB-1 at a central laboratory (SRL Inc, Tokyo, Japan) for assessment by a

central review board. Ki67 index was calculated as the ratio of Ki67 positive cells to total cells.

We assessed quality of life with patient-reported completion of the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire[18] (version 4), together with an Endocrine Subscale (ES) questionnaire.[19] The FACT-B endpoints assessed were the subscales of emotional wellbeing and social and family wellbeing and trial outcome index (TOI).

Adverse events were recorded at every patient visit and assessed according to Common Terminology Criteria for Adverse Events version 3.0.

The primary endpoint was best overall tumour response (complete response or partial response), assessed with calliper, during the 24-week neoadjuvant treatment period. Secondary endpoints were histopathological response, change in Ki67 expression, changes in serum and breast-tumour tissue concentrations of oestrone and oestradiol, quality of life, and tolerability.

Statistical analysis

We planned a sample size of 97 patients per group (194 in total) to show, with 80% power, the non-inferiority of anastrozole versus tamoxifen. This calculation was based on a two-sided 95% CI for the difference in tumour response between treatment groups, by use of calliper measurement, with a non-inferiority margin of 10%.

For best overall tumour response and histopathological response, we calculated the estimated difference between anastrozole and tamoxifen together with 95% CIs. Non-inferiority of anastrozole versus tamoxifen was to be concluded if the lower limit for the 95% CI was 10% or less. Superiority of anastrozole versus tamoxifen was to be assessed if non-inferiority was established. We also did an exploratory analysis of best overall tumour response using a logistic regression model, adjusted for PgR status (positive, negative), tumour grade (≤2, >2, missing, or unknown), and the longest breast tumour measurement at baseline (≤3 cm, >3 cm). We estimated the difference between treatment groups in changes from baseline in quality of life, together with 95% CI, using an analysis of covariance model, including treatment and baseline as covariates. We used SAS version 8.2 for all analyses.

We summarised Ki67 index, serum and breast tumour tissue concentrations of oestrone and oestradiol, laboratory test values, bone mineral density, and bone turnover markers using descriptive statistics. We summarised adverse events by system organ class and preferred term.

All analyses of efficacy and quality of life were based on the intention-to-treat population (all randomised patients). Where patients discontinued treatment, we used assessments up to discontinuation to determine the best overall tumour response. We included all patients who received study medication at least once in the safety analysis set.

This trial is registered with ClinicalTrials.gov, number NCT00605267.

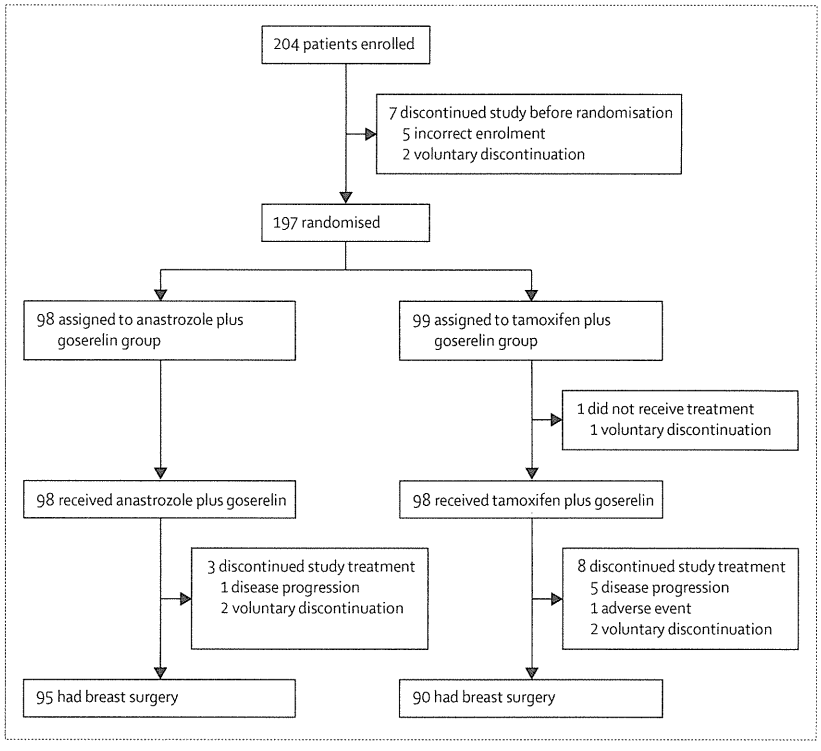

Figure: **Trial profile**

Role of the funding source

AstraZeneca employees participated in the conception and design of the study, collection and assembly of data, data analysis and interpretation, and drafting of the manuscript. All authors had full access to the study data and the corresponding author had the final responsibility to submit for publication.

Results

Between Oct 2, 2007, and May 29, 2009, at 27 centres in Japan, 197 patients were randomly assigned to receive anastrozole plus goserelin (anastrozole group, n=98) or tamoxifen plus goserelin (tamoxifen group, n=99; figure). 185 patients completed the 24-week neoadjuvant treatment period and received breast surgery (figure).

Patient demographics and baseline characteristics were generally well balanced between the treatment groups (table 1). The number of patients with tumour grade 3 was higher in the tamoxifen group than in the anastrozole group (table 1). More patients had a negative PgR status in the tamoxifen group (12 of 98 [12%]) than in the anastrozole group (5 of 98 [5%]; table 1).

Significantly more women in the anastrozole group achieved a complete or partial response (measured with callipers) than did those in the tamoxifen group from baseline to week 24 (table 2). More patients in the anastrozole group had an overall tumour response than in the tamoxifen group when response was measured by ultrasound, MRI or CT (table 2).

	Anastrozole plus goserelin (n=98)	Tamoxifen plus goserelin (n=99)
Age group at baseline (years)		
20–29	2 (2%)	0
30–39	21 (21%)	20 (20%)
40–49	65 (66%)	68 (69%)
50–59	10 (10%)	11 (11%)
Body-mass index (kg/m²)		
Mean (SD)	22·2 (3·5)	22·1 (3·3)
Body-mass index >25 kg/m²	21 (21%)	13 (13%)
Histology type		
Infiltrating ductal carcinoma	87 (89%)	91 (92%)
Infiltrating lobular carcinoma	3 (3%)	3 (3%)
Other*	8 (8%)	5 (5%)
Tumour grade		
1	42 (43%)	48 (48%)
2	36 (37%)	26 (26%)
3	4 (4%)	14 (14%)
Not assessable	1 (1%)	0
Not done	15 (15%)	11 (11%)
Longest breast tumour diameter at baseline (calliper measurement; cm)		
Mean (SD)	3·21 (0·85)	3·24 (0·97)
Median	3·00	3·00
Hormone-receptor status		
ER-positive	98 (100%)	99 (100%)
PgR-positive	93 (95%)	87 (88%)
HER2 status		
Negative	98 (100%)	99 (100%)

Data are n (%) unless otherwise stated. ER=oestrogen receptor. PgR=progesterone receptor. HER2=human epidermal growth factor receptor 2. *Including adenocarcinoma (n=3), mucinous carcinoma (n=9), and scirrhous carcinoma (n=1).

Table 1: **Patient demographics and baseline tumour characteristics**

	Anastrozole plus goserelin (n=98)	Tamoxifen plus goserelin (n=99)
Best overall tumour response		
Calliper*		
CR	12 (12·2%)	7 (7·1%)
PR	57 (58·2%)	43 (43·4%)
CR+PR	69 (70·4%)	50 (50·5%)
Ultrasound†		
CR	1 (1·0%)	0
PR	56 (57·1%)	42 (42·4%)
CR+PR	57 (58·2%)	42 (42·4%)
MRI or CT‡		
CR	2 (2·0%)	0
PR	61 (62·2%)	37 (37·4%)
CR+PR	63 (64·3%)	37 (37·4%)
Histopathological response§		
Grade 0 (no response)	12 (12·2%)	19 (19·2%)
Grade 1a (mild response)	42 (42·9%)	44 (44·4%)
Grade 1b (moderate response)	28 (28·6%)	18 (18·2%)
Grade 2 (marked response)	12 (12·2%)	9 (9·1%)
Grade 3 (complete response)	1 (1·0%)	0
Missing	3 (3·1%)	9 (9·1%)
Grade ≥1b	41 (41·8%)	27 (27·3%)

Data are n (%). CR=complete response. PR=partial response. *Estimate of difference between treatment groups 19·9% (95% CI 6·5–33·3); p=0·004. †Estimate of difference between treatment groups 15·7% (95% CI 1·9–29·5); p=0·027. ‡Estimate of difference between treatment groups 26·9% (95% CI 13·5–40·4); p=0·0002. §Estimate of difference between treatment groups 14·6% (95% CI 1·4–27·7); p=0·032. p values calculated by χ^2 test.

Table 2: **Summary of best overall tumour response and histopathological response from baseline to week 24 (intention-to-treat population)**

These differences were still apparent after adjustment for PgR status, tumour grade, and longest length of tumour measurement, irrespective of means of measurement: calliper odds ratio [OR] 2·23, 95% CI 1·22–4·06, p=0·009; ultrasound OR 1·71, 0·96–3·06, p=0·071; and MRI or CT OR 2·76, 1·52–5·03, p=0·0009.

Tumour responses increased gradually throughout the 24-week treatment period for both treatment groups (table 3). At every visit, tumour responses were higher for anastrozole versus tamoxifen with calliper measurement (table 3).

See Online for appendix

One patient (1%) showed no tumour shrinkage in the anastrozole group compared with eight (8%) in the tamoxifen group. All patients received breast surgery except those who withdrew prematurely. 84 (86%) of 98 patients in the anastrozole group had breast-conserving surgery, compared with 67 (68%) of 99 patients in the tamoxifen group.

A significantly higher proportion of patients in the anastrozole group had a histopathological response (tumours of grade 1b or higher at week 24) than in the tamoxifen group (table 2).

Mean Ki67 index at baseline was 21·9% in the anastrozole group (n=92) and 21·6% in the tamoxifen group (n=96). At week 24, Ki67 index was reduced in both treatment groups (2·9% in the anastrozole group [n=91] and 8·0% in the tamoxifen treatment group [n=87]). Reduction in Ki67 index from baseline to week 24 was significantly greater with anastrozole versus tamoxifen (estimated ratio of reduction between groups 0·35, 95% CI 0·24–0·51; p<0·0001).

Geometric mean serum concentrations of oestrone and oestradiol decreased from baseline in both treatment groups, with maximum decrease of both oestrone and oestradiol achieved in both groups by week 4; this was maintained throughout the 24-week treatment period for both oestrone and oestradiol (appendix). Reductions in concentrations of oestrone and oestradiol were significantly greater with anastrozole than with tamoxifen at week 24 (p<0·0001 for both oestrone and oestradiol). In an exploratory analysis of histopathological samples (n=13 for anastrozole and n=21 for tamoxifen), concentrations of oestrone and oestradiol in the breast tumour tissue were reduced in both treatment groups from baseline to week 24 (appendix). Oestrone suppression was greater in the anastrozole group than in the tamoxifen group (estimated ratio 0·14, 95% CI 0·06–0·31; p<0·0001), whereas

	Anastrozole plus goserelin (n=98)		Tamoxifen plus goserelin (n=99)	
	n (%)	95% CI	n (%)	95% CI
Week 4	10 (10·2%)	5·0–18·0	6 (6·1%)	2·3–12·7
Week 8	35 (35·7%)	26·3–46·0	20 (20·2%)	12·8–29·5
Week 12	49 (50·0%)	39·7–60·3	34 (34·3%)	25·1–44·6
Week 16	61 (62·2%)	51·9–71·8	47 (47·5%)	37·3–57·8
Week 20	69 (70·4%)	60·3–79·2	50 (50·5%)	40·3–60·7
Week 24	74 (75·5%)	65·8–83·6	56 (56·6%)	46·2–66·5

Where patients discontinued treatment, tumour response was considered non-response at each timepoint following discontinuation. CR=complete response. PR=partial response.

Table 3: **Tumour response rates by visit (CR+PR; intention-to-treat population)**

	Anastrozole plus goserelin (n=98)	Tamoxifen plus goserelin (n=98)
Vascular disorders	52 (53%)	53 (54%)
Hot flush	51 (52%)	51 (52%)
Musculoskeletal and connective tissue disorders	49 (50%)	29 (30%)
Arthralgia	35 (36%)	19 (19%)
Musculoskeletal stiffness	19 (19%)	9 (9%)
Joint stiffness	5 (5%)	1 (1%)
Myalgia	5 (5%)	1 (1%)
Nervous system disorders	22 (22%)	13 (13%)
Headache	10 (10%)	10 (10%)
Reproductive system and breast disorders	20 (20%)	13 (13%)
Menopausal symptoms	6 (6%)	4 (4%)
Metrorrhagia	5 (5%)	2 (2%)
Gastrointestinal disorders	9 (9%)	14 (14%)
Constipation	3 (3%)	10 (10%)
General disorders and administration site conditions	9 (9%)	14 (14%)
Fatigue	3 (3%)	5 (5%)
Psychiatric disorders	9 (9%)	10 (10%)
Insomnia	6 (6%)	6 (6%)
Skin and subcutaneous tissue disorders	8 (8%)	11 (11%)
Hyperhidrosis	4 (4%)	8 (8%)

Data are n (%). System organ class or preferred term.

Table 4: **Treatment-related adverse events occurring in at least 5% of patients (safety-analysis-set population)**

oestradiol suppression did not differ between groups (estimated ratio 0·63, 95% CI 0·26–1·54; p=0·301).

In both treatment groups, the ES and FACT-B TOI scores decreased slightly from baseline at week 12 and week 24. Mean ES score decreased from 64·7 at baseline to 55·5 at week 24 in the anastrozole group and from 63·4 at baseline to 57·1 at week 24 in the tamoxifen group. The FACT-B TOI mean score decreased from 69·6 at baseline to 64·9 at week 24 in the anastrozole group and from 68·8 at baseline to 66·2 at week 24 in the tamoxifen group. Although the study was not specifically powered to detect a difference in the quality-of-life outcome measures, groups did not differ significantly (estimated difference for anastrozole–tamoxifen; ES subscale −2·14, 95% CI −4·58 to 0·29, p=0·084; FACT-B TOI −1·52, −4·02 to 0·98, p=0·231). No significant changes from baseline to week 24 were observed for the subscales of emotional wellbeing and social and family wellbeing in either treatment group.

Adverse events were reported by 87 (89%) of 98 anastrozole-treated patients and 84 (86%) of 98 tamoxifen-treated patients. Treatment-related adverse events were reported by 82 (84%) patients in the anastrozole group and 75 (77%) patients in the tamoxifen group. Table 4 shows the most common treatment-related adverse events.

Most adverse events were mild or moderate (grade 1 or 2). Treatment-related grade 3 adverse events were reported in two patients in the anastrozole group (arthralgia and syncope) and one patient in the tamoxifen group (depression). No events at grade 4 were recorded. One serious adverse event was reported in the anastrozole group (grade 3 incidence of benign neoplasm), which was not considered related to treatment. No serious adverse events were reported in the tamoxifen group. One patient in the tamoxifen group discontinued treatment because of a grade 1 adverse event (liver disorder), which was considered related to treatment.

Mean bone mineral density at lumbar spine decreased by 5·8% in the anastrozole group and by 2·9% in the tamoxifen group, and mean bone mineral density at cervical thighbone decreased by 2·5% in the anastrozole group and by 0·8% in the tamoxifen group. The reduction in bone mineral density was significantly greater in the anastrozole group at lumbar spine (p<0·0001) and cervical thighbone (p=0·0045) than in the tamoxifen group. Bone turnover marker BAP increased slightly in the anastrozole group (EIA method [n=66], mean 20·97 to 28·11 U/L; CLEIA method [n=32], 10·98 to 16·58 µg/L), whereas no change was recorded in the tamoxifen group. Bone turnover marker NTX increased numerically in both treatment groups (anastrozole mean 13·22 to 22·43 nmol BCE/L [bone collagen equivalents per L of serum]; tamoxifen 12·66 to 14·99 nmol BCE/L).

No clinically important changes in laboratory parameters or vital signs were recorded. Treatment compliance for the tablet medication, measured by confirmed tablet counting, was 98·9% for the anastrozole group and 99·3% for the tamoxifen group.

Discussion

During 24 weeks of neoadjuvant treatment, a greater proportion of premenopausal women with ER-positive, HER2-negative breast cancer who received anastrozole plus goserelin showed a tumour response benefit than did those who received tamoxifen plus goserelin. Further, a higher proportion of patients in the anastrozole group

Panel: Research in context

Systematic review

We searched PubMed and ClinicalTrials.gov with the search terms "aromatase inhibitor", "goserelin", "premenopausal", and "neoadjuvant", to identify all studies and publications to July, 2007. We did not find any randomised trials and, therefore, we identified the need for a new study comparing an aromatase inhibitor with tamoxifen in the neoadjuvant treatment setting for premenopausal breast cancer.

Subsequently, we have identified studies investigating the use of aromatase inhibitors in premenopausal breast cancer, including a single-arm, phase 2 study of anastrozole plus goserelin in premenopausal advanced breast cancer,[31] which reported a clinical benefit rate (partial response plus complete response plus stable disease ≥6 months) of 71·9%. Additionally, we identified a non-randomised study[32] that suggested that concomitant goserelin plus letrozole together with presurgical chemotherapy was effective in premenopausal women with locally advanced breast cancer in terms of improved disease-free survival. Results from a phase 3 study (ABCSG-12),[11] comparing anastrozole plus goserelin with tamoxifen plus goserelin in the adjuvant setting in premenopausal women, showed disease-free survival rates to be similar between the treatment groups. A recent analysis of ABCSG-12[24] suggests that body-mass index significantly affects the efficacy of anastrozole plus goserelin in premenopausal patients with breast cancer. Given the available evidence at the time, we decided to undertake this randomised phase 3 trial to compare an aromatase inhibitor with tamoxifen in the neoadjuvant treatment setting for premenopausal breast cancer.

Interpretation

To our knowledge, our results have shown for the first time that neoadjuvant treatment with anastrozole plus goserelin has a better risk-benefit profile than does tamoxifen plus goserelin as neoadjuvant treatment for premenopausal women with early-stage breast cancer. As such, this combination could represent an alternative neoadjuvant treatment option for premenopausal women with early-stage breast cancer.

than in the tamoxifen group received breast-conserving surgery. These data suggest that anastrozole plus goserelin is an effective neoadjuvant treatment option in this patient population, and might enable tumour downstaging to allow for breast-conserving surgery.

A favourable response to neoadjuvant therapy usually translates into a better clinical prognosis.[20] In the ABCSG-12 study,[11] which compared anastrozole plus goserelin with tamoxifen plus goserelin in the adjuvant setting in premenopausal women, disease-free survival rates were similar between the treatment groups. It might be expected that the greater efficacy in the anastrozole group in the neoadjuvant setting noted in this present study would translate to improved disease-free survival compared with the tamoxifen group with continued treatment in the adjuvant setting.

This study recruited only patients with ER-positive and HER2-negative tumours. Our own experience, together with data from other studies, has shown ER-positive and HER2-negative tumours to be more hormone dependent and therefore more responsive to endocrine therapy than ER-positive and HER2-positive tumours.[21]

Although similar disease-free survival rates were reported between the groups in the ABCSG-12 study,[11] a strong trend was noted for improved overall survival in the tamoxifen group compared with the anastrozole group. Although the precise reason for improved overall survival in favour of tamoxifen is unclear, it was speculated that the absence of palliative treatment with aromatase inhibitors in the anastrozole group after relapse could affect overall survival.[22,23]

Interestingly, a retrospective analysis of the ABCSG-12 data[24] reported that the better overall survival for tamoxifen plus goserelin than for anastrozole plus goserelin was only noted in a subset of patients with body-mass index (BMI) higher than 25 kg/m², but not in those patients with BMI lower than 25 kg/m².[24] Similarly, obese women (BMI >30 kg/m²) treated with anastrozole in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial[25] were associated with poorer overall prognosis than were women with BMI lower than 23 kg/m². The proportion of women with BMI higher than 25 kg/m² was lower in the STAGE study (34 [17·3%] of 197 women) than in the ABCSG-12 study (573 [33·0%] of 1736 women),[24] which might also partly explain the better efficacy for anastrozole than for tamoxifen in STAGE.

The optimum duration of neoadjuvant hormone therapy has yet to be fully elucidated. We report an increase in tumour responses from week 16 to week 24 of 13·3% in the anastrozole group and 9·1% in the tamoxifen groups. As a result, although we have shown that treatment duration of 24 weeks was preferable over 16 weeks, it is possible that the optimum treatment duration may even be greater than 24 weeks. These results correspond to those reported by Dixon and colleagues,[26] in which clinical response was greater with extended neoadjuvant letrozole treatment beyond 3 months, than with a shorter treatment duration.

The clinical response during the 24-week treatment period of 70% achieved by the anastrozole group in our study seems similar to the clinical response rate of 66% achieved with chemotherapy in a similar patient population in a previous study,[27] but a definitive randomised trial that compares neoadjuvant endocrine therapy with chemotherapy has yet to be reported.[28] Although clinical response might not be consistent with the pathological response,[29] and it is possible that pathological responses might ultimately be higher with chemotherapy, anastrozole plus goserelin might offer a treatment option for patients with large ER-positive and HER2-negative tumours for which downstaging could allow breast-conserving surgery.

A possible limitation of this study is that, although a higher proportion of patients in the anastrozole group received breast-conserving surgery, a prediction of the expected method of surgery was not done at baseline, which would be necessary for a meaningful comparison between best overall tumour response and the actual surgical method used. With only two treatment groups, the effect of the individual treatments (anastrozole, tamoxifen, or goserelin) used in the study could not be

determined. Definitive results are also unlikely to be shown for long-term outcomes because of the small sample size.

Reduction in Ki67 index was significantly greater with anastrozole than with tamoxifen treatment, consistent with results observed in the IMmediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial.[21] The relation between reduction in Ki67 index in the IMPACT trial correlated with the long-term outcome of improved disease-free survival for anastrozole versus tamoxifen in the adjuvant ATAC trial.[25] However, the tumour response rates under neoadjuvant treatment did not seem to predict for long-term outcome with adjuvant therapy.[23]

Both treatment regimens were well tolerated during the 24-week neoadjuvant treatment period, consistent with the known safety profile of the individual treatments. The incidence of hot flushes reported here was higher than that reported for any of the drugs as monotherapy.[23] However, as hot flushes are a known side-effect of all three drugs, an additive effect of combination therapy cannot be discounted. An exploratory analysis showed that no significant relation existed between those patients who responded to treatment and those patients who had hot flushes in both treatment groups (data not shown). Consistent with the known safety profiles of each treatment, musculoskeletal disorders seemed higher with anastrozole than with tamoxifen treatment.[30] Although this was a short-term study, results of bone mineral density and bone turnover markers BAP and NTX seem consistent with the known safety profile of anastrozole.

In conclusion, results from this study have, to the best of our knowledge (panel), shown for the first time that neoadjuvant treatment with anastrozole plus goserelin has a better risk–benefit profile than tamoxifen plus goserelin as neoadjuvant treatment for premenopausal women with early-stage breast cancer.

Contributors

NM, YS, TK, HIwat, SNa, YY, RN, HIwas, SK, and HT contributed to provision of study patients, data collection, data interpretation, and writing. SNo contributed to study design, data interpretation, and writing. All authors critically reviewed the draft manuscript and approved the final report.

Conflicts of interest

HIwas has received honoraria from AstraZeneca and Pfizer. SNo has received honoraria, consultancy fees, and research funding from AstraZeneca. The other authors declare that they have no conflicts of interest.

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Current Organ Topics:

Breast and Endocrine Tumor
乳腺・内分泌腫瘍

Ⅱ．術前ホルモン療法の現状と課題

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はじめに

術前薬物療法は歴史的には原発巣の切除が不能な局所進行乳癌の治療として行われてきた。術前化学療法では生存率，無再発生存率は術後化学療法と同等であるが，病理学的完全奏効（pathological complete response: pCR）は予後と相関する生存率の代替指標 surrogate marker であり乳房温存率を高めることと，薬剤感受性を早く知ることができるという利点がある[1]。一方，術前ホルモン療法は，高齢者や合併症を有するような患者で，術前化学療法を施行することができない症例を適応としてきた。術後治療におけるタモキシフェンやアロマターゼ阻害（AI）剤のエビデンスが蓄積されるのに伴い，より早期のホルモン受容体陽性乳癌に対する術前ホルモン療法も治療戦略として検討されるようになった。さらには術前化学療法における surrogate marker とされる pCR 率はホルモン受容体陽性乳癌では高くなく，必ずしも予後と相関する surrogate marker とならないという事実も後押ししている。

ホルモン療法の術後治療における至適投与期間は5年から，最近ではさらに長期にわたる。治療効果のある患者にとっては副作用の程度が軽い・よい治療といえるが，効果のない患者にとっては長期にわたるただの毒である。短期間で治療が終了し pCR を surrogate marker とする術前化学療法のコンセプトと異なり，術前ホルモン療法は長期間のホルモン療法の妥当性を判定するための治療とも位置付けられる。

最近では，遺伝子マーカーなどの生物学的指標を組み合わせて，化学療法の適否の決定をしたり，術前ホルモン療法の新たな surrogate marker の開発などさらなる治療の個別化が進んでいる。本稿では，これまでの術前ホルモン療法を検討した臨床試験を概説し，今後の課題について述べる。

1．閉経後乳癌に対する術前ホルモン療法

1）タモキシフェンを用いた術前ホルモン療法

タモキシフェンによる術前療法の奏効率は約40%である。手術や化学療法といった侵襲性の強い治療を行うのが困難な高齢者や合併症を有する患者を対象に術前タモキシフェン療法の研究が行われた。75歳以上，もしくは75歳未満で合併症を有する閉経後乳癌患者47名に対して，タモキシフェン20 mg/日を3〜6か月内服させ，その後手術を施行し，術後もタモキシフェンを5年間内服する臨床試験が行われた。タモキシフェンの奏効率は47%であり，pCR は6%であった。乳房温存率は11%（5人）で，2年，5年生存率はそれぞれ83，59%であった[2]。また，術前療法ではないが70歳以上の閉経後乳癌患者に対して，タモキシフェン5年間内服のみ手術（−）群と手術施行後5年間タモキシフェンを内服する群を比較したランダム化試験（GRETA trial）が行われた。タモキシフェン内服により臨床的完全奏効率（cCR）9.2%，奏効率41.6%であった。また，局所制御に関しては手術群のほうが優れていたものの，全生存率に関しては両群間で差は認めなかった[3]。この結果，特定の対照群においては術前タモキシフェン療法が有効である可能性が示唆された。

2）AI剤を用いた術前ホルモン療法

進行再発例や術後補助療法におけるタモキシフェンと第三世代 AI 剤とを比較した複数のランダム化比較試験の結果では AI 剤の有効性が示されている。閉経後ホルモン受容体陽性乳癌患者を対象に術前ホルモン療法として AI 剤とタモキシフェンを比較する臨床試験が実施された（表1）。代表的なものに，letrozole P024 trial，Immediate Preoperative Anastrozole, Tamoxifen or Combined with Tamoxifen（IMPACT）trial，Preoperative 'Arimidex' Compared to Tamoxifen（PROACT）trial がある。

letrozole P024 trial では，ホルモン受容体陽性閉経後乳癌患者に対し，レトロゾール2.5 mg を術前4か月内服する群と，タモキシフェン20 mg を術前4か月内服する群とのランダム化比較試験が行われた[4]。奏効率は55 vs 36%（$p<0.001$）とレトロゾールのほうが優れ，また乳房温存率も45 vs 35%とレトロゾール群のほうが優れていた。また，有害事象には差を認めなかった。

IMPACT trial ではアナストロゾール1 mg を術前3か月内服する群，タモキシフェン20 mg を術前3か月内

表 1 閉経後乳癌に対する術前ホルモン療法のランダム化第Ⅲ相試験

臨床試験	GRETA	Letrozole P024	IMPACT	PROACT
患者数	239	337	330	451
ホルモン受容体陽性の定義	なし	ER/PgR 染色 >10%	ER 染色 >1%	ER+/PgR+
治療	・タモキシフェン（T）day 1 に loading dose として 160 mg，その後手術を行わず 20 mg/日 5 年間内服 ・手術施行後タモキシフェン 5 年間内服（S+T）	・レトロゾール（L）2.5 mg/日 ・タモキシフェン（T）20 mg/日	・アナストロゾール（A）1 mg/日 ・タモキシフェン（T）20 mg/日 ・A+T	・アナストロゾール（A）1 mg/日 ・タモキシフェン（T）20 mg/日
治療期間	5 年	4 か月	12 週	3 か月
化学療法併用の有無	なし	なし	なし	あり
プライマリーエンドポイント	全生存期間	奏効率 触診で計測	奏効率 触診で計測	奏効率 超音波で計測
奏効割合	41.6%（T）	55%（L）vs 36%（T） p<0.001	37%（A）vs 36%（T）vs 39%（A+T） NS	39.5%（A）vs 35.4%（T） NS
乳房温存術施行割合	—	45%（L）vs 35%（T） p=0.022	44%（A）vs 31%（T）vs 24%（A+T） NS	43.0%（A）vs 30.8%（T） p=0.04
中央生存期間	71.2 か月（T）vs 70.9 か月（S+T） NS	—	—	—

（腫瘍内科第 7 巻 4 号，p318 を改編）

服する群，アナストロゾールとタモキシフェンを併用する群の 3 群におけるランダム化比較試験が行われた[5]。奏効率に差を認めず（36 vs 37 vs 39%），乳房温存率にも差を認めなかったが，HER2 陽性群においてアナストロゾールの奏効率が高い傾向にあった（58 vs 22 vs 31%）。さらに，有害事象はアナストロゾール単独群において最も軽度であった。

PROACT trial では，アナストロゾール 1 mg を術前 3 か月内服する群とタモキシフェン 20 mg を術前 3 か月内服する群のランダム化比較試験が行われた[6]。奏効率に差を認めず（39.5 vs 35.4%），有害事象発現率においても差を認めなかった。

これらの結果から，術前ホルモン療法として AI 剤はタモキシフェンと同等かそれ以上の臨床効果があると評価された。引き続き American College of Surgeons Oncology Group（ACOSOG）は，エキセメスタン，レトロゾール，アナストロゾールの 3 剤の術前ホルモン療法のランダム化比較試験を行い，2011 年の ASCO annual meeting において ACOSOG Z1031 の結果を発表した[7]。ステージⅡ/Ⅲのエストロゲン受容体陽性閉経後乳癌患者を対象とし，エキセメスタン 25 mg，レトロゾール 2.5 mg，またはアナストロゾール 1 mg を術前 16 週投与する 3 群に割り付けたランダム化比較試験である。377 名が登録され，奏効率はエキセメスタン，レトロゾール，アナストロゾールそれぞれ 60.5, 70.9, 62.2%であった。統計的には有意差はないものの，非ステロイド AI 剤が術前ホルモン療法として有望であるとの結果であった。

3）術前化学療法と術前ホルモン療法の比較

手術可能乳癌に対してもいくつかのエビデンスから術前化学療法は標準治療法として位置付けられるようになってきたが，ホルモン受容体陽性乳癌においては，術前化学療法により pCR となる患者の割合が低く，化学療法の効果が限定的であることが明らかになってきた。MD アンダーソンがんセンターでの検討では，術前化学療法後の pCR 率がホルモン受容体陰性乳癌患者では 24%であったのに対し，陽性乳癌患者では 8%であった[8]。これらの臨床的背景から，ホルモン受容体陽性乳癌患者に対する術前化学療法と術前ホルモン療法を比較した臨床試験が行われた。Semiglazov らはエキセメスタン 25 mg またはアナストロゾール 1 mg を術前ホルモン療法として 3 か月間投与する群とドキソルビシン 60 mg/m^2，パクリタキセル 200 mg/m^{2}を 3 週ごとに 4 サイクル投与する群のランダム化比較第Ⅱ相試験を行った[9]。臨床的奏効率はいずれも 64%で同等で，pCR は 3, 6%であった。乳房温存率は 33, 24%とホルモン療法群で高い傾向があり，副作用の頻度に関してもホルモン療法が軽度であった。これらの結果より，閉経後ホルモン

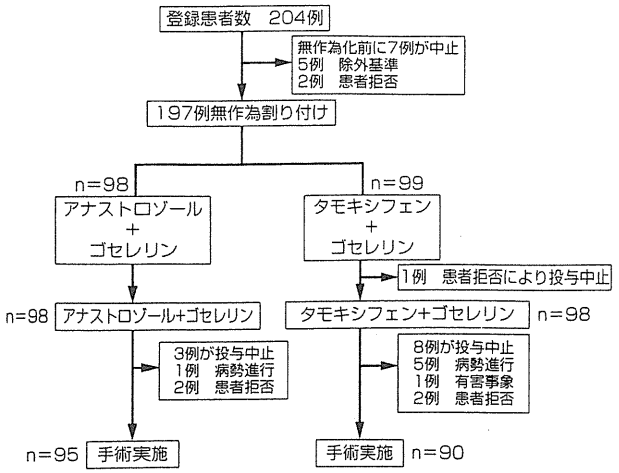

図 1　STAGE 試験　試験デザイン
（Masuda N: *Lancet Oncol* **13** (4): 345-352, 2012. p347 より改編）

受容体陽性乳癌患者に対する術前化学療法のメリットは術前ホルモン治療と比較して相対的に少ない可能性が示唆された。

2．閉経前乳癌に対する術前ホルモン療法

エストロゲン受容体陽性 HER2 陰性閉経前乳癌患者に対して，術前，術後ホルモン療法として LHRH アナログであるゴセレリンにタモキシフェンまたはアナストロゾールを加えた 2 群を比較した第Ⅲ相比較試験である Study of Tamoxifen or Arimidex given with Goserelin to compare Efficacy and Safety（STAGE trial）（図 1）の術前療法の結果が 2012 年に論文化された[10]。国内より 197 人が参加し，ゾラデックス® 3.6 mg を月 1 回投与しアナストロゾール 1 mg を 24 週投与する群（A+G 群，98 人）とゾラデックス® 3.6 mg を月 1 回投与しタモキシフェン 20 mg を 24 週投与する群（A+T 群，99 人）に割り付けられた。その結果，奏効率が触診で A+G 群，T+G 群それぞれ 70.4（うち CR が 12.2）%，50.5（うち CR が 7.1）%，超音波検査では A+G 群，T+G 群それぞれ 58.1（うち CR が 1）%，42.4（うち CR が 0）%，MRI/CT 検査では 64.4（うち CR が 2）%，37.4（うち CR が 0）%といずれの評価方法でも A+G 群が優れていた。病理学組織学的評価ではグレード 2 以上の効果が A+G 群，T+G 群それぞれ 13.2%（グレード 3 が 1 例），9.1%（グレード 3 が 0 例）であった。乳房温存率は A+G 群，T+G 群それぞれ 85.7，67.7%であった。A+G 群で関節症状や筋骨格痛などがより高頻度にみられたが，両群ともに副作用は軽微であった。この結果より閉経前ホルモン受容体陽性乳癌患者に対してもゾラデックス® 3.6 mg を月 1 回投与しアナストロゾール 1 mg を 24 週投与する A+G 療法は短期間で腫瘍縮小効果が達成可能であるため術前化学療法に代わるオプションになり得ることが実証された。

表 2　術前内分泌療法予後インデックス（PEPI）

組織，バイオマーカー	無再発生存割合		乳癌死亡率	
	HR	Points	HR	Points
腫瘍径				
T1/2	—	0	—	0
T3/4	2.8	3	4.4	3
腋窩リンパ節転移				
陰性	—	0	—	0
陽性	3.2	3	3.9	3
Ki67 レベル				
0～2.7%	—	0	—	0
>2.7～7.3%	1.3	1	1.4	1
>7.3～19.7%	1.7	1	2.0	2
>19.7～53.1%	2.2	2	2.7	3
>53.1%	2.9	3	3.8	3
ER（Allred score）				
0～2	2.8	3	7.0	3
3～8	—	0	—	0

PEPI: preoperative endocrine prognostic index, HR: hazard ratio, ER: estrogen receptor
（腫瘍内科第 7 巻 4 号，p320 を改編）

3．術前ホルモン療法の予後予測因子と治療効果予測因子

術前ホルモン療法の効果判定には術前化学療法と異なり pCR 率が非常に低いため，乳房温存率の向上に病理学的効果判定を加えた総合的評価が用いられる。これらでは不十分であるため新たな効果指標としての予後因子が必要となっている。Dowsett らは術前ホルモン療法開始 2 週間後の針生検で Ki67 発現の減少率が治療効果や予後予測の surrogate marker であると報告している[11]。Ellis らは P024 試験の解析より，術前ホルモン療法後の組織学的腫瘍径，腋窩リンパ節転移の有無，Ki67 labeling index，ER Allred score が予後因子であると報告した[12]。これらを用いて術前ホルモン療法後予後予測（preoperative endocrine prognostic index: PEPI）スコア（表 2）を作成した[12]。PEPI スコアが低い（0.1）場合には予後良好で，化学療法の追加が不要であると示された。

おわりに

術前ホルモン療法において未解決の課題として，再発のリスクが高い場合に，術前ホルモン療法が著効した場合でも化学療法を省略できないのか，またその至適投与期間の不明である。術前ホルモン療法と予後を比較した試験もない。予後予測因子の surrogate marker を評価するためであれば投与期間は数週間でよいかもしれないし，乳房温存率向上など術前の臨床的効果をめざすのであればより長い投与期間は必要であろう。単に乳房温存率の向上ばかりでなく術前ホルモン療法から得られる新

たな情報によりホルモン高感受性乳癌に対する化学療法の省略の可能性が高まることが期待される。

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乳癌の検査・診断
乳癌の病理検査・診断

非浸潤性小葉癌(LCIS)の治療方針

Management for treatment of lobular carcinoma *in situ* (LCIS)

垂野香苗　　木下貴之

Key words：LCIS，非浸潤性小葉癌

はじめに

非浸潤性小葉癌(LCIS)は，終末乳管小葉単位(TDLU)に発生する非浸潤性腫瘍であり，全乳癌の1-4％を占める．LCISは壊死性病変を伴わないかぎりそれ単独で画像上異常を示すことは少なく，他病変手術時に偶発的に合併が発見されることが多い[1]．近年は，検診で発見されるLCISが増え，その治療方針に関して問題になることが増えてきている．LCISそれ自体が治療対象となる症例も増加してきている．

1 LCISの臨床

これまでLCISは，それ自体が治療対象となることが少なく，正確な発症率は不明である．画像診断や生検の精度が向上し，近年その発見の頻度は増加している．The SEER databaseによると，3.19人/100,000人の女性に発症するといわれている[2]．日本乳癌学会の全国乳がん患者登録調査2008年度確定版によると，全乳がん患者30,297例中，LCISは66例(0.2％)にすぎない．また，他の報告によると，LCISは切除生検のうちの0.3-3.8％，針生検のうちの0.02-3.3％に存在するといわれている[3]．更に，手術検体のうちの約5％にLCISが併存するといわれている[4]．以前は，LCISはそれ自体が浸潤癌の前駆状態ではなく，LCISが存在すること自体が両側乳房に浸潤癌が発症するリスクといわれて，乳房全摘が施行されることが多かった．National Adjuvant Breast and Bowel Project(NSABP)の調査では，LCISの約10％が12年以内に浸潤癌を発症するとある．LCISが存在した場合の浸潤性乳癌の発症の累積リスクは，同側乳房で18％，対側乳房で14％であり，偶然にLCISが発見された場合，近年は全摘ではなく，慎重な経過観察が基本方針となっている[5]．

2 LCISの病理

LCISは，TDLUに発生する非浸潤性腫瘍である．病理組織学的には，腫瘍細胞間接着性が緩く，pagetoid spreadが特徴である．また，免疫染色にてE-カドヘリン染色が陰性であることも特徴である．LCISは，古典型(classical LCIS, type A)と多形型(pleomorphic LCIS, type B)のサブタイプに分けられる(**表1**)．古典型は，核が小型，類円形で異型に乏しく，核小体を認めず，細胞質の乏しい細胞が特徴である(**図1**)．多形型は，細胞質が広く核は多形的，時に核小

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表1 LCIS古典型，多形型の特徴的所見と比較

	古典型 classical LCIS，type A	多形型 pleomorphic LCIS，type B
細胞の特徴	小型，類円形．異型に乏しい	細胞質が広い．核は多形的核小体を認める
形態的特徴	clover leaf pattern	壊死型，アポクリン型，印環細胞型
免疫組織学的特徴	ER，PR陽性，HER-2陰性が多い	ER，PR陰性，HER-2陽性が多い
マンモグラフィで石灰化	認めない	伴うことあり

体を認める，より異型の強い細胞で形成されるのが特徴であり，より悪性度が高い（図2）．多形型LCISには，壊死型，アポクリン型，印環細胞型があり，非浸潤性乳管癌（DCIS）に近い所見である．多形型LCISは，生物学的挙動もDCISとほぼ同じ特徴を示すといわれ，その取扱いについては，今後の検討が必要である[6]．古典型，多形型では免疫組織学的特徴も異なる．古典型は典型的には，ER，PR陽性，HER-2陰性が多く，多形型は，ER，PR陰性，HER-2陽性が多いことが特徴である．

LCISの診断

LCISに特徴的な典型的臨床所見はない．多形型LCISの場合石灰化を伴うことがあり，その際はマンモグラフィにて，微小石灰化として認識される．また，そのほかにも，その形態によって，腫瘤形成やdistortionなど様々な所見を呈するが，LCISに特異的な画像所見はない．何らかの異常所見を認めた場合，通常針生検にて診断を行うことが多い．針生検にてLCISの診断となった病変のうち27％が，のちの切開生検にて浸潤癌などの悪性病変を認めることが報告されている．特に，針生検にて多形型LCISの診断がついたものでは，41％と高率にDCIS，浸潤癌を含んでいたと報告されている[7]．

また，著者らの施設でのLCIS切除症例（病理組織上，LCIS成分が50％以上を占める症例）25例の検討では，平均腫瘍径は3.8 cm，他病変

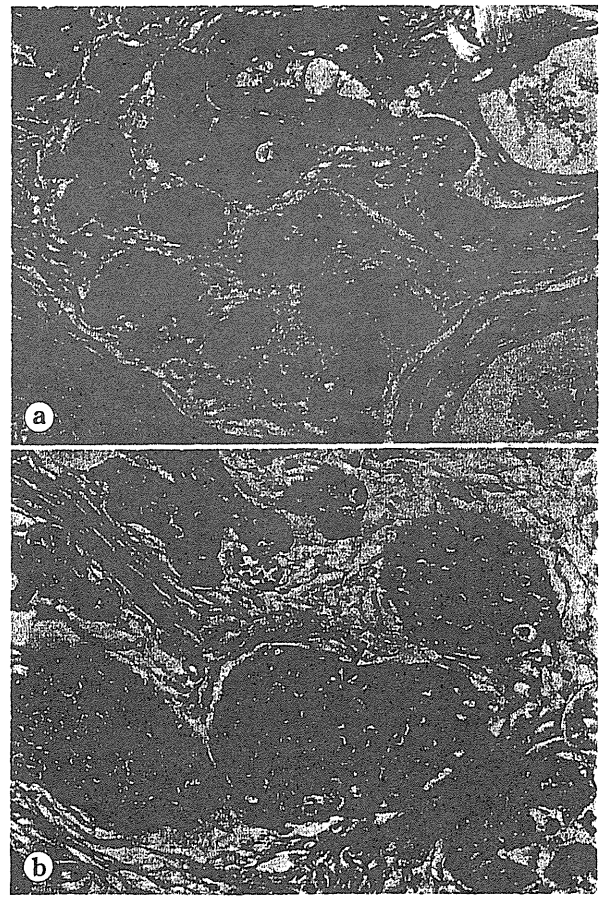

図1-a 古典型LCIS（40倍）
小葉細乳管の構築は保たれ，腫瘍細胞の増殖程度により様々に拡張している．

-b 古典型LCIS（100倍）
腫瘍細胞は単調な様相を呈し，小型円形核と少量胞体を有する．腫瘍細胞相互の接着はDCISに比較して緩く（矢印），細胞境界は不明瞭である．

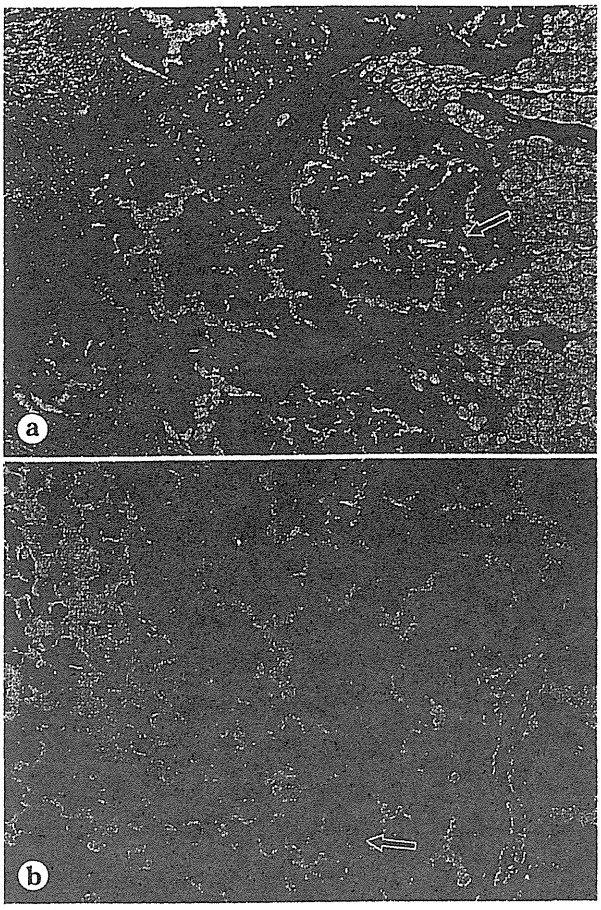

図2-a 多形型LCIS(40倍)
DCISに似た壊死，石灰化を伴う(矢印).

-b 多形型LCIS(100倍)
古典型と比較し細胞がより大型で多形，不均一，核小体が明瞭である．矢印：胞体内に細胞質内腺腔(intracytoplasmic lumen: ICL)を認める.

切除の際に偶然に発見されたLCIS症例(偶発型)ではないLCIS症例(LCIS顕在型)13例の腫瘍径は4.3 cmとやや大きく，最大のものは径10 cmの症例もあった．また，偶発型でなく，LCIS自体の臨床所見や症状で手術となったLCIS顕在型例は，多形型が85％を占めた．偶発型では多形型が33％であったのに比較し高い割合であった．また，浸潤癌を合併したLCIS 5例の平均径は6.1 cmと，やや腫瘍径が大きい傾向にあった．今後更なる検討が必要であるが，腫瘍径が大きいものは多形型LCISの割合が高く，病変内に浸潤癌が存在する可能性も高い．また，しこりなどの臨床所見を有するLCIS顕在型は多形型LCISの可能性も考慮し，治療方針を決定する必要がある.

治療指針

古典的な偶発型のLCISの基本的な治療方針は経過観察となる．ただし，この場合でも病変すべてが切除にてLCISであると確認されていることが前提となっている．前述のように，針生検にてLCISと診断された場合，病変全体としては，DCISや浸潤癌を含んでいる場合がある．よって確定診断を行うためには，切除生検が必要となる.

2011年改訂のNCCN guidelineにてLCISの治療アルゴリズムが示された(**図3**)．これを受け，日本乳癌学会の乳癌診療ガイドラインも，近日中に改訂予定となっている．NCCNガイドラインでは，針生検，細胞診にてLCISの診断の場合，切除生検を追加することが推奨される．切除生検にて，LCISが確実であり，DCISや浸潤癌を含まない場合，断端陽性は許容される．組織型のサブタイプ別の明確な治療指針はないが，多形型LCISの場合は，より悪性病変を含む率が高いので，切除生検にて断端陽性の場合，断端陰性の完全切除を考えるべきである．しかし，断端にLCISが存在する場合の外科的切除や放射線療法の有効性に関するデータは不足している．LCISは，浸潤癌の発症危険因子であるため，慎重な経過観察とともに，リスク軽減のためのホルモン療法も推奨されているが，明確なガイドラインは現時点ではまだない.

おわりに

検診の普及に伴い，LCISは，他病変の切除に伴って偶然発見されるものから，それ自体が臨床的症状や検診異常として発見される機会が増えてきている．しかし，治療方針，経過観察の期間，検査の頻度・方法や，ホルモン療法や放射線療法のエビデンスは明確ではなく今後の検討課題である.

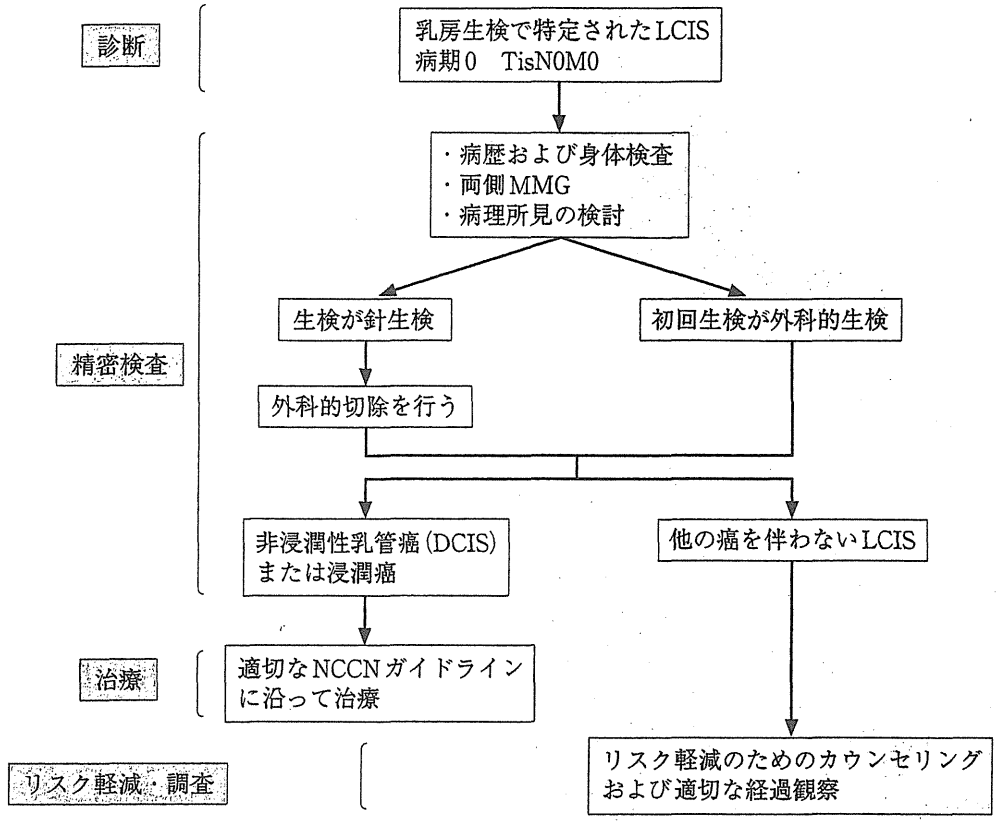

図3 NCCNアルゴリズム：LCISのマネージメント
（NCCN Clinical Practice Guideline in Oncology（NCCN guidelines™）for Breast Cancer v2. 2011より引用）

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乳癌の疫学

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覚えておきたいデータ

- 欧米諸国では乳がんの罹患率は漸増しているが，死亡率は1990年代から減少に転じている．一方で，日本においては，罹患・死亡率ともに年々増加傾向にある．
- 日本におけるマンモグラフィ検診受診率は，欧米の70～80%に比べ，20%程度と低い．このことが，日本の乳がん死亡率が低下しない理由の1つとして挙げられる．
- 日本における乳がん発生年齢は45～49歳，60～64歳と2峰性のピークがあり，閉経前乳がんの比率が欧米諸国に比べ高い．しかし，今後閉経後乳がんが増加し，欧米に年齢分布も近づくと予測されている．
- 全乳がんの5～10%が遺伝子異常に伴って発症するといわれており，家族性乳がんのうち20～30%は*BRCA1/2*遺伝子異常（変異）が関与している．

発見動機・初発症状

乳がんはその解剖的部位から，乳房腫瘤自覚・乳頭分泌・乳房痛などの自己発見が受診動機の多数を占める（**表1**）[1]．また，2000年から導入されたマンモグラフィを用いた乳がん検診の普及により，自覚症状のない早期乳がんの発見が増えてきており，全乳がんに占める早期乳がんの割合も相対的に増加してきている．日本における乳がん検診は1987年から30歳以上の女性を対象に視触診検診として開始された．しかし，視触診による検診では検診実施医師間による偏りが大きく，客観性に乏しいことから，検診としては不向きであった．そこで，欧米諸国で乳がん検診として広く普及していたマンモグラフィ検診が，わが国でも2000年に第4次老人保健事業（老健第65号）で50歳以上を対象にまず導入され，さらに，2004年に第5次老人保健事業（老老発第0427001号）で40歳台へのマンモグラフィ検診が導入された（**表2**）[2]．検診の客観性・精度を保つため，精度管理中央委員会が設置され，マンモグラフィの読影医・実施施設を認定制度とし，定期的な更新を義務付けている．

マンモグラフィを併用した検診が，乳がん死亡率低下に有効であることは欧米での多くのデータにて立証されているが，一方で視触診単独による乳がん検診は，死亡率低下に対する有用性の根拠は示されていないため[3]，検診から触診を省略する傾向にある．実際，2009年の米国予防医療専門委員会（USPSTF）の報告書においては，マンモグラフィに視触診を追加する有益な科学的根拠がないとされ，「推奨しない」と明記された[4]．また，検診受診に対する利益（乳がんの早期発見）・不利益（偽陽性・被曝・検診実施コストなど）を鑑みると，40歳台および75歳以上に実施するマンモグラフィ検診も推奨度は低いとしている[5]．しかし，45～49歳に乳がん罹患年齢ピークの1つがあるわが国の実情にはそのまま合致するわけではない．さらに，検診発見で受診する乳がん患者のなかに腫瘤触知や乳頭分泌などの理学所見を有する症例が少なからず存在することは，理学的検査を日々の検診・外来において安易に省略すべきではないことを示している．

わが国における罹患数・率，死亡数・率ならびにその年次別推移

わが国の女性における部位別がん罹患数の18%を乳がんが占めており，第1位となっている．25年前と比べるとその発症頻度は約2.5倍になっており，依然増加傾向は続いている．1975～2005年における年齢階級別乳がん罹患数および死亡数の変遷を示す（**図1，2**）[6]．国立がん研究センターがん対策情報センターによると，わが国の女性の2005年における乳がん罹患者