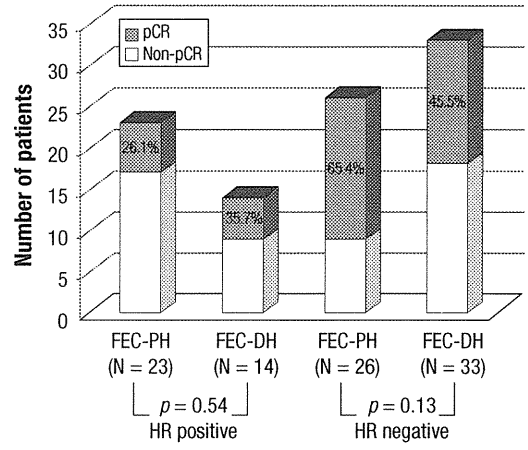
Table 1 Patient Characteristics

	FEC-PH (n = 49)	FEC-DH (n = 47)
Median Age (Range), y	51 (34-65)	53 (28-63)
Clinical Stage, No. (%) Patients		
IIA[a]	21 (42.9)	16 (34.0)
IIB	19 (38.8)	22 (46.8)
IIIA	9 (18.4)	9 (19.1)
Tumor, No. (%) Patients		
T1	1 (2.0)	1 (2.1)
T2	38 (77.6)	34 (72.3)
T3	10 (20.4)	12 (25.6)
Axillary Lymph Node-Positive Determination, No. (%) Patients		
Ultrasonography	27 (55.1)	33 (70.2)
SLNB	5 (10.2)	2 (4.3)
HER2 Status, No. (%) Patients		
IHC 3+	43 (87.8)	43 (91.5)
IHC 2+/FISH +	6 (12.2)	4 (8.5)
Hormone Receptor Status No. (%) Patients		
ER+/PgR+	12 (24.5)	4 (8.5)
ER+/PgR−	1 (20.4)	10 (21.3)
ER−/PgR+	1 (2.0)	0 (0)
ER−/PgR−	26 (53.1)	33 (70.2)

Abbreviations: DH = docetaxel; ER = estrogen receptor; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PgR = progesterone receptor; PH = paclitaxel; SLNB = sentinel lymph node biopsy.
[a] Including patients with tumor 2 cm in greatest dimension (T1c) and N0.

Figure 3 Pathologic Results According to Hormone Receptor (HR) Status. The Left Side Shows Pathologic Complete Response (pCR) in Patients With HR^+ Disease and the Right Side Shows pCR in Those With HR^- Disease



therapy for left ventricular systolic dysfunction. After 2 months, her symptoms had resolved with treatment, and she underwent BCT. Her LVEF had recovered to 58% one year after completion of PST. Four patients with adverse events were hospitalized during the trastuzumab plus taxane phase (1 patient received PH and 3 received DH). All remaining 84 patients who completed PST underwent surgery.

Twenty-nine (31.9%) of 91 patients who received trastuzumab plus taxane experienced infusion reactions during the first cycle of trastuzumab (14 patients with PH and 15 with DH). Among patients with infusion reactions, rigors and/or chills, fever, and pain were commonly observed; all events were grade 1 or 2. Eight (27.6%; 8.8% of all patients receiving trastuzumab plus taxane) of 29 patients who experienced infusion reactions during the first cycle of trastuzumab experienced a further infusion reaction during a later cycle.

Discussion

This study showed high pCR rates (46.9% with FEC-PH and 42.6% with FEC-DH) and that 62 (73.8%) of 84 patients undergoing surgery were able to receive BCT. The results of this study are consistent with the high pCR rates reported in previous trials that evaluated the combination of chemotherapy and trastuzumab as PST.[13-20,27] However, there was no significant difference in pCR rates between the 2 treatment groups. There was a trend to a higher rate of BCT with FEC-PH compared with FEC-DH, but the difference was not statistically significant. The small sample size may explain the lack of significant difference between the regimens.

The pCR rates were significantly higher in HR^- tumors than in HR^+ tumors with both treatments. This result is consistent with findings from several other studies of trastuzumab combined with anthracycline- and nonanthracyline-based regimens, including NOAH (concurrent anthracycline/taxane)[14] NeoSphere (docetaxel),[28] and NeoALTTO (paclitaxel).[29] Analysis of the data from these studies suggests that patients with $HER2^+$ and HR^- disease will obtain greatest benefit from a trastuzumab-containing chemotherapeutic regimen. Although other findings, reported by Peintinger et al[30] and Buzdar et al[13] contrast with results from NOAH, NeoSphere, NeoALTTO and the present study, the larger studies have demonstrated higher pCR rates in HR^- than HR^+ breast cancer after trastuzumab-based regimens. Moreover, after the initial conclusions from Buzdar[13] and Peintinger,[30] additional data from the M.D. Anderson group demonstrated a statistically higher pCR rate in HR^- than HR^+ breast cancer (61.1% vs. 38.9%, respectively). Recently, von Minckwitz et al[31] presented data from a meta-analysis of 7 trials (n = 6377) of neoadjuvant therapy, including anthracyclines and taxanes with or without trastuzumab, that showed that pCR is a surrogate for survival in patients with HER2+ HR^- breast cancer but not in those with HR^+ disease. It is also relevant to note that, in large trials of adjuvant therapy, prognosis is not different between HR^- and HR^- tumors.[8-10] Therefore, longer follow-up is required in the setting of PST before definitive conclusions can be made about the importance of HR status and therapeutic outcomes. Further clinical and translational

Table 2 Clinical and Pathologic Response Rates

	FEC-PH (n = 49)		FEC-DH (n = 47)	
	No. Patients	%	No. Patients	%
Completion of PST	43	87.8	41	87.2
Clinical Response by Palpation[a]	39	79.6	36	76.6
CR	30	–	28	–
PR	9	–	8	–
SD	0	–	2	–
PD	1	–	1	–
Breast Surgery	43	87.8	41	87.2
Mastectomy	8	–	14	–
BCT	35	71.4	27	57.4
AxLND	36	–	36	–
Lymph Nodes (Pathologic)				
Negative	32	–	28	–
Positive	4	–	8	–
SLNB Without AxLND[b]	6	–	4	–
Pathologic CR[c] ITT	23	46.9	20	42.6
Per protocol	23/43	53.5	20/40	50.0
DCIS in Breast	10	–	14	–

Abbreviations: AxLND = axillary lymph node dissection; BCT = breast conserving therapy; CR = complete response; DCIS = ductal carcinoma in situ; DH = docetaxel; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; PD = progressive disease; PH = paclitaxel; PR = partial response; PST = preoperative systemic therapy; SD = stable disease; SLNB = sentinel lymph node biopsy.

[a] Including 7 patients not evaluable for response (4 in the FEC-PH group and 3 in the FEC-DH group).

[b] SLNB was performed before PST.

[c] Including one patient not evaluable for pathologic response in the FEC-DH group.

research on the interaction between HR status, HER2 status, and pCR is warranted.

In the NOAH trial, the addition of trastuzumab to preoperative chemotherapy and postoperative trastuzumab for 52 weeks improved disease-free survival relative to chemotherapy alone (71% vs. 56% at 3 years; $P = .006$).[14] It remains to be determined whether the addition of postoperative trastuzumab will further improve disease-free and overall survival in patients who have achieved a pCR with sequential anthracycline and taxane plus trastuzumab. However, longer survival has been demonstrated in patients achieving pCR compared with those not achieving pCR, even in the $HER2^+$ subgroup,[21,22] although it may be different in patients with HR^- and HR^+ breast cancer, and needs to be viewed cautiously.

In studies with trastuzumab and nonanthracycline-containing regimens (eg, combination of taxane and platinum), pCR rates have ranged from 17% to 76%.[16–20] Studies of preoperative concurrent anthracycline and taxane with trastuzumab (for 12-24 weeks) have shown pCR rates of 38%-66%.[13–15] Results of these studies suggest that concurrent anthracycline and trastuzumab has a considerable antitumor effect, although, cardiotoxicity remains a concern with this regimen. A review of the medical literature provides reassurance that the cardiac toxicity of concurrent trastuzumab and anthracycline is acceptable and manageable.[13–15] The dose of anthracycline is an important factor in cardiac safety. In the current study, the dose of anthracycline (epirubicin 100 mg/m^2 for 4 cycles was higher than in previous studies that used doxorubicin (60 mg/m^2 for 3 cycles) or epirubicin (75 mg/m^2 for 4 cycles). Therefore, cardiotoxicity may be avoided by reducing the dose of anthracycline when used in combination with trastuzumab. Sequential administration of trastuzumab after anthracycline, as used in the present study, is also an appropriate approach to reduce the risk of cardiotoxicity. However, it might relate to an administration order of anthracycline and taxane, not concurrent administration of anthracycline and trastuzumab, because concurrent administration of anthracycline and trastuzumab has less cardiotoxicity in the report by Buzder et al.[13] Longer follow-up is required to further evaluate the cardiac safety profile of anthracyline-trastuzumab PST to determine a preferable method; dose reduction or sequential administration, including an administration order of anthracycline and taxane.

Twelve (12.5%) of 96 patients in our study did not complete PST. The major reasons for discontinuation of PST were chemotherapy-related adverse events. One patient in the FEC-PH group experienced grade 3 left ventricular systolic dysfunction. A limitation of this study was the evaluation of LVEF by echocardiogram only at study entry and completion of surgery if patients showed no symptoms of left ventricular failure. Experience of cardiotoxicity in this study suggests that LVEF by echocardiogram should be monitored at completion of FEC and again at completion of trastuzumab plus taxane therapy. Long-term follow-up of cardiotoxicity is required for patients in this study who received preoperative and adjuvant trastuzumab.

Because FEC-PH and FEC-DH demonstrated similar efficacy overall, differences in safety profile are important in determining the most appropriate PST regimen to offer to candidates for BCT. Paclitaxel was associated with an increased incidence of peripheral neuropathy, whereas use of docetaxel produced greater neutropenia, febrile neutropenia, peripheral edema, and mucositis. The choice of PST, therefore, should be individualized according to patient characteristics and preferences. Although analysis of data suggested a possible advantage for paclitaxel in terms of higher pCR in the subgroup of patients with HR^- disease and a higher rate of BCS, the differences were not statistically significant.

Conclusion

FEC, followed by concurrent trastuzumab with taxane (weekly paclitaxel or 3-weekly docetaxel), seems active and feasible as PST for $HER2^+$ breast cancer. There was no significant difference in pCR rate between FEC-PH and FEC-DH, although there was a trend to a higher rate of pCR with the paclitaxel-containing regimen in patients with HR^- breast cancer. Whether this trend is clinically significant is not yet known. Long-term follow-up of patients in this study treated with preoperative and adjuvant trastuzumab will provide further information on cardiac safety and disease-free survival.

Randomized comparisons of PST regimens, comprising various permutations of anthracyclines, taxanes, and platinum administered with concurrent and/or sequential trastuzumab, together with long-term follow-up of cardiac safety and disease-free

Table 3 Adverse Events During Primary Systemic Therapy (NCI CTCAE version 3.0 grading)

Toxicity	FEC-PH (grade, %)				FEC-DH (grade, %)			
	FEC (n = 49)		PH (n = 46)		FEC (n = 47)		DH (n = 45)	
	All	3/4	All	3/4	All	3/4	All	3/4
Hematologic								
Neutropenia	46.9	28.6	39.1	2.2	36.2	27.7	15.6	8.9
Febrile neutropenia	12.2	12.2	0	0	10.6	10.6	6.7	6.7
Anemia	44.9	2.0	54.3	0	44.7	0	55.6	2.2
Thrombocytopenia	4.1	0	0	0	8.5	0	2.2	0
Nonhematologic								
Anorexia	46.9	2.0	8.7	0	40.4	0	17.8	0
Nausea/vomiting	87.8	2.0	21.7	0	91.5	0	24.4	0
Vomiting	44.9	4.1	15.2	0	65.9	6.4	15.6	0
Diarrhea	12.2	0	30.4	0	19.1	0	35.6	0
Mucositis and/or stomatitis	53.1	0	19.6	0	61.7	0	57.8	0
Taste alteration	38.8	–	41.3	–	44.7	–	53.3	–
Fatigue	49.0	0	50.0	0	68.1	2.1	64.4	0
Peripheral neurotoxicity	4.1	0	95.7	4.3	8.5	0	51.1	0
Arthralgia and/or myalgia	0	0	39.1	0	0	0	42.2	0
Peripheral edema	6.1	0	39.1	0	12.8	0	62.2	2.2
Infection	6.1	0	6.5	0	8.5	0	13.3	0
Elevated AST, ALT	38.8	2.0	47.8	0	25.5	0	31.1	0
Arrhythmia	0	0	4.3	0	2.1	0	2.2	0
Left ventricular dysfunction	0	0	2.2	2.2	0	0	0	0
Hyperglycemia	0	0	0	0	0	0	2.2	2.2
Nail changes	63.3	–	73.9	–	51.1	–	60.0	–
Skin rash	16.3	0	21.7	0	4.3	0	26.7	0
Infusion reaction	–	–	30.4	0	–	–	33.3	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = progressive disease; PH = paclitaxel.

survival are required before definitive recommendations can be made for patients with $HER2^+$ breast cancer.

Clinical Practice Points

- PST is a standard management option for patients with operable breast cancer and can facilitate breast conservation.
- The addition of trastuzumab to primary systemic chemotherapy achieves a high rate of pCR in patients with $HER2^+$ breast cancer, but the optimal treatment regimen has not yet been defined.
- Concurrent use of trastuzumab and anthracycline-based therapy must be used with caution because of the potential risk for cardiac toxicity.
- Preoperative treatment regimens comprising FEC followed by either trastuzumab and paclitaxel or trastuzumab and docetaxel were similarly effective in patients with $HER2^+$ breast cancer and both achieved high rates of pCR.
- The pCR rates were higher in patients with HR^- tumors than in those with HR^+ disease.
- The paclitaxel-containing regimen showed a trend to a higher pCR rate in patients with HR^- tumors and a higher rate of breast conserving surgery compared with the docetaxel-containing regimen.
- Sequential use of trastuzumab-taxane after FEC was generally well tolerated, although cardiac safety remains an important consideration. It is important that LVEF is monitored at study entry, at the completion of FEC, and again at the completion of trastuzumab-taxane combination therapy.

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Disclosure

The authors have stated 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.

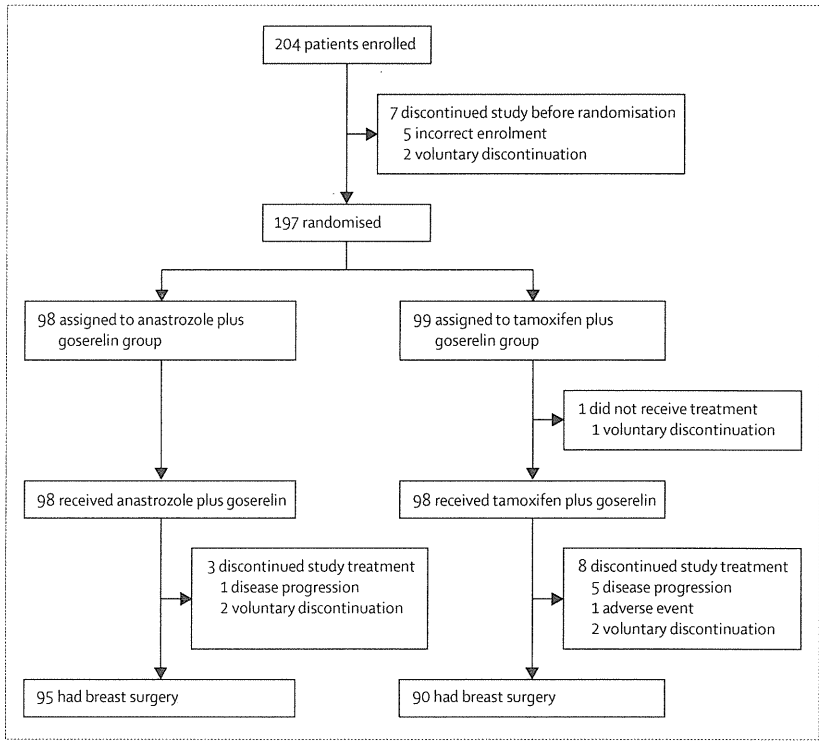

Figure: **Trial profile**

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.[10] 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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Clinical Trial Note

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A Randomized Controlled Trial Comparing Primary Tumour Resection Plus Systemic Therapy With Systemic Therapy Alone in Metastatic Breast Cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017

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This trial is being conducted to confirm the superiority, in terms of overall survival, of primary tumour resection plus systemic therapy to systemic therapy alone in patients with Stage IV breast cancer who are not refractory to primary systemic therapy. The inclusion criteria for the study are as follows: untreated patients with histologically confirmed invasive breast cancer with one or more measurable metastatic lesions diagnosed by radiological examination. All patients receive primary systemic therapy according to the estrogen receptor and human epidermal growth factor receptor type-2 status of the primary breast cancer after the first registration. After 3 months, the patients without disease progression are randomized to the primary tumour resection plus systemic therapy arm or the systemic therapy alone arm. The primary endpoint is the overall survival, and the secondary endpoints are proportion of patients without tumour progression at the metastatic sites, yearly local recurrence-free survival, proportion of local ulcer/local bleeding, yearly primary tumour resection-free survival, adverse events of chemotherapy, operative morbidity and serious adverse events. The patient recruitment was commenced in May 2011. Enrolment of 410 patients for randomization is planned over a 5 year recruitment period. We hereby report the details of the study.

Key words: breast medicine – metastasis – breast-basic – surgery

INTRODUCTION

The incidence of metastatic breast cancer (Stage IV), defined as a primary breast tumour with distant metastasis, is increasing, accounting for ~3% of all newly diagnosed patients with breast cancer in Japan, not significantly different from the 6% reported from the USA according to the Surveillance, Epidemiology and End Results data. The treatment of Stage IV breast cancer has traditionally been palliative care with chemotherapy, hormonal therapy and/or radiation therapy (1,2). According to the Hortobagyi algorithm (3), hormonal therapy is chosen as the first therapy for hormone receptor-positive Stage IV breast cancer without life-threatening metastases. If the tumour is hormone receptor-negative or resistant to hormone therapy, chemotherapy is used, although it might severely impair the quality of the patient's life. Current anti-tumour drugs, such as

anthracyclines and taxanes, are quite effective, as are molecular-target drugs, such as trastuzumab. Resection of the primary tumour is not considered a curative treatment; it is used solely as local therapy to prevent uncontrolled chest wall disease. Therefore, the local surgery is performed relatively late in the treatment course, and only if the primary tumour and metastases have been reduced and controlled with the systemic therapy.

The possibility of surgical procedures improving the survival of these patients has been reported by several retrospective studies (4–8); however, these studies essentially suffer from biases such as arbitrary patient selection, diverse timing of surgery or various regimens of systemic therapy. Therefore, this subject still remains a hotly debated topic at major breast conferences. Improvements in primary systemic therapies have increased the numbers of Stage IV patients with resectable small primary tumours and metastatic lesions controllable by treatment. With all of these new developments, we need definitive guidelines for the treatment of these patients. It will be necessary to perform prospective studies for evaluation of the efficacy of primary tumour resection for Stage IV breast cancer. This trial is being conducted to investigate the efficacy of primary tumour resection plus systemic therapy and that of systemic therapy alone for patients with Stage IV breast cancer. Breast cancers with resistance to primary systemic therapy (PST) increase during the primary resection and need to take next regimen immediately. So we randomize only Stage IV breast cancer which is still sensitive to systemic therapy in this study.

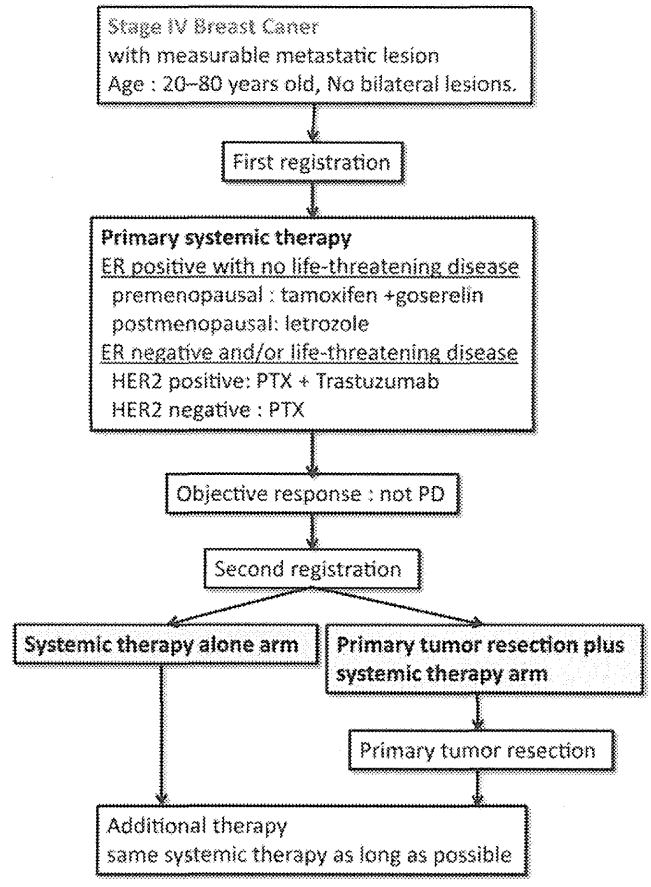

Figure 1. Study Schema. A randomized controlled trial comparing primary tumour resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017. ER, estrogen receptor; HER2, human epidermal growth factor receptor type-2; PTX, paclitaxel; PD, progressive disease.

STUDY PROTOCOL

Purpose

This study is being conducted to confirm the superiority, in terms of overall survival, of primary tumour resection plus systemic therapy to systemic therapy alone in untreated breast cancer patients with metastatic lesions (Stage IV) who are not refractory to conventional PST according to the estrogen receptor (ER) and human epidermal growth factor receptor type-2 (HER2) status of the primary lesions (Fig. 1).

Study Setting

This study is a multi-institutional prospective randomized controlled trial being conducted with the participation of 30 hospitals belonging to the JCOG Breast Cancer Study Group.

Endpoints

The primary endpoint is overall survival (OS), which is defined as the number of days from randomization (second registration) to death from any cause, and it is censored at the last follow-up date when the patient is alive. The secondary endpoints are the proportion of patients without tumour progression at the metastatic sites, yearly local recurrence-free survival, proportion of local ulcer/local bleeding, yearly primary tumour resection-free survival, adverse events of chemotherapy, operative morbidity and serious adverse events.

Eligibility Criteria

Inclusion criteria

First registration

(1) Histologically confirmed invasive breast cancer in biopsy specimens obtained from the tumour.
(2) The presence/absence of overexpression of ER and HER2 in the tumour examined.
(3) Neither bilateral breast cancer nor invasion to the contralateral breast.
(4) At least one measurable metastatic lesion other than the breast tumour and axillary lymph nodes detected by computed tomography or magnetic resonance imaging before primary registration.
(5) No brain metastasis.
(6) Women aged 20–80 years old.

(7) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. PS 2 caused by the symptoms of bone metastasis is also eligible.
(8) No surgery, chemotherapy or radiotherapy for any other malignancies within the previous 5 years.
(9) No history of invasive breast cancer. Non-invasive breast cancer resected completely by partial mastectomy is also eligible.
(10) Neither prior chemotherapy for breast cancer nor prior radiotherapy for the ipsilateral breast (radiotherapy for bone metastasis within 30 Gy and up to 10 times before the registration is allowed).
(11) Adequate organ functions.
(12) Availability of written informed consent.

Second registration (after primary therapy)

(1) Primary therapy was administered after the first registration and the protocol treatment has not been discontinued.
(2) Objective response to primary chemotherapy was not progressive disease or not evaluable (NE).
(3) Within 28 days from the date of response evaluation.
(4) Adequate organ functions.
(5) Complete resection expected to be possible by total or partial mastectomy without resection of adjacent organs and/or wide skin transplantation.
(6) No active bleeding from the breast tumour necessitating blood transfusion within 28 days prior to the second registration.

Exclusion criteria (no exclusion criteria at the second registration)

First registration

(1) Simultaneous or metachronous (within 5 years) double cancers.
(2) Infectious disease requiring treatment.
(3) Body temperature of 38°C or higher.
(4) Pregnant or breast-feeding women.
(5) Psychiatric diseases.
(6) Systemic and continuous steroid treatment.
(7) Comorbid unstable angina pectoris or history of myocardial infarction within the previous 6 months.
(8) Uncontrolled hypertension.
(9) Uncontrolled diabetes mellitus or the disease being treated by continuous insulin administration.

Primary Systemic Therapy

All enrolled patients for the first registration receive the PST. PST is decided according to the ER and HER2 status and the disease situation and continued for three cycles.

(i) ER-positive patients with no life-threatening diseases receive the following hormonal therapy.
  (a) Pre-menopausal patients: oral tamoxifen 20 mg/body daily plus goserelin 3.6 mg/body every 4 weeks.
  (b) Post-menopausal patients: oral letrozole 2.5 mg/body daily for 4 weeks.
(ii) ER-negative and/or life-threatening diseases receive the following chemotherapy.
  (a) HER2-positive: paclitaxel (PTX) 80 mg/m^2 (Days 1, 8, 15) plus weekly trastuzumab 2 mg/kg (Days 1, 8, 15, 22) every 4 weeks.
  (b) HER2-negative: PTX 80 mg/m^2 (Days 1, 8, 15) every 4 weeks.

Randomization

After three cycles of PST, the JCOG Data Center confirms the patient eligibility, and randomizes the patients either to the primary tumour resection plus systemic therapy arm or to the systemic therapy alone arm. The randomization is conducted by the minimization method with balancing the arms according to ER status (positive/negative), HER2 status (positive/negative), metastatic site(s) (presence/absence of visceral metastasis) and institution.

Treatments

Primary tumour resection plus systemic therapy arm

The patients undergo the complete resection of the primary lesions after the second registration. Prophylactic axillary lymph node dissection and/or resection of adjacent organs are not allowed. As long as the tumour is resected completely, it does not matter whether the surgical procedure is partial mastectomy or total mastectomy. After the operation, the patients restart to receive the same systemic therapy as before for as long as possible as additional therapy.

Systemic therapy alone arm

After the second registration, the patients continue to receive the same systemic therapy as additional therapy for as long as possible.

All randomized patients are followed for 6 years. Physical, blood and radiological examinations of distant metastases are conducted every 6 months.

Statistical Analysis

Primary analysis and statistical hypothesis

If the overall survival of the patients treated by primary tumour resection plus systemic therapy is significantly longer than that of the patients administered systemic therapy alone, the primary tumour resection will be judged to be the new standard treatment. The estimated median overall survival of patients with Stage IV breast cancer is commonly 24 months (9,10). The duration between the first and the second registration is 4 months. In this study, we shall assume that the median OS in the systemic therapy alone arm after the second registration will be 20 months, and it will be considered a clinically relevant prolongation if

the median OS of primary tumour resection plus systemic therapy is longer by 6.0 months (hazard ratio: 0.77).

SAMPLE SIZE AND FOLLOW-UP PERIOD

The primary endpoint will require 359 events in total to be assessed, in order to obtain a statistical power of 80% with a one-sided significance level of 0.05. Thus, the planned sample size is 410 patients for the second registration and 500 patients for the first registration (assuming that 20% of the patients may not proceed to the second registration.) for comparing the two survival curves, assuming an accrual time of 5 years and a follow-up time of 4 years according to the calculation by the method of Schoenfeld and Richeter (11).

INTERIM ANALYSIS AND MONITORING

An interim analysis is planned to be performed twice, taking into account multiplicity using the Lan and DeMets alpha spending function. The Data and Safety Monitoring Committee (DSMC) of the JCOG independently reviews the interim analysis report, and an early termination of the trial may be considered at that stage. In-house interim monitoring is performed by the Data Center to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. The monitoring reports are submitted to and reviewed by the DSMC every 6 months.

REGISTRATION OF THE PROTOCOL

The protocol was registered at the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID UMIN000005586), on 11 May 2011. The details are available at the following web address: http://www.umin.ac.jp/ctr/

PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)

Hokkaido Cancer Center, Tochigi Cancer Center, Jichi Medical University, Gunma Prefectural Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo Medical Center, Keio University Hospital, St. Luke's International Hospital, Tokai University School of Medicine, Kanagawa Cancer Center, Kitasato University School of Medicine, Yokohama Rosai Hospital, Niigata Cancer Center Hospital, Shizuoka General Hospital, Aichi Cancer Center Hospital, Nagoya Medical Center, Kinki University School of Medicine, Osaka National Hospital, Okayama University Hospital, Kure Medical Center Chugoku Cancer Center, Fukuyama Medical Center, Hiroshima City Asa Hospital, Shikoku Cancer Center, National Kyushu Cancer Center, Kitakyushu Municipal Medical Center and Nagasaki Medical Center.

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Conflict of interests statement

Hiroji Iwata receives honoraria for speaking events from Chugai Pharmaceutical Co., Ltd.

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特 集 遺伝性乳癌卵巣癌診療の新時代

わが国における Triple Negative 乳癌治療の現状と課題

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Current Status and Future Perspectives for the Treatment of Triple-Negative Breast Cancer in Japan: Norikazu Masuda, Hiroyuki Yasojima, Makiko Mizutani and Jun Yamamura (*Dept. of Surgery, Breast Oncology, National Hospital Organization Osaka National Hospital*)

Summary

Triple-negative breast cancer (TNBC) is negative for all three markers, namely the hormone sensitivity receptors: estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2). TNBC accounts for approximately 15% of all primary breast cancer cases. In general, patients with this disease have a higher risk of recurrence and a poorer prognosis compared with those with other subtypes of breast cancer. Patients with TNBC are defined as those for whom endocrine or anti-HER2 therapy are not indicated due to poor response. It is a heterogeneous disease group that shows various characteristics. There is a group that achieves a complete response to chemotherapy and has an excellent prognosis, a group that does not respond to chemotherapy and has a poor prognosis, and a group that has an excellent inherent prognosis and does not need chemotherapy. The subdivision of TNBC cases based on the prognosis and response to therapy is an issue for the future.

In addition to classifying TNBC into basal and non-basal types by testing cytokeratin 5/6 (CK5/6) and epidemic growth factor receptors (EGFR) by the immunohistochemical staining method, Ki-67 may predict sensitivity to anticancer agents and a change in Ki-67 before and after therapy may potentially predict prognosis. Patients with a non-pathologic complete response (non-pCR) to preoperative chemotherapy have a high risk of early recurrence, and measures to deal with it are therefore needed. At present, the most commonly used perioperative chemotherapy is sequential combination therapy of an anthracycline drug and a taxane drug; however, it is limited because the pathologic complete response (pCR) rates following preoperative chemotherapy range from 30 to 40%. There is also an urgent need to develop a regimen that will overcome this problem. In association with BRCA gene mutations, sensitivity to DNA-damaging anticancer agents may lead to promising therapies. However, unfortunately, the use of DNA-damaging agents such as cisplatin and carboplatin is not covered by health insurance in Japan. Various new molecular targeted drugs aimed at blocking cell proliferation factors are expected to be developed in the future.

Here we have summarized the current status and issues based on the clinical experience with the diagnosis and treatment of TNBC. **Key words**: Triple-negative breast cancer, Basal-like breast cancer, Ki-67, BRCA-1, Primary systemic therapy, **Corresponding author**: Norikazu Masuda, Department of Surgery, Breast Oncology, National Hospital Organization Osaka National Hospital, 2-1-14 Houenzaka, Chuo-ku, Osaka 540-0006, Japan

要旨　ホルモン感受性（ER/PgR）と上皮増殖因子の HER2 発現のすべて三つのマーカーが陰性の triple negative 乳癌（TNBC）は，原発性乳癌の約 15%を占める。一般的に他のサブタイプに比べ，再発高危険群，つまり予後不良である。TNBC は内分泌療法と抗 HER2 療法が不適であるという治療反応性から規定される集団であり，化学療法が著効し予後が良好な群，化学療法が無効で予後不良な群，元来予後良好で化学療法が不要な群，といった様々な性格を有する heterogeneous な疾患群である。今後は TNBC のなかでも予後と治療反応性に基づく細分化が課題である。

組織免疫染色法を用いた CK5/6，EGFR による basal vs non-basal の分類に加え，Ki-67 が抗癌剤感受性を予測し，またその治療前後での変化が予後予測に有望な可能性がある。術前化学療法無効（non-pCR）例は早期の再発危険性が高く，その対策が望まれる。現在，最も標準的な周術期化学療法はアントラサイクリン系とタキサン系の順次併用療法であろうが，術前での pCR 率は 30～40%と限界がある。これを卓越するレジメンの開発も急務である。BRCA 遺伝子異常に関連し，DNA 障害性抗癌剤の感受性が期待されるが，残念ながらわが国では cisplatin，carboplatin などの薬剤が保険未承認である。細胞増殖系因子をターゲットにした様々な新規の分子標的治療薬の今後の開発に期待される。

本稿では TNBC の診断および治療の臨床的経験から，その現状と課題をまとめた。

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はじめに

分子生物学的解析とその概念の進歩に伴い，近年，乳癌治療体系はホルモン感受性とHER2発現状況から分類されるサブタイプに応じて，その構築を要するようになってきた。日常臨床で免疫組織化学（IHC）法を用いて検査ができるエストロゲン受容体（ER），プロゲステロン受容体（PgR），human epidermal growth factor receptor type 2（HER2）による蛋白発現からみた分類と，マイクロアレイなどを用いた遺伝子発現プロファイリングからみた分類とが，必ずしも一致しない点が若干の混乱を来しているのが現状ではあるが，本稿では前者の臨床診療の側面からアプローチしたい。

Ⅰ．Triple negative乳癌（TNBC）の臨床学的特徴

IHC法でER，PgR，HER2のすべてが陰性の場合，TNBCとして分類される。ホルモン陽性やHER2陽性のように既知のtargetを有しないことから，内分泌療法や抗HER2療法（trastuzumab，lapatinibなど）が無効で不適である。幾種のtarget療法剤の開発は進行中であるが，現時点では化学療法剤のみが全身療法の唯一の手段である。

ER/PgRのcut-offは，旧来は10%未満を陰性とされていたが，ホルモン療法の適応に基づく概念から，昨今は1%未満が陰性と定義することが多い。しかし，後述のように，このcut-offの狭間に存在するER/PgR発現が1～9%の場合のbiologyはどちらかというとTNBCに近い性格を有する。ゆえに本稿での対象は，ER/PgR＜10%，HER2（IHCで0，1もしくはFISH陰性）の浸潤癌をTNBCとする。

TNBCは原発性乳癌の約15%を占める[1]。大阪医療センターデータベースでは乳癌全体の12%，浸潤癌の13%である（図1）。日本乳癌学会の登録統計からの解析によると，TNBCには，圧排性，充実性増殖パターンが特徴な充実腺管癌の割合が高く，metaplastic/apocrine/medullaryタイプの特殊型では，TNBCの占める割合が高い（65～80%）のが特徴的である[2]。また，同統計によると，TNBC 1,797例のなかで234例（13%）で，特殊型の形態に分類される（図2）。Pratらの報告[3]によると，臨床的なTNBCのなかには，遺伝子プロファイリングの観点からみると，basal-like（39～54%），claudin-low（25～39%），HER2 enriched（7～14%），Luminal B（4～7%），Luminal A（4～5%）に細分化される。同じく，PARP阻害剤のBSI-201の開発臨床第Ⅲ相試験にエントリーされた症例を遺伝子プロファイリングからみる

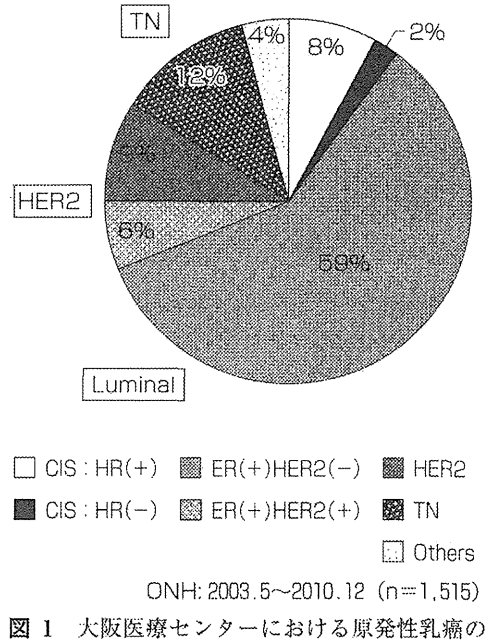

図1　大阪医療センターにおける原発性乳癌のER/HER2別の割合
CIS: carcinoma *in situ*，DCISもしくはLCIS，HR: hormone receptor，TN: triple negative

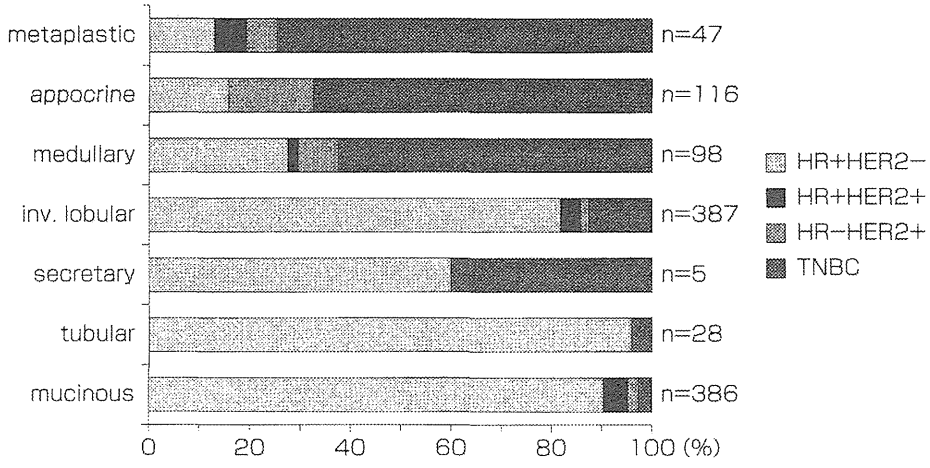

図2　特殊型に分類される浸潤性癌のサブタイプ別比率（文献[2]より引用改変）
特殊型は乳癌全体の9.1%を占め，一方，TNBCのなかの13%が特殊型である。

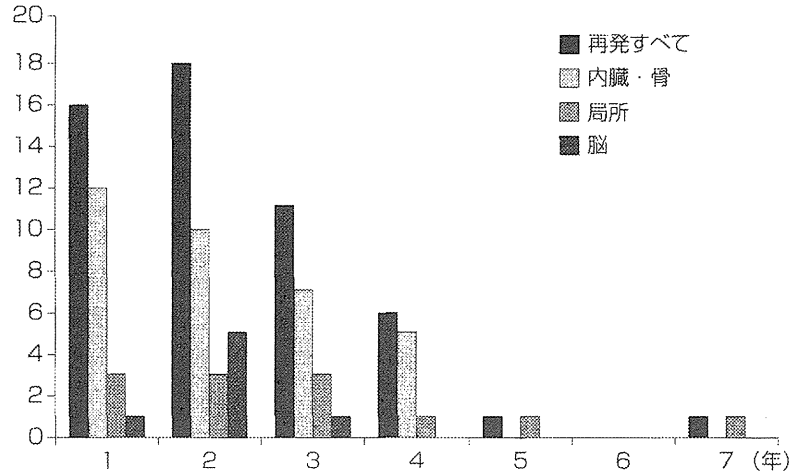

図 3　TNBC の年次別再発症例数と初発再発部位分布（大阪医療センター：2003.5～2011.12　n＝53）

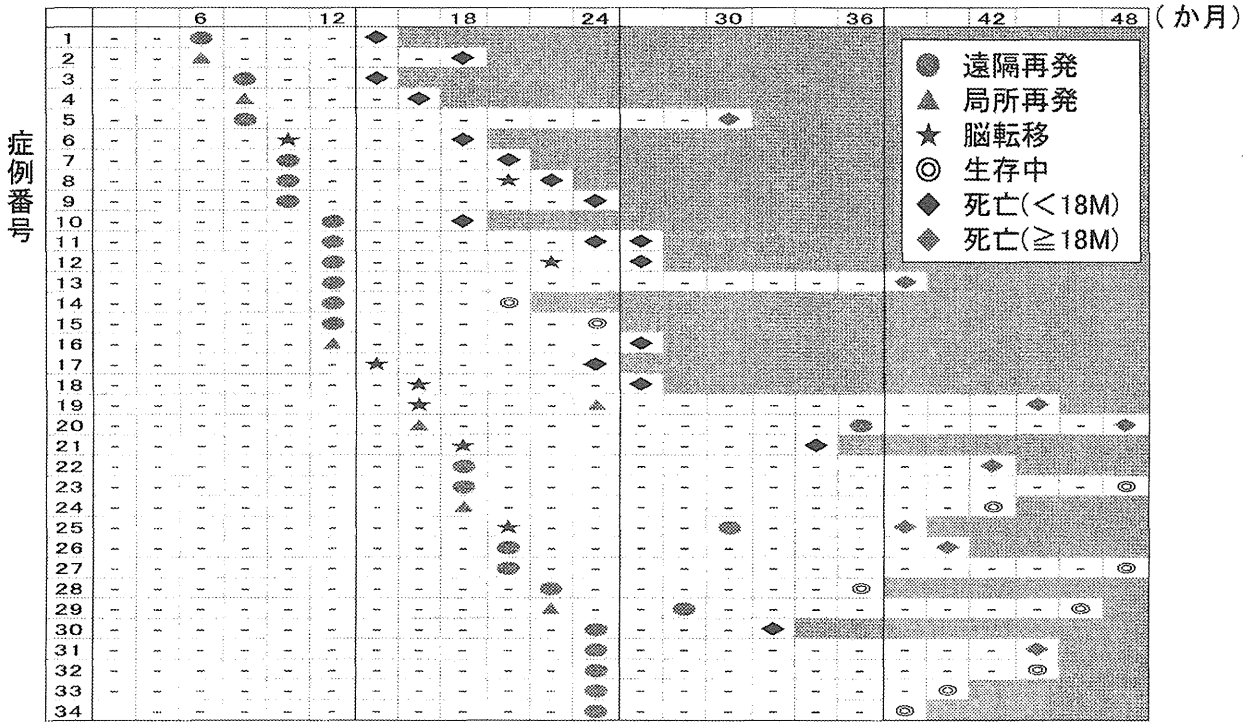

図 4　2 年以内再発例の再発形式とその予後
34 例中 24 例（71%）が原病死し，うち 67%（16/24）が再発後 18 か月以内に死亡。

と，normal-like，basal-like をはじめ，各サブタイプに細分化され，TNBC はいわゆる雑多な疾患単位であることがわかってきた。この点が TNBC の治療法の開発をさらに難しくし，複雑化させる要因でもあろう。

Ⅱ．TNBC の予後

各種報告から概して TNBC は他のサブタイプの乳癌と予後を比較検討した場合，遠隔再発ならびに死亡リスクは有意に高く，予後不良とされる。年次ごとの再発リスクは術後 1～3 年がピークであり，遠隔再発・死亡ともに 5 年以内にみられる傾向があり，またそれ以降は，むしろ non-TNBC のほうが年次再発リスクが高い報告もみられる[4,5]。図 3 に 2003～2011 年の 8 年間に大阪医療センターで経験した TNBC 再発乳癌 45 例における年次別再発症例数と初再発部位を示す。全体の 64%（34/53）が初期治療から 2 年以内に再発が確認されている。5 年以降の再発はわずかであり，その 2 例は局所領域の再発であった。また，再発後の予後も不良であり，2 年以内の再発 34 例中 24 例（71%）が原病死し，うち 67%（16/24）が再発後 18 か月以内に死亡していた。その再発形式と予後の状況を図 4 に図示した。余命予後の厳しい脳転移のみならず，図 5 に示すような薬剤耐性を得た悪性度の高い乳癌の鎧状形態を示す胸壁局所再発は，絞扼感と滲出液を伴い QOL を著しく低下させるが，これも

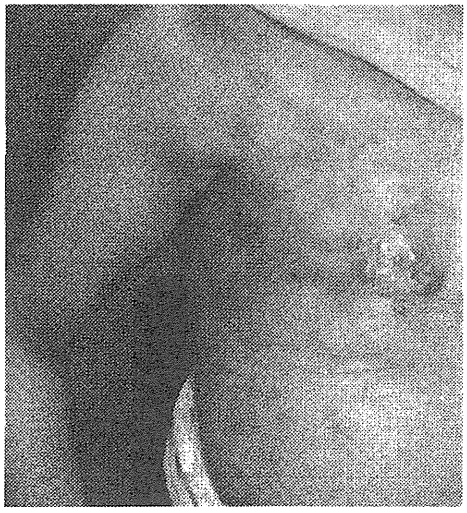

図 5　QOLを著しく低下させる再発
胸壁再発-鎧状に進展し，絞扼感と多量の滲出液を伴う。

TNBCの特徴の一つである。

この再発形式から考察するに，現在，乳癌の初期治療後のfollow-upは一律10年の再発有無チェックが行われているが，そのスクリーニングの個別化の必要性がうかがえる。また，TNBCのなかで再発高リスク群と予後良好群を区別することも重要な課題であろう。

Ⅲ．TNBCの治療―薬物療法―

TNBCの周術期薬物療法の基本は化学療法剤であり，NCCNガイドラインにおいても，浸潤径10 mm以上もしくは腋窩リンパ節陽性（転移巣2 mm以上）であればそれは必須とされ，6 mm以上もしくは5 mm以下でpN1mic（微小転移）を伴えば，化学療法を考慮すべきとされる。そのレジメンの標準は，アントラサイクリン系とタキサン系の逐次投与である。アントラサイクリン系レジメンとして，adriamycin/cyclophosphamide（AC），cyclophosphamide/adriamycin/5-FU（CAF），epirubicin/cyclophosphamide（EC），5-FU/epirubicin/cyclophosphamide（FEC）の多剤併用療法が選択される。タキサン系の薬剤としては，docetaxel（DOC）の3週ごと投与，paclitaxel（PTX）の毎週投与が代表的であり，近年ではDOCとcyclophosphamideを併用するTC療法も注目されている。アントラサイクリン系とタキサン系レジメンの投与順序はcontroversialである。

TNBCの場合，手術を先行しても術後に必ず化学療法を必須とすることから，術前化学療法を適応し，腫瘍縮小効果から整容性の高い乳房温存術を期待し，その概念が徐々に広まってきた。TNBCでは他のサブタイプに比べ化学療法感受性が高く，pCR（病理学的完全奏効）が得られる機会も多い[6-8]。またMD Anderson Cancer Centerの多数例の報告によると[5]，TNBCは他のサブタイプよりも術前化学療法により高いpCR率が得られ，またpCRが得られたTNBCは非常に予後が良好であり，non-pCRのTNBCは極めて予後不良であった。図6に術前化学療法著効例（pCR例）と無効例を提示する。non-pCR例には化学療法経過中，まったく縮小を得ない場合（図6b）や臨床的奏効が著明でも遺残した細胞にはまったく病理学的効果が確認できない場合（図6c）もある。TNBCの場合，その予後には臨床効果よりもpCRか否かが重要な予測因子である。このように，TNBCは一般的には化学療法の感受性が高い一方で，全体としてその無病生存期間や生存期間が短い傾向にあり，正に「triple negative paradox」と評価されるいわれである[9]。

われわれは，大阪医療センターで術前化学療法（アントラサイクリン系とタキサン系の逐次投与）を実施した33例を対象に，pCR予測因子とその予後を検討した[10]。Nielsenの分類[11]に従い，IHC法でCK5/6もしくはEGFRが陽性の場合をbasal-likeと定義した際に，basal-likeであればpCRは23%（5/22）であったのに対し，non-basal-likeでは64%（7/11）の高いpCRが得られた（p=0.02）。一般的にbasal-likeの癌のほうが予後が悪いという報告に合致する。Ki-67も有意なpCR予測因子であり，50%をcut-offにした場合，Ki-67高値群では50%（10/20）でpCRが得られたのに対し，低値症例では15%（2/13）であった[10]。検討症例が少ないゆえに有意差までは得られなかったが，HER2発現がIHC法で2＋（FISHは陰性）の場合，0もしくは1＋の症例に比べ，pCRは高い傾向がみられた。アントラサイクリン系の感受性を反映している可能性もある。予後との相関をみたところ，再発例のすべてが治療開始前からKi-67が高く，化学療法により低下させ得なかった症例，もしくは初期値が50%未満であっても治療終了時に増加のみられた症例であり，治療に伴うKi-67の変化が，術前化学療法と手術後の予後予測に有用であった。Keamらの報告でも同様の傾向であり，non-pCR例でもKi-67が10%未満になった症例はpCRに近い良好な経過が期待できる[11]。

このように術前治療という手法や概念を用いて，TNBCの治療における個別化を適応することができるのではと期待が高まる。術前治療でnon-pCR例の予後の改善をめざして，術後のcapecitabineが有効か否か（CREATE-X/JBCRG-04），臨床試験が進行中である。TNBCのなかには比較的予後良好な群があることも事実であり，化学療法の必要性の可否に関する見極めも今後は重要な課題であろう。