の小病変の発見にUSが有用だと考えていることの表れであると思われる．ただし被曝がないこと，外来で簡便に施行できるため安易に行われている可能性もある．スクリーニングUSの有用性について，乳癌診断にUSをいち早く広く取り入れている日本発の客観的なデータ（Japan Strategic Anti-Cancer Randomized Trial：J-START[9]）の結果が望まれる．

術後乳房定期検査の施行期間は若年性を区別している施設では各検査とも10年以下で終了が8割を占めた．20代の若年性乳癌患者を考えると術後10年時の年齢は30代であり，一般乳癌検診が始まる40歳以下である．このため術後10年を過ぎると検診を受診しない期間が生じていることになる．若年性乳癌は乳癌ハイリスクであり，遺伝性乳癌・卵巣癌症候群（Hereditary Breast and Ovarian Cancer：HBOC）の可能性もある群である．術後定期的な検診を継続して受けることが望まれる群であり，今後はMRIを含めた定期検診や，遺伝カウンセリングも考慮した術後乳房検診のあり方も検討する必要があると思われる[10]．

術後10年後に一般検診へ回った場合，検診を受け入れる側は乳癌術後患者の片側のみのMMGや乳房部分切除後のMMGを読影することになるが，検診初年度でも比較読影ができるように検診を受け入れる側と治療施設との連携が望まれる．

今回の調査は日本の各施設における若年性乳癌の術後乳房定期検査の現状を明らかにすることに主眼を置いた．この現状が適切か否かを判断するには客観的なエビデンスが得にくい分野ではあるが，今後若年性乳癌が術後何年にどの検査で乳房内再発もしくは対側乳癌が発見され，予後はどうであったかについての検討は必要である．

結　語

日本の若年性乳癌術後の乳房定期検査の現状が本アンケート調査により明らかとなった．USの有用性の検証と術後10年以降の検診の受け入れ体制の構築が望まれる．

今回の結果内容の一部は一般女性向けに書き換え，班研究が作成したホームページ http//www.jakunen.com/ で公開されている．

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文　献

1）日本乳癌学会：科学的根拠に基づく乳癌診療ガイドライン2　疫学・診断編　2011年版．金原出版，東京，2011
2）National Institute for Clinical Excellence：Early and locally advanced breast cancer：diagnosis and treatment. National Collaborating Center for Cancer, Wales, 2009
3）Montgomery DA, Krupa K, Cooke TG：Alternative methods of follow up in breast cancer：a systematic review of the literature. *Br J Cancer* 96：1625-1632, 2007
4）Montgomery DA, Krupa K, Cooke TG：Follow-up in breast cancer：does routine clinical examination improve outcome? A systematic review of the literature. *Br Journal Cancer* 97：1632-1641, 2007
5）Khatcheressian JL, Wolff AC, Smith TJ, et al：American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol* 24：5091-5097, 2006
6）森本忠興，長尾妙子，岡崎憲二，他：乳癌検診の現状．外科治療 101：637-645，2009
7）大貫幸二，宇佐美伸：超音波併用MMG検診　同時併用検診の意義と課題．映像情報 Medical 41：1293-1296，2009
8）Kataja V, Castiglione M, and on behalf of the ESMO Guidelines Working Group：Primary breast cancer：ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 20 (Supplement 4), 2009
9）Ohuchi N, Ishida T, Kawai M, et al：Randomized controlled trial on effectiveness of ultrasonography screening for breast cancer in women aged 40-49 (J-START)：research design. *Jpn J Clin Oncol* 41：275-277. Epub 2011
10）Narod SA：Screening of women at high risk for breast cancer. *Prev Med* 53：127-130. Epub 2011

Efficacy of goserelin plus anastrozole in premenopausal women with advanced or recurrent breast cancer refractory to an LH-RH analogue with tamoxifen: Results of the JMTO BC08-01 phase II trial

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Abstract. The aim of the present study was to assess the efficacy and tolerability of a luteinizing hormone-releasing hormone (LH-RH) analogue plus an aromatase inhibitor following failure to respond to standard LH-RH analogue plus tamoxifen (TAM) in premenopausal patients. Premenopausal women with estrogen receptor (ER)-positive and/or progesterone-receptor positive, advanced or recurrent breast cancer refractory to an LH-RH analogue plus TAM received goserelin (GOS) in conjunction with anastrozole (ANA). The primary endpoint was the objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR) and safety. Between September 2008 and November 2010, 37 patients were enrolled. Thirty-five patients (94.6%) had ER-positive tumors, and 36 (97.3%) had human epidermal growth factor receptor (HER) 2-negative tumors. Thirty-six (97.3%) had measurable lesions and 1 (2.7%) had only bone metastasis. The ORR was 18.9% [95% confidence interval (CI), 8.0-35.2%], the CBR was 62.2% (95% CI, 44.8-77.5%) and the median PFS was 7.3 months. Eight patients had adverse drug reactions but none resulted in discontinuation of treatment. GOS plus ANA is a safe effective treatment for premenopausal women with hormone receptor-positive, recurrent or advanced breast cancer. The treatment may become viable treatment in the future, particularly when TAM is ineffective or contraindicated. Further studies and discussion are warranted.

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Key words: aromatase inhibitor, breast cancer, luteinizing hormone-releasing hormone analogue, premenopausal patient, tamoxifen

Introduction

Approximately 70% of all cases of breast cancer are hormone receptor-positive. Endocrine therapy is generally used for adjuvant treatment and the management of recurrence in hormone-sensitive breast cancer. Ovarian suppression induced surgically or with a luteinizing-hormone-releasing hormone (LH-RH) analogue as a postoperative adjuvant therapy can prevent recurrence and prolong survival in premenopausal women with breast cancer. The effectiveness of these treatments is comparable to that of chemotherapy (1,2). In premenopausal women, estrogen is synthesized primarily by the ovaries, and high estrogen concentrations are maintained in the blood. After menopause, the decline in ovarian function is accompanied by a significant decrease in estrogen concentrations in the blood, although levels remain high enough to stimulate the proliferation of breast cancer cells. Estrogen in postmenopausal patients is largely produced in peripheral adipose tissue and in cancer cells, and the peripheral aromatase is not under gonadotropin regulation (3). Therefore, aromatase inhibitors are used as standard treatment in postmenopausal

women with breast cancer following the cessation of ovarian function. Particularly in patients with recurrent or metastatic breast cancer, the major treatment objectives are to maintain or improve the quality of life (QOL) and to prolong survival. Treatment should therefore be initiated with endocrine therapy.

Endocrine therapy basically involves sequential administration of single agents. However, the combined use of an LH-RH analogue and tamoxifen (TAM) is superior to monotherapy (4) and is, therefore, the treatment of choice for premenopausal women with advanced or recurrent breast cancer. However, when the disease is resistant to combination therapy involving LH-RH analogue and TAM, alternative regimens for endocrine therapy are currently unavailable, with the exception of synthetic progesterone agents (medroxyprogesterone acetate). A number of patients must therefore receive chemotherapy. Consequently, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend that premenopausal women with advanced or recurrent breast cancer undergo ovarian ablation or suppression and then receive treatment similar to that recommended for postmenopausal women. The above mentioned guidelines recommend that premenopausal breast cancer patients undergo a combination treatment that includes an LH-RH analogue and an aromatase inhibitor. However, few studies support this treatment regime for premenopausal patients. Forward *et al* (5) studied goserelin (GOS) plus anastrozole (ANA) as a second-line endocrine therapy in 16 premenopausal women with advanced breast cancer who had previously received an LH-RH analogue plus TAM. After 6 months of treatment, 1 patient had partial response (PR), 9 had stable disease (SD) and 2 had a biochemical response. The clinical benefit rate was 75%. Serum estradiol levels were measured during treatment. Introduction of GOS and TAM reduced mean estradiol levels by approximately 89%. Substitution of TAM with ANA further decreased estradiol levels by 76%. This represents a marked decrease compared with the level during treatment using GOS and TAM.

These results suggest that combination therapy with an LH-RH analogue and an aromatase inhibitor is a viable treatment option for premenopausal women with breast cancer. To confirm this hypothesis, we studied the response rate to an LH-RH analogue plus ANA in women who failed to respond to an LH-RH analogue plus TAM. Progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR) and safety were also assessed.

Patients and methods

Study design. This open-label, single-arm, multi-center, phase II study (registration no. UMIN000001217) was conducted to assess the efficacy and safety profile of an LH-RH analogue and an aromatase inhibitor combination therapy in patients with TAM-refractory, ER-positive, premenopausal metastatic breast cancer in Japan between September 2008 and February 2012. The following treatment was initiated within 4 weeks after enrollment. Anastrozole (Arimidex) 1-mg tablets were administered orally once daily. A 3.6-mg depot of GOS acetate (Zoladex) was injected subcutaneously into the lower abdomen once every 4 weeks (28 days). Treatment was continued until the development of progressive disease (PD) or unacceptable adverse events.

This study was conducted in accordance with the Declaration of Helsinki, and the Ethical Guidelines for Clinical Studies, July 30, 2003 (Amended December 28, 2004) by the Ministry of Health, Labor and Welfare, Japan. This protocol was approved by JMTO (The Japan-Multinational Trial Organization) Ethics Committee in February 2008 and was also approved by the Ethics Committee of each institution. The local assessment [complete response (CR), PR or prolonged SD of ≥24 weeks] was confirmed independently by two radiologists.

Eligible patients. Eligible patients had to meet all of the following inclusion criteria at study entry: premenopausal women 20-55 years of age (at enrollment); a confirmed diagnosis of metastatic or recurrent breast cancer; measurable lesions [according to Response Evaluation Criteria in Solid Tumors (RECIST)] or assessable bone lesions; refractoriness to previous treatment with an LH-RH analogue plus TAM; compliance with one of the following four conditions: i) recurrence while receiving postoperative therapy with an LH-RH analogue plus TAM; ii) recurrence within 1 year after the completion of at least 2 years of postoperative treatment with an LH-RH analogue plus TAM; iii) recurrence while receiving postoperative treatment with TAM alone after at least 2 years of treatment with an LH-RH analogue plus TAM or recurrence within 1 year after the completion of treatment with TAM, or iv) progressive disease while receiving combination therapy with an LH-RH analogue plus TAM for the management of advanced or recurrent breast cancer; estrogen receptor (ER)- and/or progesterone receptor (PgR)-positive breast cancer (positivity rate ≥10% on immunohistochemical analysis), an Eastern Cooperative Oncology Group performance status of 0 or 1; in patients who were receiving bisphosphonates, measurable lesions in sites other than the bone able to be followed up for antitumor response; with no serious complications; and written informed consent to participate in the study, received directly from the patient.

Patients were excluded from the study if they met any of the following criteria: i) a history of allergy to the study drug or concurrently used drugs; ii) treatment with other antitumor agents after prior therapy (LH-RH analogue plus TAM or LH-RH analogue plus TAM→TAM); iii) continuous treatment with systemic corticosteroids (orally or intravenously); iv) advanced cancer in other organs <5 years after treatment; v) a history of thrombosis, such as deep vein thrombosis or cerebral infarction; vi) a history of serious cardiac disease, such as myocardial infarction, valvular disease, or heart failure; vii) hormone-replacement therapy for climacteric symptoms received for ≤4 weeks at the time of enrollment; viii) women who were pregnant, breast feeding, or possibly (planning to be) pregnant; ix) treatment with antineoplastic agents other than an LH-RH analogue plus ANA, bisphosphonates, or radiotherapy of target lesions scheduled to be received after the start of the study; and x) patients considered unsuitable for the study by the investigator.

Study variables. The variables investigated included age, body-mass index, tumor diameter of the primary lesion, lymph-node metastasis, ER, PgR, human epidermal growth factor receptor (HER) 2 status, sites of metastasis or recurrence, performance

status at enrollment (according to the Eastern Cooperative Oncology Group), the presence or absence of postoperative radiotherapy, and the presence or absence of chemotherapy. Immunohistochemical staining was used to evaluate ER, PgR and HER2. ER and PgR were judged to be positive if the percentage of positive cells was ≥10%. HER2-positivity was defined as 3+ by immunohistochemistry or HER2 amplification by fluorescent *in situ* hybridization (HER2/CEP17 >2.0).

Endpoints. The primary endpoint was the response rate. Tumor shrinkage was evaluated according to the RECIST version 1.0 (6), and response was categorized as CR, PR, SD or PD. Bone lesions are generally considered non-target lesions as they are unmeasurable. However, bone is a common site of metastasis from breast cancer, in which the rate of metastasis is as high as 70-80%. In the present study, bone metastases were considered target lesions for the evaluation of response only in patients who only had bone metastases. The response of bone lesions was evaluated according to the standards of the Japanese Breast Cancer Society (7). If lesions existed in sites other than bone, bone lesions were evaluated as non-target lesions.

Secondary endpoints were PFS, OS, CBR and safety. PFS was defined as the number of days from enrollment to an initial event (disease progression or mortality from any cause, whichever occurred first). CBR was defined as the percentage of patients who had a CR, PR or prolonged SD maintained for at least 24 weeks among all eligible subjects. Safety was evaluated according to the Common Terminology Criteria of Adverse Events (CTCAE), version 3.0 (8).

Statistical analysis. The design of this study was based on a binomial distribution with no planned interim analysis. Assuming a null hypothesis of a 6% ORR and an alternative hypothesis of a 20% ORR, with one-sided type I error = 0.025 and type II error = 0.2, the required sample size was calculated to be 33. The planned sample size was set at 35, with the consideration of ~5% of patients being ineligible.

Exact confidence intervals (95% CI) were calculated for CBR and ORR. PFS and OS were estimated by the Kaplan-Meier method. The incidence of grade 3 or 4 adverse events is shown according to type. If an adverse event of the same type and the same grade developed twice in the same patient, it was counted as one event. Statistical analysis was performed with SAS System Release 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. From September 2008 to November 2010, a total of 37 patients were enrolled in the study. The patients were followed up and outcomes were confirmed in February 2012. Table I shows the demographic characteristics of the 37 patients. The median age was 43.0 years (range, 33-53), and the median body-mass index was 21.6 kg/m^2 (range, 16.9-30.3). The median disease-free interval (DFI) was 58.0 months (range, 0.9-201.3) and 12 patients (42.9%) had longer DFI (>60 months). ER/PgR status was ER+/PgR+ in 27 patients (73.0%), ER+/PgR- in 8 (21.6%) and ER-/PgR+ in 2 (5.4%). HER2 was negative in 36 patients (97.6%). During prior treatment with an LH-RH analogue plus TAM, 26 patients (70.3%) had PD, and 6 (16.2%) had recurrence during postoperative adjuvant therapy; 5 patients (13.5%) had completed the previous course of adjuvant therapy. Previous treatment included radiotherapy in 13 patients (35.1%) and chemotherapy in 20 (54.1%).

Table I. Patient characteristics.

Characteristics (n=37)	Median	Range
Age (years)	43.0	33-53
BMI (kg/m^2)	21.6	16.9-30.3
Disease-free interval (months; 28 recurrent cases)	58.0	0.9-201.3

Characteristics (n=37)	No. of patients	%
ER and PgR status		
ER+ and PgR+	27	73.0
ER+ and PgR-	8	21.6
ER- and PgR+	2	5.4
HER2 status		
Negative	36	97.3
Unknown	1	2.7
Description of previous treatment (LH-RHa + TAM)		
Recurrence during postoperative therapy	6	16.2
Recurrence within 1 year after completing postoperative therapy	1	2.7
Recurrence during continued adjuvant therapy with TAM alone or within 1 year after completion	4	10.8
Disease progression during treatment for advanced or recurrent breast cancer	26	70.3
History of other previous treatments		
Prior radiotherapy	13	35.1
Prior chemotherapy	20	54.1
Presence of metastatic sites (n=37)		
No	6	16.2
Yes	31	83.8
Metastatic sites (n=31)		
Breast	2	6.5
Skin	2	6.5
Lymph nodes	12	38.7
Bone	14	45.2
Lung	9	29.0
Pleura	1	3.2
Liver	9	29.0
Type of treated lesions (n=37)		
Measurable disease	15	40.5
Measurable + bone	21	56.8
Bone only	1	2.7

LH-RHa, luteinizing hormone-releasing hormone analogue; TAM, tamoxifen; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PgR, progesterone receptor.

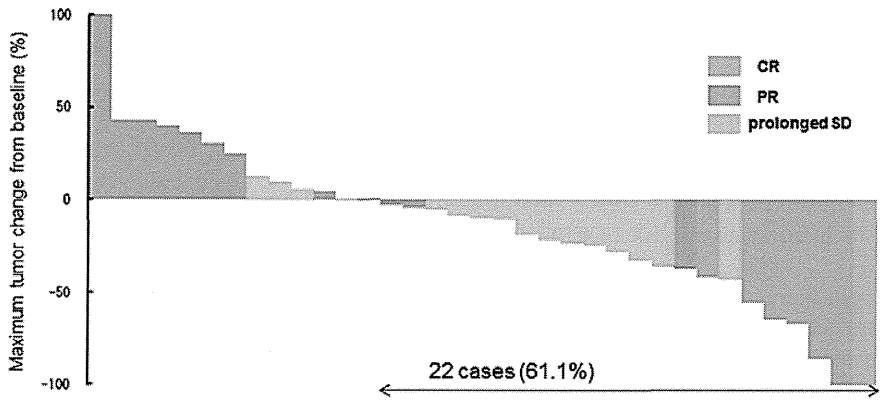

Figure 1. Waterfall plot of maximal change (%) in RECIST-evaluable tumor size from baseline. Thirty-six patients had measurable disease at baseline, and tumor shrinkage was found in 22 patients (61.1%). Of the patients with long-SD, 12 patients (75%) had tumor shrinkage. CR, complete response; PR, partial response; SD, stable disease.

Table II. Objective response rates and clinical benefit rates.

Response	No. of patients	%	95% CI
Complete response	1	2.7	
Partial response	6	16.2	
Objective response	7	18.9	8.0-35.2
Stable disease ≥24 weeks	16	43.2	
Clinical benefit	23	62.2	44.8-77.5
Stable disease <24 weeks	2	5.4	
Progressive disease	11	29.7	
Not evaluable[a]	1	2.7	

[a]Response was not assessable in 1 patient who withdrew her informed consent as she wanted to receive a folk remedy. CI, confidence interval.

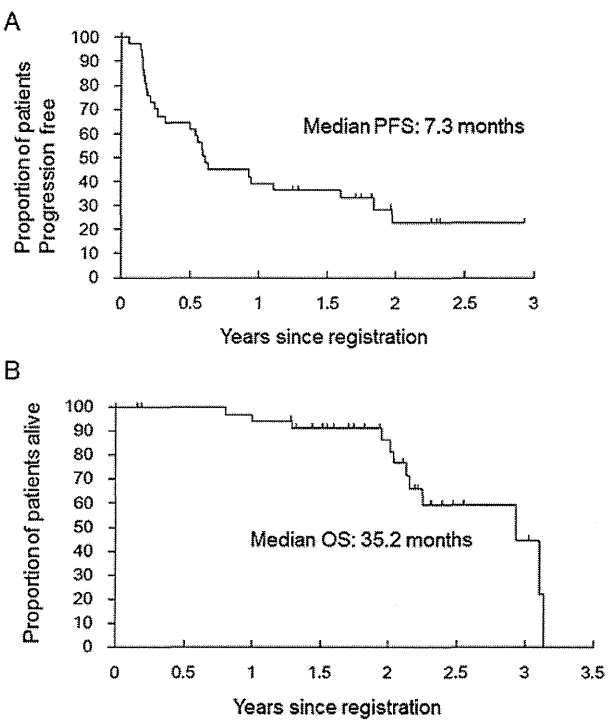

Figure 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) since registration of the 37 enrolled patients. The median PFS and OS were 7.3 and 35.2 months, respectively. New lesions developed in 12 patients, 9 had progression of non-target lesions and 1 had progression of target lesions. Breast cancer was responsible for the 12 deaths.

Thirty-one patients had distant metastases and 6 had locally advanced disease. The sites of metastasis were bone in 14 patients, lymph nodes in 12, liver in 9, lung in 9, contralateral breast in 2, distant skin in 2 and pleura in 1. Thirty-six patients (97.3%) had measurable disease, 21 (56.8%) of the patients also had bone lesions and 1 had only bone metastasis.

Clinical effectiveness. Clinical effectiveness is summarized in Table II. One patient (2.7%) had a CR, and 6 (16.2%) had PR for a response rate of 18.9% (95% CI, 8.0% to 35.2%; P=0.006 under the null hypothesis of a 6% ORR). Sixteen patients (43.2%) had prolonged SD. The CBR was thus 62.2% (23 patients, 95% CI, 44.8-77.5%). Eleven patients (29.7%) had PD. One patient with a response of not evaluable withdrew her informed consent as she wanted to receive a folk remedy. Fig. 1 shows a waterfall plot of maximal change (%) in RECIST-evaluable tumor size from baseline. Thirty-six patients had measurable disease at baseline, and tumor shrinkage was found in 22 patients (61.1%). Of the patients with prolonged SD, 12 patients (75%) had tumor shrinkage.

Regarding the previous treatment (LH-RH analogue + TAM) status, the ORR of the patients was as follows; 16.7% (1/6) in the recurrence group during postoperative therapy, none (0/1) in the recurrence group within 1 year after completing postoperative therapy, none (0/4) in the recurrence group during continued adjuvant therapy with TAM alone or within 1 year after completion, and 23.1% (6/26) in the disease progression group during treatment for advanced or recurrent breast cancer.

Patient outcomes. Fig. 2 shows PFS and OS. The median PFS was 7.3 months. New lesions developed in 12 patients, 9 had progression of non-target lesions, and 16 had progression of target lesions. The median OS was 35.2 months. Breast cancer was responsible for the 12 deaths.

Table III. Adverse events and adverse drug reactions.

	Adverse events		Adverse drug reactions	
Event	Grade 1	Grade 2	Grade 1	Grade 2
Hot flashes	9		3	
Joint pain	5	1	1	1
Sweating	7		1	
Laboratory abnormalities[a]	3		3	
Insomnia	3		1	
Pain (limbs)	3			
Arthritis (non-septic)	2			
Fracture[b]		1		
Precordial pain	1		1	
Fatigue	1		1	
Nausea	1		1	

[a]Laboratory abnormalities: abnormal RBC, total cholesterol and ALT values occurred in 1 patient each. [b]Fracture: a fissured fracture occurred after stumbling. There were no grade 3 or 4 adverse events.

Adverse events. Adverse events are shown in Table III. Most adverse events were grade 1. One patient had grade 2 arthralgia and 1 had a grade 2 bone fracture. Adverse drug reactions for which a causal relationship to treatment could not be ruled out are shown. A total of 13 events occurred in 8 patients. With the exception of the grade 2 arthralgia (1 patient), all other events were grade 1. Treatment was not discontinued due to adverse events in any patient. There were no safety issues according to the IDMC.

Discussion

Few confirmatory studies have been performed with aromatase inhibitors in combination with luteinizing hormone-releasing hormone (LH-RH) analogue in premenopausal women with recurrent or advanced breast cancer. Therefore, we studied the clinical effectiveness of creating a goserelin (GOS) and anastrozole (ANA) combination therapy for breast cancer patients who failed to respond to an LH-RH analogue plus tamoxifen (TAM). The response rate was 18.9%, with a clinical benefit rate (CBR) of 62.2%, a median progression-free survival (PFS) of 7.3 months, and a median overall survival (OS) of 35.2 months. On disease progression, second-line treatment options include other types of endocrine therapy for estrogen receptor (ER)-positive breast cancer. Moreover, hormone resistance includes primary (*de novo*) and secondary (acquired) resistance, and the mechanism of resistance between them may differ. It was reported (9) that the patients with secondary resistance responded to the second-line treatment. According to the previous treatment status (LHRH analogue + TAM), the objective response rate (ORR) in the patients (possibly primary resistance) with recurrence during adjuvant therapy or within 1 year after completion was low [total, 9.1% (1/11)]. On the other hand, the ORR was high (23.8%, 6/26) in the patients with disease progression during treatment for advanced or recurrent breast cancer. Although there were several cases with longer disease-free interval (DFI) (possibly secondary resistance), it was difficult to distinguish between primary and secondary hormone resistance in the present study.

Aromatase inhibitors have been shown to increase gonadotropin secretion and to activate ovarian function in premenopausal women (10,11). By contrast, LH-RH analogues inhibit ovarian function and create a postmenopausal hormone environment, facilitating a response to treatment with an aromatase inhibitor. The above mentioned treatment suggests that the combination of aromatase inhibitors with an LH-RH analogue could obtain a complete estrogen blockade by suppressing the ovarian function and the synthesis of peripheral estrogen. In addition, this treatment may produce substantial antitumor activity in premenopausal women (8). Forward *et al* (5) and Carlson *et al* (12) clearly described this hormonal environment.

A meta-analysis comparing an LH-RH analogue alone with an LH-RH analogue plus TAM in premenopausal women with advanced breast cancer showed that the ORR was 29.7 and 38.8%, the median PFS was 5.4 and 8.7 months, and the median OS was 2.5 and 2.9 years, respectively. Outcomes were significantly improved in patients who also received TAM (13). On the basis of these results, an LH-RH analogue plus TAM is currently the standard therapy for premenopausal breast cancer. Regarding the treatment of postmenopausal women with recurrent breast cancer, aromatase inhibitors can be considered a standard endocrine therapy as first-line and second-line treatments (14-18). Aromatase inhibitors appear to be a viable treatment option in combination with an LH-RH analogue given to induce a postmenopausal hormonal environment for premenopausal women with breast cancer.

In the present study, an LH-RH analogue plus an aromatase inhibitor were administered to premenopausal women who failed to respond to an LH-RH analogue plus TAM. In a separate study of first-line treatment with an LH-RH analogue and an aromatase inhibitor in 32 premenopausal women with metastatic breast cancer (12), 1 patient (3.1%) had complete response (CR) and 11 (34.4%) had partial response (PR). All patients had a clinical benefit rate (CBR) of 71.9% and a time to progression of 8.3 months (range, 2.1-63). These results were better than those obtained in our study. The majority of the patients were hormone-naïve (12), while all patients in our study were treated with an LH-RH analogue plus TAM, including the patients who developed recurrence within 1 year after the completion of postoperative treatment with an LH-RH analogue plus TAM. This data supports the recommendations of the NCCN which indicates that the patients who received prior endocrine therapy within 1 year are potential candidates for this treatment.

With regard to the second-line treatment, a retrospective study of GOS plus letrozole (n =16) in premenopausal women with advanced breast cancer (19) reported an ORR of 12.5% (1/16) and a CBR of 56.3% (9/16), which is similar to the results obtained in our study. Furthermore, our prospective study demonstrates the benefits of the GOS plus ANA treatment in premenopausal women refractory to an LH-RH analogue with TAM.

The Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) compared an LH-RH analogue plus TAM with an LH-RH analogue plus an aromatase inhibitor as an adjuvant therapy in premenopausal women with endocrine-responsive breast cancer (20). They found that there was no significant difference between the two endocrine therapy groups and that further observation is necessary. In a retrospective study evaluating the effectiveness of letrozole plus an LH-RH analogue administered concurrently with preoperative chemotherapy and as an adjuvant treatment in premenopausal women with locally advanced ER-positive breast cancer (21), the pathological CR rate, decrease in Ki-67 level, and a higher 5-year disease-free survival rate were significantly improved compared to those in a control group of similar patients who received preoperative chemotherapy followed by TAM plus and an LH-RH analogue after surgery.

The STAGE study by Masuda *et al* (22) was a randomized, double-blind trial of ANA vs. TAM in patients receiving GOS for premenopausal breast cancer in the neoadjuvant setting. The study showed that ANA demonstrated a superior benefit-risk profile compared with TAM as a neoadjuvant treatment in premenopausal women with ER+ breast cancer receiving GOS.

Only 1 patient in our study had a grade 2 adverse drug reaction (arthralgia) and the rest had grade 1 events. No patient discontinued treatment due to adverse events, which were relatively low and were considered symptoms associated with ANA in postmenopausal women. Previous studies have also reported that GOS plus ANA is safe, with no serious adverse events (12).

In conclusion, our results suggest that combination therapy with GOS and ANA is a safe, highly effective, viable treatment for premenopausal women with hormone-sensitive, recurrent or advanced breast cancer. We consider that GOS plus ANA will be recognized as a standard treatment for premenopausal ER-positive recurrent breast cancer, particularly when TAM is contraindicated or ineffective. Further studies and discussion are required to support these results.

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References

1. Jonat W, Kaufmann M, Sauerbrei W, Blamey R, Cuzick J, Namer M, Fogelman I, de Haes JC, de Matteis A, Stewart A, Eiermann W, Szakolczai I, Palmer M, Schumacher M, Geberth M and Lisboa B; Zoladex Early Breast Cancer Research Association Study: Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the 'Zoladex' Early Breast Cancer Research Association study. J Clin Oncol 20: 4628-4635, 2002.
2. Kaufmann M, Jonat W, Blamey R, Cuzick J, Namer M, Fogelman I, de Haes JC, Schumacher M and Sauerbrei W; Zoladex Early Breast Cancer Research Association (ZEBRA) Trialists' Group: Survival analyses from the ZEBRA study: goserelin (Zoladex) versus CMF in premenopausal women with node-positive breast cancer. Eur J Cancer 39: 1711-1717, 2003.
3. Ackerman GE, Smith ME, Mendelson CR, MacDonald PC and Simpson ER: Aromatization of androstenedione by human adipose tissue stromal cells in monolayer culture. J Clin Endocrinol Metab 53: 412-417, 1981.
4. Jonat W, Kaufmann M, Blamey RW, Howell A, Collins JP, Coates A, Eiermann W, Jänicke F, Njordenskold B and Forbes JF: A randomized study to compare the effect of the luteinising hormone releasing hormone (LH-RH) analogue goserelin with or without tamoxifen in pre- and perimenopausal patients with advanced breast cancer. Eur J Cancer 31A: 137-142, 1995.
5. Forward DP, Cheung KL, Jackson L and Robertson JF: Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. Br J Cancer 90: 590-594, 2004.
6. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92: 205-216, 2000.
7. Japan Breast Cancer Society: General Rules for Clinical and Pathological Recording of Breast Cancer. 14th edition. Kanehara Publications, Tokyo, 2000 (In Japanese).
8. National Cancer Institute: Common Terminology Criteria for Adverse Events version 3.0 (CTCAE). http://ctep.cancer.gov.
9. Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, Abadie-Lacourtoisie S, Eymard JC, Debled M, Spaëth D, Legouffe E, Allouache D, El Kouri C and Pujade-Lauraine E: Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. J Clin Oncol 30: 2718-2724, 2012.
10. Smith IE and Dowsett M: Aromatase inhibitors in breast cancer. N Engl J Med 348: 2431-2442, 2003.
11. Smith IE, Dowsett M, Yap YS, Walsh G, Lønning PE, Santen RJ and Hayes D: Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol 24: 2444-2447, 2006.
12. Carlson RW, Theriault R, Schurman CM, Rivera E, Chung CT, Phan SC, Arun B, Dice K, Chiv VY, Green M and Valero V: Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor-positive, metastatic carcinoma of the breast in premenopausal women. J Clin Oncol 28: 3917-3921, 2010.
13. Michaud JB, Jones KL and Buzdar AU: Combination endocrine therapy in the management of breast cancer. Oncologist 6: 538-546, 2001.
14. Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, Steinberg M, Webster A and von Euler M: Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. J Clin Oncol 18: 3758-3767, 2000.
15. Paridaens RJ, Dirix LY, Beex LV, Nooij M, Cameron DA, Cufer T, Piccart MJ, Bogaerts J and Therasse P: Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol 26: 4883-4890, 2008.
16. Mouridsen H, Gershanovich M, Sun Y, Pérez-Carrión R, Boni C, Monnier A, Apffelstaedt J, Smith R, Sleeboom HP, Jänicke F, Pluzanska A, Dank M, Becquart D, Bapsy PP, Salminen E, Snyder R, Lassus M, Verbeek JA, Staffler B, Chaudri-Ross HA and Dugan M: Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol 19: 2596-2606, 2001.
17. Osborne CK, Pippen J, Jones SE, Parker LM, Ellis M, Come S, Gertler SZ, May JT, Burton G, Dimery I, Webster A, Morris C, Elledge R and Buzdar A: Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 20: 3386-3395, 2002.
18. Kaufmann M, Bajetta E, Dirix LY, Fein LE, Jones SE, Zilembo N, Dugardyn JL, Nasurdi C, Mennel RG, Cervek J, Fowst C, Polli A, di Salle E, Arkhipov A, Piscitelli G, Miller LL and Massimini G: Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. J Clin Oncol 18: 1399-1411, 2000.

19. Yao S, Xu B, Li Q, Zhang P, Yuan P, Wang J, Ma F and Fan Y: Goserelin plus letrozole as first- or second-line hormonal treatment in premenopausal patients with advanced breast cancer. Endocr J 58: 509-516, 2011.
20. Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, Pöstlberger S, Menzel C, Jakesz R, Seifert M, Hubalek M, Bjelic-Radisic V, Samonigg H, Tausch C, Eidtmann H, Steger G, Kwasny W, Dubsky P, Fridrik M, Fitzal F, Stierer M, Rücklinger E and Greil R; ABCSG-12 Trial Investigators and Marth C: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 360: 679-691, 2009.
21. Torrisi R, Bagnardi V, Rotmensz N, Scarano E, Iorfida M, Veronesi P, Luini A, Viale G, Santoro A, Colleoni M and Goldhirsch A: Letrozole plus GnRH analogue as preoperative and adjuvant therapy in premenopausal women with ER positive locally advanced breast cancer. Breast Cancer Res Treat 126: 431-441, 2011.
22. Masuda N, Sagara Y, Kinoshita T, Iwata H, Nakamura S, Yanagita Y, Nishimura R, Iwase H, Kamigaki S, Takei H and Noguchi S: Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. Lancet Oncol 13: 345-352, 2012.

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SPECIAL FEATURE

The current status and future perspectives of clinical trial groups in Japan

An overview of the Japan Breast Cancer Research Group (JBCRG) activities

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Abstract The purpose of this article is to describe the current status and future perspectives of the Japan Breast Cancer Research Group (JBCRG). The JBCRG was organized in 2002, with the following purpose: to plan and promote clinical trials and basic research in breast cancer domestically and multilaterally; to conduct research and surveys on domestic and foreign information on medical care for breast cancer and to diffuse and highlight such information; to improve and promote clinical technologies for breast cancer; to act as an intermediary to liaise and strengthen alliances with affiliated organizations; and, to contribute to the public welfare by improving outcomes in breast cancer. The clinical trials are led by doctors/investigators in the JBCRG. And the purpose is to establish standard treatment for patients and provide substantial evidence. The JBCRG implements international collaboration in some researches/studies. As of January 2012, fourteen trials have been closed and nine are open to recruitment.

Keywords Clinical trials · Clinical research · Preoperative systemic therapy · Breast cancer

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Introduction

The incidence of breast cancer in Japan has increased yearly; thus, more attention has been given to breast cancer treatment, among all cancers. In order to save as many breast cancer patients as possible, and to improve their quality of life (QOL), new diagnostic methods, treatments, and prophylaxes for breast cancer should be developed.

The JBCRG shall carry out the following, to serve the aforementioned purpose:

1. Basic and clinical research
2. Collection, analysis, and publication of information
3. Mutual exchange of information
4. Ordinary/extraordinary general meetings
5. Any other affairs required to accomplish the purpose of the JBCRG

The JBCRG has conducted mainly phase II trials to give answers to clinical questions, and now is planning to start phase III ones to achieve clinical approval of new standard therapies. The JBCRG is soliciting donations from organizations and individuals who wish to support its activities. The JBCRG usually manages data quality by central monitoring at data centers including the JBCRG Data Center, which is located in the Kyoto Technoscience Center, Kyoto; however, in some studies such as the SOLE trial, the JBCRG conducted site visits for source document verification.

As of January 2012, 243 doctors from 154 institutes are registered as JBCRG members who are specialists from the breast cancer treating hospitals around Japan. Also, the JBCRG is a member of the Breast International Group (BIG), which is an international breast cancer research group. Tables 1 and 2 summarize the closed and ongoing clinical trials, respectively.

Table 1 JBCRG trials closed/in follow-up

Trial	Design	No. of pts	Primary endpoints	Regimen	Enrollment start date
Neoadjuvant setting					
1	Phase II	202	Clinical response, safety	FEC100 q3w×4 → Doc75 q3w×4	Jun 02
2	Phase II	31	Clinical response, safety	FEC100 q3w×4 → Doc100 q3w×4	Aug 04
2′	Validation	19	Clinical response, histological effects, safety	FEC100 q3w×4 → Doc100 q3w×4	Dec 05
3	Phase II	130	Histological effects, safety	Doc75 q3w×4 → FEC100 q3w×4	Oct 05
5	Phase II	33	Response rates	Doc75 q3w×4 → letrozole 12 (−18) w	Sep 07
6	Phase II	40	Response rates	Letrozole 12 (−18) w	Sep 07
7	Phase II	40	Response rates	Letrozole + cyclophosphamide 24 w	Oct 07
10	Randomized phase II	180	Pathological CR rate	(1) FEC×4 → TCH×4, (2) TCH×4 → FEC×4, (3) TCH×6	Jun 09
13	Phase II	40	Pathological CR rate	Metronomic PCX 4 → FEC×4	Jan 10
Postoperative setting					
4 (CREATE-X)	Phase III	900	Disease-free survival	Any preoperative systemic therapy ± capecitabine	Feb 07
SOLE with BIG	Phase III	4,800	Disease-free survival	Intermittent or continuous letrozole	Apr 10
8 ALTTO	Phase III	140	Disease-free survival	Lapatinib and/or trastuzumab	Jul 07
Metastatic setting					
M01	Phase I	6	MTD, DLT, RD	CPT11 + S1	Jul 06
M01	Phase II	37	Response rates, clinical efficacy	CPT11 + S1	Jul 06
M02	Phase II	50	Response rates	Letrozole	Nov 06
Cohort study					
C01	Cohort	1,500	Disease-free survival	Trastuzumab	Sep 07

Data correct as of 31 March 2012

CR complete response, *MTD* maximum tolerated dose, *DLT* dose limiting toxicity, *RD* recommended dose, *FEC* 5-fluorouracil + epirubicin + cyclophosphamide, *Doc* docetaxel, *TCH* docetaxel + cyclophosphamide + trastuzumab, *PCX* paclitaxel + cyclophosphamide + capecitabine

Neoadjuvant pharmacotherapy

The first clinical trial conducted by the JBCRG was JBCRG-01, a phase II trial of preoperative systemic therapy (PST) using fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by docetaxel (Doc) in patients with primary operable breast cancer [1–3]. Subsequently, JBCRG-02 study was conducted using FEC followed by Doc 100 to investigate the safety and feasibility of 100 mg/m^2 Doc as PST. JBCRG-03 was a study to clarify the most effective sequence of FEC and Doc75 [4]. From the results of these studies, we defined new criteria of pathological response to PST, quasi pathological complete response (QpCR), total or near total disappearance of the invasive tumor in the removed breast. QpCR following preoperative chemotherapy predicts favorable disease-free survival (DFS). HER2 overexpression and clinical response to FEC predict QpCR [5, 6].

JBCRG-01

JBCRG-01 was started in 2002 [1–3]. This multicenter phase II study examined the impact of pathological effect on survival after preoperative chemotherapy in Japanese women with early-stage breast cancer (ESBC). Prior to surgery, patients received four cycles of FEC (fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2 q3w) followed by four cycles of docetaxel (75 mg/m^2 q3w). The primary endpoint was 3-year DFS stratified by the absence or presence of QpCR (absence of invasive tumor or only focal residual tumor cells). Secondary endpoints were predictors for QpCR, clinical response, breast conservation rate, and safety. Between June 2002 and June 2004, 202 women were enrolled. Among 191 assessable patients, 25 % achieved QpCR. With 40 months median follow-up, 3-year DFS was estimated at 91 % for all patients. The 3-year DFS for patients

Table 2 JBCRG trials open to recruitment

Trial	Design	No. of pts	Primary endpoints	Regimen	Enrollment start date
Neoadjuvant setting					
9	Randomized phase II	195	Histological response	TC×6, FEC×3 → TC×3,TC×3 → FEC×3	Sep 09
11CPA	Phase II	55	Response rates	Letrozole ± low dose cyclophosphamide	Oct 10
11TC	Phase II	60	Clinical response	Exemestane 12w or exemestane 12w+TC×4	Oct 10
Postoperative setting					
15	Phase II	30	Pharmacokinetics	Toremifene	Mar 09
SUPREMO with IBCSG	Phase III	3,700	Overall survival	Chest wall radiation	Jul 09
Metastatic setting					
12	Phase II	200	CYP2D6 and pharmacokinetics	Tamoxifen and toremifene	Jan 10
Cohort study					
C02	Cohort	100	Progression-free survival	Trastuzumab	Jul 09

Data correct as of 31 March 2012

TC docetaxel + cyclophosphamide, *FEC* 5-fluorouracil + epirubicin + cyclophosphamide

with QpCR was 98 vs. 89 % for those without QpCR (hazard ratio 0.38 [95 % confidence interval 0.09–0.84], $P = 0.0134$). HER2 status and response to FEC were independent predictors of QpCR. The overall clinical response rate was 75 %; 85 % of patients achieved breast conservation. Grade 3/4 neutropenia was the most common adverse event, observed in 44 and 35 % of patients during FEC and docetaxel treatment, respectively. Treatment-related side effects were manageable; there were no treatment-related fatalities.

JBCRG-02

The JBCRG-02 study was conducted to evaluate the safety and clinical and histologic effects of primary systemic chemotherapy using FEC followed by docetaxel in primary breast cancer. The primary endpoints were safety and clinical and histologic effects. Secondary endpoints were breast-conserving rate and DFS. Fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2, q3w ×4 cycles, were followed by docetaxel 100 mg/m^2, q3w ×4 cycles, as primary systemic chemotherapy. Among patients receiving this regimen, 19.5 % experienced a pathological complete response and 9.7 % had a near pathological complete response, resulting in a QpCR of 29.2 %.

JBCRG-03

JBCRG-03 was a multicenter, open-label, single-arm, phase II study assessing the efficacy of a neoadjuvant chemotherapy with docetaxel (75 mg/m^2 q3w) followed by 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 q3w in patients with ESBC [4]. The primary endpoint was the pathological complete response (pCR) rate defined for the breast alone, assessed by a central review committee. Secondary endpoints included clinical response and safety. Of the 132 patients assessable for pathologic response, 23 % experienced a pCR and 6 % had a near pathological complete response (few remaining cancer cells), resulting in a QpCR of 29 %. Clinical response rate following the initial docetaxel regimen was 64 %. The overall clinical response rate was 79 %. Breast-conserving surgery was performed in 79 % of patients. More patients with triple-negative disease experienced a pCR (14/29, 48 %) versus those with other molecular subtypes. The safety profile was acceptable.

Oncotype DX

The 21-gene signature has been intensively studied and incorporated into major guidelines for treatment decision in early breast cancer. However, it remains to be examined whether this system is applicable to Asian populations.

Retrospective analysis

Toi et al. [7] were the first report to show that the 21-gene signature has value in providing prognostic information in Asian populations with estrogen receptor (ER)-positive, lymph node (LN)-negative breast cancer. A total of 325 tumor tissues were collected from ER-positive primary breast cancer patients who had undergone surgery and were

treated with tamoxifen between 1992 and 1998. The tissues were analyzed for the 21-gene signature, and the patients were classified into groups of low, intermediate, or high risk on the basis of the recurrence score. A total of 280 patients were eligible, with adequate reverse transcription polymerase chain reaction profiles for the recurrence score. Of those, 200 and 80 patients had LN-negative and LN-positive disease, respectively. The proportions of LN-negative patients categorized as being at low, intermediate, or high risk were 48, 20, and 33 %, respectively. In LN-negative patients, the Kaplan–Meier estimates of the distant recurrence rate at 10 years were 3.3 % (95 % CI 1.1–10.0 %), 0 %, and 24.8 % (95 % CI 15.7–37.8 %) for those in the low-risk, intermediate-risk, and high-risk groups, respectively. The risk of distant recurrence in the low-risk group was significantly lower than that in the high-risk group when the entire Kaplan–Meier plots were compared ($P < 0.001$, log-rank test). There was a significant difference for overall survival between the low-risk and the high-risk groups ($P = 0.008$, log-rank test).

Economic evaluation

JBCRG-TR03

This study evaluates the cost-effectiveness of two scenarios designed to include the assay into Japan's social health insurance benefit package: one for LN−, ER+, ESBC and another for LN±, ER+, ESBC [8]. An economic decision tree and Markov model under Japan's health system from the societal perspective is constructed with new evidence from the Japanese validation study. Incremental cost-effectiveness ratios are estimated as ¥384,828 (US$3,848) per quality-adjusted life year (QALY) for the LN− scenario and ¥568,533 (US$5,685) per QALY for the LN± scenario. Both estimates are not more than the suggested social willingness-to-pay for one QALY gain from an innovative medical intervention in Japan, ¥5,000,000/QALY (US$50,000/QALY). Sensitivity analyses show that this result is plausibly robust, because the incremental cost effectiveness ratios (ICERs) do not exceed the threshold despite various changes of assumptions made and values employed. Therefore, the inclusion of the assay in Japan's social health insurance benefit package for not only LN− diseases but also LN+ diseases is cost-effective. Such a decision can be justifiable as an efficient use of finite resources for health care.

Toxicity

Steroids and H(2) blockers are commonly used as supportive care for taxane-containing chemotherapy, but they also affect docetaxel's primary metabolizer, cytochrome P(450) 3A4. Kawaguchi et al. [9] performed a retrospective observational study to better understand the effects of these compounds on docetaxel-induced skin toxicities, specifically hand-foot syndrome (HFS) and facial erythema (FE), a relationship that is currently poorly understood. Member institutions of the JBCRG were invited to complete a questionnaire on the occurrence of grade 2 or higher HFS and FE among patients treated between April 2007 and March 2008 with docetaxel as an adjuvant or neoadjuvant chemotherapeutic treatment for breast cancer. We obtained data for 993 patients from 20 institutions. Twenty percent received H(2) blockers, and all patients received dexamethasone. Univariate and multivariate analyses revealed that H(2) blockers are associated with a significantly higher incidence of both HFS and FE. The incidence of FE was significantly higher for the docetaxel + cyclophosphamide (TC) regimen than for non-TC regimens combined. Dexamethasone usage did not affect the incidence of either HFS or FE. In conclusion, the use of H(2) blockers as premedication in breast cancer patients receiving docetaxel significantly increases the risk of both HFS and FE.

International study

The JBCRG is a member of the international breast cancer research group BIG. The JBCRG has joined in with several international clinical studies.

JBCRG-04 (CREATE-X)

This study aims to investigate the efficacy and safety of capecitabine, as a postoperative adjuvant chemotherapy, for breast cancer patients who were pathologically demonstrated to have residual cancer cells after the preoperative chemotherapy. In addition, the cost-effectiveness of capecitabine is to be investigated. The primary objective is DFS and secondary ones are overall survival, safety, and cost-effectiveness. Eligible patients had stage I-IIIB at the first diagnosis (curable breast cancer) and were non-pCR after preoperative chemotherapy including at least two cycles anthracycline agents; that is, they were confirmed pathologically by surgical and/or histological tests to have residual cancer cells. The patients had also been confirmed to be HER2 negative.

JBCRG-08 (ALTTO)

JBCRG-08 was a randomized, multicenter, open-label, phase III study of adjuvant lapatinib, trastuzumab, their sequence, and their combination in patients with HER2/ErbB2-positive primary breast cancer (BIG 2-06/N063D/EGF 106708.). The objective of this study was to compare DFS in patients with HER2 overexpressing and/or amplified

breast cancer randomized to trastuzumab for 1 year versus lapatinib for 1 year versus trastuzumab (12 weeks) followed by a 6-week treatment-free interval followed by lapatinib (34 weeks) versus trastuzumab in combination with lapatinib for 1 year. Endpoints were DFS, overall survival (OS), time to recurrence (TTR), time to distant recurrence (TTDR), safety and tolerability, cumulative incidence of brain metastases as the first site of breast cancer recurrence, presence or absence of cMyc gene amplification, expression levels of PTEN, and presence or absence of p95 HER2 domain. Trial periods were between July 2007 and February 2011 (registration, 2 years; follow-up study, 5 years). Target sample size was 140 from 15 institutions.

SOLE trial

SOLE trial is a phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4–6 years of prior adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive, node-positive ESBC. The JBCRG is collaborating with the International Breast Cancer Study Group (IBCSG) on this trial. A total of 4,800 patients are expected to be enrolled in this study. The primary endpoint is DFS, and secondary ones are OS, distant DFS, breast cancer-free interval, sites of first failure, second (non-breast) malignancies, deaths without prior cancer events, and adverse events.

SUPREMO trial

The SUPREMO trial is a randomized phase III trial assessing the role of chest wall irradiation in women with intermediate-risk breast cancer following mastectomy conducted by BIG. Postoperative radiotherapy is routinely given to patients at higher risk of recurrence with 4 or more LNs or large tumor(s). In patients with less than 4 LNs under the armpit involved by cancer or with no LNs involved but other features of the cancer that increase the risk of recurrence, it is not clear whether postoperative radiotherapy is needed. Eligibility criteria are a postoperative breast cancer patient who has had a mastectomy, and who has an intermediate risk of the cancer returning. An intermediate risk is diagnosed when there are less than 4 LNs under the armpit involved by cancer or there are no LNs involved, but there are other features of the cancer that mean it is more likely to come back. The trial will involve 1,600 women.

Conclusion

The JBCRG was founded in order to perform good-quality multicenter studies, and related clinical trials in close liaison with research institutions in other countries and regions, as well as in Japan. The JBCRG has performed a variety of studies, including primary pharmacotherapy, pharmacotherapy for recurrent breast cancer, clinical trials on postoperative pharmacotherapy, prediction of prognosis in hormone receptor-positive breast cancer, and prediction of the effect of chemotherapeutic drugs. The JBCRG has reported a number of outcomes to academic societies and in journals, and has obtained a good reputation. The incidence of breast cancer in Japan has increased yearly; thus, more attention has been given to breast cancer treatment, among all cancers. In order to save as many breast cancer patients as possible, and to improve their QOL, we will develop new diagnostic methods, treatments, and prophylaxes for breast cancer.

References

1. Ohno S, Toi M, Kuroi K, Nakamura S, Iwata H, Kusama M, et al. Update results of FEC followed by docetaxel neoadjuvant trials for primary breast cancer. Biomed Pharmacother. 2005;59:S323–3234.
2. Iwata H, Nakamura S, Toi M, Shin E, Masuda N, Ohno S, et al. Interim analysis of a phase II trial of cyclophosphamide, epirubicin and 5-fluorouracil (CEF) followed by docetaxel as preoperative chemotherapy for early stage breast carcinoma. Breast Cancer. 2005;12:99–103.
3. Toi M, Nakamura S, Kuroi K, Iwata H, Ohno S, Masuda N, et al. Phase II study of preoperative sequential FEC and docetaxel predicts of pathological response and disease free survival. Breast Cancer Res Treat. 2008;110:531–9.
4. Iwata H, Sato N, Masuda N, Nakamura S, Yamamoto N, Kuroi K, et al. Docetaxel followed by fluorouracil/epirubicin/cyclophosphamide as neoadjuvant chemotherapy for patients with primary breast cancer. Jpn J Clin Oncol. 2011;41:867–75.
5. Kuroi K, Toi M, Tsuda H, Kurosumi M, Akiyama F, Japan Breast Cancer Research Group (JBCRG). Issues in the assessment of the pathologic effect of primary systemic therapy for breast cancer. Breast Cancer. 2005;13:38–48.
6. Kuroi K, Toi M, Tsuda H, Kurosumi M, Akiyama F. Un argued issues on the pathological assessment of response in primary systemic therapy for breast cancer. Biomed Pharmacother. 2005;59:S387–92.
7. Toi M, Iwata H, Yamanaka T, Masuda N, Ohno S, Nakamura S, et al. Clinical significance of the 21-gene signature (Oncotype DX) in hormone receptor-positive early stage primary breast cancer in the Japanese population. Cancer. 2010;1:3113–8.
8. Kondo M, Hoshi S, Yamanaka T, Ishiguro H, Toi M. Economic evaluation of the 21-gene signature (Oncotype DX(®)) in lymph node-negative/positive, hormone receptor-positive early-stage breast cancer based on Japanese validation study (JBCRG-TR03). Breast Cancer Res Treat. 2011;127:739–49.
9. Kawaguchi K, Ishiguro H, Morita T, Nakamura S, Ohno S, Masuda N, et al. Correlation between docetaxel-induced skin toxicity and the use of steroids and H2 blockers: a multi-institution survey. Breast Cancer Res Treat. 2011;130:627–34.

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ORIGINAL ARTICLE

Physicians' knowledge, attitude, and behavior regarding fertility issues for young breast cancer patients: a national survey for breast care specialists

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Abstract
Background Fertility is one of the key aspects of quality of life for breast cancer patients of childbearing age. The objective of this study was to describe fertility-related practice for young breast cancer patients in Japan and to identify healthcare provider factors that contribute to physicians' behavior towards fertility preservation.
Methods A cross-sectional survey was developed in order for Japanese breast cancer specialists ($n = 843$) to self-evaluate their knowledge, attitude, and behavior regarding fertility preservation. Survey items included questions regarding knowledge of and attitude toward fertility issues in cancer patients, fertility-related practice, potential barriers for the discussion of fertility with patients, and responding physicians' socio-demographic background.
Results Four hundred and thirty-four (52%) breast oncologists responded to the survey. Female and younger oncologists (age less than 50 years) had significantly higher probability of referring patients to reproductive specialists. Physicians who had better knowledge score and positive attitudes toward fertility preservation were more likely to discuss potential fertility issues with cancer patients. This was significantly associated with consultation and referral to reproduction specialists when encountering fertility issues with cancer patients. Risk of recurrence, lack of collaborating reproductive specialists, and time constraints in the clinic were identified as major barriers to discussion of fertility preservation with breast cancer patients.
Conclusion Female and younger physicians as well as physicians working in a multidisciplinary environment had positive attitudes and behavior towards fertility preservation in breast cancer patients. The development of comprehensive and interdisciplinary programs for healthcare providers is necessary to meet the expectations and fertility needs of breast cancer patients.

Keywords Fertility preservation · Breast cancer · Survivorship

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Introduction

With improvement of cancer prognosis, fertility has become one of the key aspects of quality of life for breast cancer patients of childbearing age. Distress about interrupted childbearing is likely to persist in long-term female cancer survivors [1]. The American Society of Clinical Oncology (ASCO) has developed guidance for oncologists regarding available fertility preservation methods and related issues [2]: oncologists should address the possibility of infertility with patients during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to

reproductive specialists as early as possible during treatment planning.

However, previous studies have shown that only 23% of the patients younger than 40 years of age were informed of potential infertility after cancer treatment in a single institution in Japan and less than half of oncologists were following the ASCO guideline in the USA [3, 4]. The practice of oncologists regarding fertility preservation in cancer patients of reproductive age may depend on multiple factors: the patient's medical and psychosocial condition [5, 6], the patient's knowledge [7], and physicians' knowledge about fertility preservation [8].

We have previously analyzed the decision-making process for adjuvant treatment in young breast cancer patients of reproductive age [3]. Significantly less patients expressed interest in fertility when they had children or advanced disease. Less aggressive treatment (without chemotherapy) was recommended by oncologists for patients who voluntarily expressed an interest in preserving fertility [3]. Nearly one-third of the patients who expressed an interest in fertility selected a different adjuvant treatment from the primary recommendation of the oncologist because of their concern for preserving fertility, whereas the majority of patients who did not express an interest in preserving fertility followed the oncologists' primary recommendation [3].

The awareness and attitude of patients in the clinic might reflect the ability of healthcare providers to provide an environment in which patients could bring up fertility issues. The objectives of this study include describing fertility-related practice for breast cancer patients in a variety of clinical settings in Japan and identifying healthcare provider factors that contribute to physicians' behavior regarding fertility preservation in young breast cancer patients.

Methods

Selection of participant

A cross-sectional survey was developed in order for board-certified breast oncologists of the Japanese Breast Cancer Society (JBCS), who are the main physicians treating breast cancer patients in Japan, to self-evaluate their knowledge, perception, and behavior regarding fertility issues in young breast cancer patients.

Measures

The survey consisted of 49 items including questions regarding knowledge of and attitudes towards fertility in cancer patients, practice behavior of fertility-related discussions with patients, potential barriers for these discussions, and demographic background of the practitioners (Table 1). Survey items were derived from existing literature and multidisciplinary discussion. Physicians were asked to evaluate their agreement with the statements using a five-grade system (1, strongly agree; 2, agree; 3, cannot decide; 4, disagree; 5, strongly disagree).

1. Knowledge about fertility issues in breast cancer patients

To evaluate the accuracy of knowledge about fertility issues in breast cancer patients, the statements were developed from the latest JBCS treatment guideline [5]. For statements A-1 and A-4, the respondents were considered to have more accurate knowledge when the score was lower. For statements A-2 and A-3, the respondents were considered to have more accurate knowledge when the score was higher. Then the sum of (5 − "score for A-1") + ("score for A-2") + ("score for A-3) + (5 − "score for A-4") was calculated. The respondents with a higher sum were considered to have more accurate overall knowledge. A-5 was not used to evaluate the accuracy of knowledge because of lack of definite evidence, but correlated with the use of LHRH agonist for fertility preservation.

2. Practice behavior for breast cancer patients of reproductive age

Practice behavior statements consisted of 13 items including statements used in the US oncologist survey with some modifications to adapt to Japanese practice setting. The statements "I discuss the impact of cancer treatment on future fertility with my patients", "I consult reproductive specialists with questions about fertility issues in my patients", and "I refer patients who have questions about fertility to reproductive specialists" were considered the most important behavior according to the ASCO guideline [2].

3. Potential barriers for discussing fertility issues with breast cancer patients

Among seven potential barriers asked in the questionnaire, four were similar to statements used in the US survey [4]. We put three additional statements (patients' voluntary expression of interest, existence of spouse/partner, and support from co-medical staff) that were created by findings from our previous study [2] and by considering Japanese culture. In addition, we asked the participant to describe the greatest difficulty in discussing fertility in an open question.

4. Attitude towards fertility preservation of cancer patients

Five statements were selected from the US survey [4]. Because the hereditary aspect of breast cancer was considered to be not genuinely linked with perception of

Table 1 Questionnaire statements

A. Knowledge about fertility issues of breast cancer patients
1. Total dose of alkylating agents are related to infertility
2. Pregnancy after breast cancer increases risk of recurrence
3. Pregnancy after chemotherapy increases risk of deformity of the child
4. Pregnancy should be avoided during tamoxifen treatment
5. Luteinizing hormone releasing hormone (LHRH) analogue reduces the risk of chemotherapy-induced amenorrhea
B. Practice behavior
1. Patients voluntarily bring up the fertility issues in the clinic
2. I discuss the impact of cancer treatment to future fertility with my patients
3. I do not feel comfortable to discuss fertility issue with my patients
4. I take into account the history of childbirth when I discuss fertility issue with my patient
5. I take into account whether she has a spouse/partner when I discuss fertility issue with my patient
6. I take into account economical status of the patient when I discuss fertility issue with my patient
7. I discuss fertility issues with breast cancer patients with high risk of recurrence
8. Patients talk to co-medical staff about their concern about fertility
9. I ask co-medical staff if a patient has an interest in fertility
10. I provide my patients with educational material about fertility preservation
11. I use LHRH analogue to preserve fertility
12. I consult a reproductive specialist with questions about fertility issues in my patients
13. I refer patients who have questions about fertility to reproductive specialists
C. Barriers for discussing fertility issues
1. The patient does not express their interest in fertility
2. The patient has high risk of recurrence
3. The patient has economic problems
4. The patient does not have a spouse/partner
5. There is no place/person to refer my patients to for fertility preservation
6. Time constraints affect my ability to discuss fertility preservation
7. There is no support from co-medical staff
8. What is the greatest difficulty in discussing fertility issues with young breast cancer patients?
D. Attitude toward fertility preservation
1. Patients with poor prognosis should not pursue fertility preservation
2. Posthumous parenting is troublesome for bereaved family
3. Losing mothers will negatively affect bereaved children
4. I fear passing hereditary cancer to a biological child
5. Treating cancer is more important than fertility preservation
E. Demographics and medical backgrounds
1. What is your gender?
2. What is your age?
3. What is your religious background?
4. When did you graduate from medical school?
5. What is your specialty?
6. Where is your primary practice located?
7. What kind of institution do you practice in?
8. Is your institution a community-base hospital for cancer care?
9. How many physicians are in your practice setting including you?
10. Are there any female physicians in your practice setting?
11. Are there any medical oncologists in your practice setting?
12. Are there any breast cancer specialized nurses in your practice setting?
13. Are there any cancer-specialized pharmacists in your practice setting?
14. Is there a genetic counseling clinic in your practice setting?
15. In a typical week, how many breast cancer surgeries are performed in your practice setting?
16. In a typical week, how many breast cancer patients under 40 years of age do you see?
17. Do you have a spouse/partner?
18. Do you have children?
19. Do you have relatives or close friends who passed away leaving behind minor children?

fertility preservation, the item was not included in our analysis. Participants were considered to be positive toward fertility preservation if the sum of scores was higher than 3. The sum of scores for statements from D-1 through D-5 was calculated and the respondents with higher total score were considered as physicians with a "positive attitude" towards fertility preservation.

5. Individual and institutional background

The items included physicians' gender, age, religious background, length of professional career, and specialty. We also asked for a description of the practicing institution: the number of breast surgeries, the number of young breast cancer patients, presence of female colleagues in the team, the presence of one or more medical oncologist(s), breast cancer certified clinical nurse specialist (CNS), and board-certified pharmacists in the institution.

Procedures

The study was carried out according to the National Guideline for Epidemiological Studies. The names of study participants and the institutions of breast oncologists were obtained from the JBCS website. After confirmation of each physician's affiliation, anonymous paper surveys were sent out to all 843 breast oncologists by mail with a return

postage-paid envelope. The survey was sent out on 28 May 2010 and the mailed surveys postmarked by 31 July were included in the analysis. The consent from the participants was waived because of the anonymity of the survey. No honorarium was offered for completing the survey.

Data analysis

All analyses were conducted using IBM SPSS statistics version 18. Accuracy of knowledge about fertility was scored on the basis of four questions (A-1, 2, 3, 4, Table 1) concerning the standard knowledge about chemotherapy and the effect of chemotherapy on fertility. Respondents with appropriate knowledge were considered "accurate". Four questions (D-1, 2, 3, 5, Table 1) concerning the perspective and opinion about the fertility preservation were asked and scored as attitude score. Respondents were divided into "positive attitude group" and "negative attitude group" depending on the attitude score. Chi-square test was applied for correlation analysis between physician knowledge, attitude, and background. Physicians' background demographics, knowledge, and attitude regarding fertility issues were associated with physicians' practice behavior regarding fertility issues. Odds ratios (OR) and their 95% confidence interval (CI) were estimated to compare physician background factors, knowledge, and attitude with physician practice pattern, using simple and multivariable logistic regression models. All p values are two sided, and the statistical significance level was set at $p < 0.05$. No adjustments for multiple comparisons were considered because of the exploratory nature of this study.

Results

Response rate

The response rate was calculated as the number of breast oncologists completing the survey ($n = 434$) divided by the initial sample size minus undeliverable ($843 - 8 = 835$): this yielded a 52% response rate. This is higher than the previous survey on fertility preservation referral targeting oncology specialists in the USA [4].

Demographic and characteristics of responding breast oncologists

The background of respondents is shown in Table 2. A total of 16.6% of the respondents were female. More than 95% of the respondents were experienced physicians reflecting the requirement of basic board certification in general medicine, surgery, radiation oncology, or pathology in order to obtain JBCS Breast Oncologists certification. The majority was surgeons. Less than half responded that they have medical oncologists in their institutions. About 70% were the institutions in which they operated on less than five breast cancer patients per week (less than approximately 200 cases per year).

Association between knowledge, attitude, and physician background

Two hundred and seventy-nine (64%) respondents were considered to have accurate knowledge. Accuracy of knowledge about fertility was correlated with the number of young breast cancer patients treated ($p = 0.006$), presence of children of the physician ($p = 0.01$), age of the physician ($p = 0.019$), and the presence of female colleagues ($p = 0.019$).

The existence of a spouse/partner ($p = 0.011$), age ($p = 0.032$), and gender ($p = 0.023$) of the physician were the factors significantly correlated with a positive attitude toward fertility considerations of breast cancer patients. Physicians who have a spouse/partner, physicians who are younger than 50 years, and female physicians had more positive attitudes toward fertility issues for breast cancer patients.

Practice of fertility issues among breast oncologists

A total of 83% of the participants responded that they were positive in discussing fertility issues with young breast cancer patients.

Twenty-one percent responded that patients voluntarily bring up fertility issues in the clinic. Physicians who treat two or more young patients per week perceived that patients voluntarily express their concern in the clinic compared to physicians who treat fewer (OR 1.84, 95% CI 1.13–3.00, $p = 0.008$). Physicians who treat two or more young patients per week (OR 1.30, 95% CI 1.05–2.45, $p = 0.023$), who have board-certified nurse colleagues (OR 1.55, 1.19–2.03, $p < 0.001$) and have more than six breast surgeries per week (OR 1.20, 1.02–1.41, $p = 0.014$) responded that they perceived that patients talk to co-medical staff about their concerns about fertility. A total of 24% of the respondents consulted reproductive specialists when they encountered fertility problems in their patients and 42% referred patients to reproductive specialists when patients expressed concerns regarding fertility.

The association between physicians' behavior related to fertility issues and their knowledge, attitude, and background demographics are shown in Table 3. Fair knowledge had the strongest impact on physicians' positive behavior towards discussing fertility issue with patients. Positive attitude, presence of breast cancer-specialized CNS, young age, and female gender were also significant

Table 2 Demographic background of the responding physicians

	n	%
Total	434	100
Gender		
Female	72	16.6
Male	357	82.3
Unknown	5	1.2
Age		
20–29	1	0.2
30–39	52	12.0
40–49	183	42.2
50–59	148	34.1
60–69	41	9.4
70–	4	0.9
Unknown	5	1.2
Religion		
Buddhist	144	33.2
Christian	9	2.1
No special religion	276	63.5
Others	5	1.2
Year graduated from medical school		
–1994	347	80.0
1995–2000	76	17.5
2001–2005	6	1.4
Unknown	5	1.2
Specialty		
Surgery	412	94.9
Medical oncology	6	1.4
Radiation oncology	9	2.1
Gynecology	1	0.2
Others	6	1.4
Type of affiliation		
Cancer center	40	9.2
General hospital	190	43.8
University hospital	122	28.1
Private clinic	74	17.1
Unknown	8	1.8
Number of physicians		
1–3	164	37.8
4–7	137	31.8
8–	125	28.8
Unknown	8	1.8
Female physician colleague		
Present	276	63.6
Absent	150	34.6
Unknown	8	1.8
Medical oncologist		
Present	172	39.6
Absent	255	58.8
Unknown	7	1.6
Breast cancer specialized nurse		
Present	202	46.5
Absent	225	51.8
Unknown	7	1.6
Board-certified pharmacists		
Present	227	52.3
Absent	196	45.2
Unknown	11	2.5
Number of breast surgeries (per week)		
0–5	310	71.4
5–10	85	19.5
11–15	14	3.2
16–20	3	0.7
20–	14	3.2
Unknown	8	1.8
Number of patients aged <40 (per week)		
0–1	122	28.1
2–4	202	46.5
5–	103	23.7
Partner/spouse		
Present	401	92.4
Absent	25	5.8
Unknown	8	1.8
Children		
Present	351	80.9
Absent	64	14.7
Unknown	19	4.4

factors associated with positivity towards the discussion. Female oncologists and medical oncologists were more likely to take into account patients' social backgrounds such as history of childbirth, presence of a spouse/partner, and patients' economic status when discussing fertility issues.

Physicians with a positive attitude, physicians younger than 50 years, and female physicians were more likely to discuss fertility issues with patients with poorer prognoses. Positive attitude was the strongest factor related to consultation and referral to reproductive specialists.

Barriers for discussion with patients

High risk of disease recurrence (51%), lack of reproductive specialists or infertility clinic for referral (45%), and time constraints in the clinic (45%) were regarded as major barriers for discussing fertility issues. When only physicians who were negative in discussing fertility issues ($n = 69$) were analyzed, high risk of recurrence (57%), no signal of interest in fertility from patients (49%), and lack

Table 3 Factors associated with fertility-related practice behavior

	I discuss the impact of cancer treatment on future fertility with my patients				I do not feel comfortable discussing fertility issues with my patients				I take into account the history of childbirth when I discuss fertility issues with my patients			
	p	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI	
			Min	Max			Min	Max			Min	Max
Knowledge												
Fair	0.000	1.717	1.321	2.231	0.063				0.799			
Not fair		1.000										
Attitude												
Conservative	0.012	1.000			0.180				0.697			
Aggressive		1.542	1.145	2.079								
Gender												
Female	0.005	1.166	1.080	1.258	0.807				0.022	1.130	1.041	1.227
Male		1.000								1.000		
Age												
<50	0.000	1.584	1.280	1.959	0.203				0.625			
>50		1.000										
Specialty												
Surgery	1.000				0.625				0.756			
Others												
Affiliation												
University hospital/cancer center	0.032	1.235	1.047	1.457	0.147				0.900			
General hospital/private hospital		1.000										
Female physician colleague												
Present	0.079				1.000				1.000			
Absent												
Medical oncologist colleague												
Present	0.432				0.366				0.043	1.190	1.003	1.141
Absent												
Breast cancer-specialized nurse												
Present	0.606				0.480				0.327			
Absent												
Board-certified cancer pharmacist												
Present	0.001	1.510	1.220	1.868	0.721				0.324			
Absent		1.000										
Number of breast surgeries per week												
1–5	0.884				0.692				0.495			
6–												
Number of young patients per week												
0–1	0.474				0.113				0.500			
2–												
Partner/spouse												
Present	0.281				0.008	1.000			0.193			
Absent						1.158	0.989	1.355				
Children												
Present	0.074				0.088				0.740			
Absent												

Table 3 continued

	I take into account whether she has a spouse/partner when I discuss fertility issues with my patients				I take into account economical status of the patient when I discuss fertility issues with my patients				I discuss fertility issues with breast cancer patients with high risk of recurrence			
	p	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI	
			Min	Max			Min	Max			Min	Max
Knowledge												
Fair	0.839				0.609				0.910			
Not fair												
Attitude												
Conservative	0.601				0.694				0.001	1.000		
Aggressive										1.640	1.250	2.150
Gender												
Female	0.033	1.089	1.002	1.185	0.622				0.047	1.089	1.000	1.185
Male										1.000		
Age												
<50	0.326				0.267				0.003	1.391	1.131	1.712
>50												
Specialty												
Surgery	0.225				0.343				0.273			
Others												
Affiliation												
University hospital/cancer center	0.364				1.000				0.219			
General hospital/private hospital												
Female physician colleague												
Present	0.412				0.194				0.649			
Absent												
Medical oncologist colleague												
Present	0.022	1.206	1.032	1.408	0.043	1.261	0.996	1.596	1.000			
Absent		1.000				1.000						
Breast cancer specialized nurse												
Present	0.434				1.000				0.588			
Absent												
Board-certified cancer pharmacist												
Present	0.694				0.136				0.745			
Absent												
Number of breast surgeries per week												
1–5	0.125				0.262				0.903			
6–												
Number of young patients per week												
0–1	0.746				0.273				0.810			
2–												
Partner/spouse												
Present	0.299				0.192				1.000			
Absent												
Children												
Present	0.183				1.000				0.025	1.116	1.029	1.211
Absent										1.000		