Combined effects of goserelin and tamoxifen on estradiol level, breast density, and endometrial thickness in premenopausal and perimenopausal women with early-stage hormone receptor-positive breast cancer: a randomised controlled clinical trial

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Background: This study is to investigate the effects of goserelin + tamoxifen (TAM) on estradiol level, breast density (BD), endometrial thickness (ET), and blood lipids in premenopausal and perimenopausal women with hormone receptor-positive early-stage breast cancer.

Methods: This study recruited 110 premenopausal and perimenopausal patients with hormone receptor-positive early-stage breast cancer between 22 June 2008 and 31 December 2009 and randomly assigned them to receive either goserelin plus TAM or TAM alone for 1.5 years. Blood levels of sex hormones and lipids and ET were determined at 0, 3, 6, 12, and 18 months. Contralateral BD was also measured at 0, 12, and 18 months.

Results: Five participants dropped out of the goserelin plus TAM group, and two participants dropped out of the TAM-alone group before initiation of endocrine therapy. The rest of patients received scheduled treatment and 3 years of median follow-up. No serious adverse effects were observed, and only two local recurrences have been observed in these patients. Estradiol level and BD were lower in the goserelin plus TAM group than in the TAM-alone group (P < 0.05). The endometrium in the goserelin plus TAM group was significantly thinner than that in the TAM-alone group (P < 0.05), and women in the TAM-alone group exhibited endometrial thickening over the course of the study. Furthermore, no significant differences in blood lipid levels were reported between the two groups.

Conclusion: The data from the current study demonstrated that the addition of goserelin to TAM results in downregulation of estradiol level, followed by significant reduction in BD and ET in premenopausal and perimenopausal women with hormone receptor-positive breast cancer, which may eventually lead to better outcome in these patients.

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Breast cancer is a kind of sex hormone-dependent disease. Factors that contribute to the international variation in incidence rates largely stem from the availability of early-detection services as well as differences in reproductive and hormonal factors, namely, risk factors associated with the level and duration of exposure to estrogen (Trials’ Collaborative Group (EBCTCG), 2005). Based on several large clinical trials, estrogen blockade agents and several aromatase inhibitors (AIs) have become the standard adjuvant treatment for postmenopausal patients with endocrine-responsive early-breast cancer (Coombes et al, 2004; Breast International Group (BIG) 1-98 Collaborative Group, 2005; Howell et al, 2005; Coates et al, 2007). In the past two decades, medical castration with luteinising hormone-releasing hormone agonists (LHRHa’s) has been proposed in clinical practice. A frequently used LHRHa, goserelin, acts on the hypothalamic–pituitary axis and achieves reversible ovarian function suppression through receptor downregulation, and reduces luteinising hormone and estradiol to postmenopausal levels (Goel et al, 2009; Sverrisdottir et al, 2011). Results from randomised clinical trials illustrated that the use of LHRHa did improve the survival duration of patients with hormone receptor-positive (estrogen receptor-positive (ERþ) and/or progesterone receptor-positive (PRþ)) breast cancers (Soreide et al, 2002; Baum et al, 2006; Cuzick et al, 2007). To elaborate the role of suppression of ovarian function in premenopausal patients with endocrine-responsive breast cancer more clearly, three trials were sponsored by the International Breast Cancer Study Group and coordinators. The results of SOFT/TEXT/PERCHE trials are awaited to answer these questions: the role of OS, the role of AI in combination with OFS, and the role of chemotherapy in addition to endocrine therapies (Regan et al, 2008).

As a kind of endocrine therapy, OFS can suppress breast cancer and improve the survival of premenopausal patients directly. Besides, OFS may also improve the survival of premenopausal patients with hormone receptor-positive breast cancer indirectly by decreasing the contralateral breast density (BD), endometrial thickness (ET), and so on. An initial BIG 1-98 study reported that postmenopausal breast cancer patients who received TAM had an increased incidence of thromboembolic events and endometrial cancer, although TAM had the predominant benefit on disease-free survival (DFS) and overall survival (OS), with a proportional reduction in contralateral breast cancer (BIG 1-98 Collaborative Group, 2005; Colleoni et al, 2011). The result of a subgroup analysis of the IBIS I Breast Cancer Prevention Trial showed that the discontinuation rate in the TAM group was high and occurred early because of gynaecological findings, most notable of which was the finding that in postmenopausal women, the median ET was significantly increased within 5 years in the TAM group (Palva et al, 2012). In contrast, goserelin was not associated with any significant thromboembolic events or with the occurrence of endometrial cancer (Cheer et al, 2005). Intriguingly, goserelin significantly decreased the mammographic BD in patients carrying a BRCA1 mutation, suggesting that goserelin may repress breast cancer recurrence by reducing mammary density. It was also confirmed that the reduction in BD apparently reduced the risk of contralateral breast cancer (Cuzick et al, 2011).

Therefore, in this study, we hypothesised that the combination of goserelin with TAM could lead to downregulation of the estradiol level, resulting in reduced BD and ET, and ultimately leading to better DFS and OS in premenopausal and perimenopausal patients with hormone receptor-positive breast cancer. Thus, we initiated a randomised controlled trial that was sponsored by the Zhejiang Cancer Hospital in 2008 to validate our hypothesis.

**PATIENTS AND METHODS**

**Participants and study design.** In this study, we recruited 110 premenopausal or perimenopausal women with hormone receptor-positive early-stage breast cancers who had undergone radical mastectomy or breast-conserving surgery at the Zhejiang Cancer Hospital in Hangzhou, China, between 22 June 2008 and 31 December 2009. Hormone receptor-positive means ERþ and/or PRþ. The patients were randomly assigned to one of the two groups: the goserelin plus TAM group (n = 56) or the TAM-alone group (n = 54). Before receiving any endocrine therapy, these patients underwent surgery, followed by various radiochemotherapy regimens (Table 1) after evaluation by a multidisciplinary team consisting of a medical oncologist, radiation oncologist, and oncological surgeon. The data on the patients’ hormone receptor status and pathological diagnoses were obtained from the Department of Pathology, and clinical data were obtained from medical records. The Ethics Committee and the Academic Committee of Zhejiang Cancer Hospital approved this clinical study. Written informed consent was obtained from all patients for our study before trial entry. Both TAM (Nolvadex) and goserelin (Zoladex) were supplied by Astra-Zeneca China Co, Ltd (Shanghai, China). This study is registered, number NCT00827307.

**Inclusion and exclusion criteria.** Patients with hormone receptor-positive early-stage breast cancers were included in the trial if there was no clinical evidence of metastatic or recurrent diseases, and if they were histopathologically confirmed as having stage-I/II ERþ and/or PRþ invasive breast cancer. The standard of hormone receptor-positive was ER ≥10% and/or PR ≥10% by immunohistochemistry stain. All patients were then characterised as premenopausal or perimenopausal (last menstruation <6 months before trial entry) according to the National Comprehensive Cancer Network guidelines. Temporary chemotherapy-induced amenorrhea was allowed, provided that the premenopausal status was confirmed by estradiol level within 8 months before the final dose of chemotherapy. These patients were also required to be tested to ensure that they had adequate haematological reserves, renal function, and liver function.

The exclusion criteria were as follows: women with a life-threatening concurrent disease were excluded from the study. Pregnant and lactating women with early-stage breast cancer and patients with distant metastasis were ineligible for this study. Patients who had had intermissions of 8 weeks or longer from the time of surgery to postoperative chemotherapy, or from chemotherapy completion to study recruitment, were rejected according to the clinical protocol. In addition, those who had a history of previous endocrine treatment, bilateral ovarian radiation or excision, a malignant tumour in the past 5 years, and/or an allergy to goserelin or TAM were excluded from our study.

Patients were randomised after enrolment into this study. Treatment allocation was based on the permuted block technique. The voluntary aspect of the study was stressed, and confidentiality was guaranteed. All parameters of the two groups were comparable.

**Intervention.** Patients were randomly assigned to receive either 20 mg of TAM alone (1 × 10-mg tablet orally twice daily) or 20 mg of TAM (1 × 10-mg tablet orally twice daily) plus 3.6 mg of goserelin (subcutaneous injection every 28 days). The treatment duration was 1.5 years, and treatment would be continued in the adjuvant setting for both treatment groups for at least 5 years. The adverse effects of the endocrine drugs were documented, and compliance was assessed with an interview at each follow-up visit. According to the adverse effect criteria of the Eastern Cooperative Oncology Group (ECOG), intermittent endocrine treatment was optional if a patient presented with life-threatening adverse effects.

**Follow-up and outcome measures.** All baseline data were collected before endocrine treatment. Blood levels of sex hormones...
(estradiol, progesterone, and human chorionic gonadotropin) and lipids (triglycerides, cholesterol, low-density lipoprotein, and high-density lipoprotein), and ultrasonic gynaecological examinations were performed at 3, 6, 12, and 18 months after initiating endocrine treatment. The minimum detectable value of estradiol by ELISA was 1.0 pg ml\(^{-1}\), with a sensitivity of 99%. Patients underwent contralateral mammography at 12 and 18 months after endocrine treatment initiation. Routine haematologic and clinical chemistry measurements were performed at every follow-up visit.

The primary end point was estradiol level, mammographic BD, ultrasonic ET, and blood lipid levels. Blood lipid and sex hormone levels were measured in the clinical laboratory, which is the central laboratory of Zhejiang province. Mammographic images performed in our hospital were all digitalised, and BD was quantitatively measured on craniocaudal images of the

| Table 1. Baseline clinical data |
|--------------------------------|
| **Group**                  | **Goserelin + TAM** | **TAM alone** | **Statistics** | **P-value** |
| Age (year)                  | 42.41 ± 5.24        | 42.52 ± 5.22  | -0.108         | 0.914       |
| Age at menarche (year)      | 15.18 ± 1.43        | 15.31 ± 1.45  | -0.496         | 0.621       |
| BMI                         | 21.96 ± 2.80        | 22.58 ± 2.75  | -1.142         | 0.256       |
| TG (mmol l\(^{-1}\))        | 2.29 ± 1.22         | 1.91 ± 1.18   | 1.638          | 0.105       |
| Chol (mmol l\(^{-1}\))      | 4.65 ± 1.11         | 4.72 ± 1.18   | -0.231         | 0.818       |
| LDL (mmol l\(^{-1}\))       | 2.72 ± 0.84         | 2.69 ± 0.69   | 0.213          | 0.832       |
| HDL (mmol l\(^{-1}\))       | 1.43 ± 0.70         | 1.35 ± 0.50   | 0.709          | 0.480       |
| E2 (pg ml\(^{-1}\))         | 41.83 ± 108.88      | 52.38 ± 95.85 | -0.522         | 0.603       |
| PRG (ng ml\(^{-1}\))        | 0.55 ± 0.55         | 1.22 ± 2.56   | 3.362          | 0.070       |
| HCG (mIU ml\(^{-1}\))       | 1.20 ± 0.98         | 1.47 ± 0.84   | -1.513         | 0.133       |
| LH (IU l\(^{-1}\))          | 13.07 ± 11.58       | 18.26 ± 16.67 | -1.832         | 0.070       |
| FSH (mIU ml\(^{-1}\))       | 20.55 ± 16.33       | 28.63 ± 24.38 | -1.972         | 0.051       |
| Endometrial thickness (cm)  | 3.77 ± 1.07         | 4.04 ± 1.20   | -1.207         | 0.230       |
| Breast density (%)          | 51.24 ± 13.66       | 56.44 ± 14.11 | -1.903         | 0.060       |
| Tumour size (cm)            | 2.87 ± 1.15         | 3.23 ± 1.21   | 2.424          | 0.017*      |
| Number of involved node      | 2.41 ± 3.31         | 1.15 ± 3.31   | 2.052          | 0.043*      |
| **Histological grade**       |                      |               | 4.859          | 0.176       |
| Unspecified                  | 17 (30.36%)         | 8 (14.81%)    |               |            |
| 1                           | 4 (7.14%)           | 8 (14.81%)    |               |            |
| 2                           | 30 (53.57%)         | 34 (62.97%)   |               |            |
| 3                           | 5 (8.93%)           | 4 (7.41%)     |               |            |
| ER                          |                        |               | 1.527          | 0.703       |
| –                           | 3 (5.36%)           | 5 (9.26%)     |               |            |
| +                           | 13 (23.21%)         | 11 (20.37%)   |               |            |
| ++                          | 22 (39.29%)         | 17 (31.48%)   |               |            |
| + +                         | 18 (32.14%)         | 21 (38.89%)   |               |            |
| PR                          |                        |               | 5.157          | 0.161       |
| –                           | 7 (12.50%)          | 9 (16.67%)    |               |            |
| +                           | 6 (10.71%)          | 12 (22.22%)   |               |            |
| ++                          | 22 (39.29%)         | 12 (22.22%)   |               |            |
| + +                         | 21 (37.50%)         | 21 (38.89%)   |               |            |
| Surgical procedure           |                       |               | 5.338          | 0.099       |
| Modified radical surgery     | 49 (87.50%)         | 52 (96.30%)   |               |            |
| Breast-conserving surgery    | 6 (10.71%)          | 1 (1.85%)     |               |            |
| Radical excision             | 0 (0%)              | 1 (1.85%)     |               |            |
| Lumpectomy                   | 1 (1.79%)           | 0 (0%)        |               |            |
| Chemotherapy regimen         |                       |               | 5.777          | 0.099       |
| No                          | 7 (12.50%)          | 6 (11.11%)    |               |            |
| TEC/TE                      | 36 (64.29%)         | 24 (44.44%)   |               |            |
| CEF                         | 12 (21.42%)         | 22 (40.74%)   |               |            |
| CEF-T/CE-T                  | 1 (1.79%)           | 2 (3.71%)     |               |            |
| Adjuvant chemotherapy        |                       |               | 0.051          | 0.822       |
| No                          | 7 (12.50%)          | 6 (11.11%)    |               |            |
| Yes                         | 49 (87.50%)         | 48 (88.89%)   |               |            |
| Adjuvant radiotherapy        |                       |               | 3.609          | 0.082       |
| Yes                         | 19 (33.93%)         | 28 (51.85%)   |               |            |
| No                          | 37 (66.07%)         | 26 (48.15%)   |               |            |

Abbreviations: BMI = body mass index; Chol = cholesterol; E2 = estradiol; ER = estrogen receptor-positive; FSH = follicle-stimulating hormone; HCG = human chorionic gonadotropin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LH = luteinising hormone; PR = progesterone receptor-positive; PRG = progesterone; TAM = tamoxifen; TG = triglyceride. *P<0.05.
Results

Characteristics of patients. In this study, we recruited 110 patients with early-stage hormone receptor-positive breast cancer to receive goserelin and TAM or TAM-alone therapy. Of these patients, 7 (6.36%), 5 in goserelin plus TAM group and 2 in TAM-alone group) declined to participate after the randomised assignment, resulting in continued administration of goserelin plus TAM or TAM alone in 103 women (51 in goserelin plus TAM group and 52 in TAM-alone group) (Figure 1). Moreover, one in TAM-alone group did not completely finish the assigned intervention. The median duration of follow-up was 3 years. In both groups of patients, the median ages at the time of diagnosis and at the time of menarche were 42 and 15 years, respectively. The body mass index was similar in both groups (Table 1). Baseline data of blood sex hormone levels in premenopausal and perimenopausal women indicated that the ovarian function of women in group A was comparable to that in group B (Figure 1). Moreover, one in TAM-alone group declined to participate after the randomised assignment, resulting in continued administration of goserelin plus TAM or TAM alone in 103 women (51 in goserelin plus TAM group and 52 in TAM-alone group) (Figure 1). Moreover, one in TAM-alone group did not completely finish the assigned intervention. The median duration of follow-up was 3 years. In both groups of patients, the median ages at the time of diagnosis and at the time of menarche were 42 and 15 years, respectively. The body mass index was similar in both groups (Table 1). Baseline data of blood sex hormone levels in premenopausal and perimenopausal women indicated that the ovarian function of women in group A was comparable to that in group B (Figure 1).

Adverse effects and recurrent events. In this study, serious adverse effects were not observed during the period of intervention and follow-up. To date, all patients were alive and two had local recurrences.
Table 3. Comparison of breast density between these two groups at various points of time

| Breast density   | Goserelin + TAM | TAM alone | F-value | P-value |
|------------------|----------------|-----------|---------|---------|
| Baseline         | 51.24 ± 13.66  | 56.37 ± 14.24 | 3.457   | 0.066 |
| 12 Months        | 44.14 ± 11.66  | 50.69 ± 14.27 | 6.443   | 0.013* |
| 18 Months        | 37.86 ± 12.44  | 44.75 ± 14.90 | 6.414   | 0.013* |

Abbreviation: TAM = tamoxifen. *P < 0.05

Multivariate analysis of the end point events. A statistical Mauchly’s test was performed to validate the sphericity symmetry hypothesis for all measures, including estradiol, BD, ET, and blood lipid levels, but the results were negative (P < 0.05). Thus, the Greenhouse–Geisser multivariate analysis was used to compare the repeated measures, and the results are shown in Table 2 and Figure 2. As expected, estradiol levels were remarkably repressed in goserelin plus TAM group relative to TAM-alone group (F = 9.949; P = 0.002), whereas blood lipid levels were not apparently altered after addition of goserelin (P > 0.05). Compared with the use of TAM alone, the addition of goserelin to TAM significantly decreased BD (F = 6.172; P = 0.015). In parallel, the endometrium of patients assigned to receive goserelin plus TAM was clearly thinner compared with that of patients who received TAM-alone treatment (F = 22.671; P < 0.001).

Moreover, a time-dependent trend was detected in the variation of BD according to a within-subject variance analysis (F = 90.371; P < 0.001), whereas interactive effects between timing and groups were not observed (F = 0.633; P = 0.483). The multivariate analysis showed that after the 12-month follow-up, BD was significantly attenuated in the goserelin plus TAM group compared with the TAM-alone group (P < 0.05, Table 3). Bonferroni statistical data showed that after the 18-month follow-up, ET in the TAM-alone group was thicker than ET in the baseline data (mean difference = -0.751; P < 0.001). There was no significant difference in ET in the goserelin plus TAM group among the various time points, although a downward trend was noted (mean difference = -0.301; P = 0.057).

DISCUSSION

Adjuvant endocrine therapy, which is an integral component in the treatment of patients with ER+ and/or PR+ breast cancer, exerts its effect by reducing the availability of estrogen to micrometastatic tumour cells (Goss et al, 2003; BIG 1-98 Collaborative Group, 2009; van de Velde et al, 2010). Thus TAM, the most commonly used hormonal treatment for breast cancer patients, was introduced into clinical practice in the 1970s and has substantially improved survival duration in patients with hormone receptor-positive breast cancers (Jaiyesimi et al, 1995; O’Regan and Jordan, 2002; Breast International Group (BIG) 1-98 Collaborative Group et al, 2005; Clarke, 2008; Rose, 2008; Masuda et al, 2012). However, TAM is also able to produce notable estrogenic effects on the skeletal system, lipid metabolism, and various gynaecological tissues, including mammary gland, vaginal mucosa, and uterus (Arimidex, Tamoxifen, Alone or in Combination Trialists’ Group, 2006; Rose, 2008; Meltnikow, 2010). Although TAM can improve survival duration in patients with estrogen-sensitive breast cancer, its long-term use inevitably increases the risk of adverse effects, such as endometrial cancer and disorders of lipid metabolism (Gardner et al, 2000; Nystedt et al, 2000; Weitzel et al, 2007).

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still continuing. However, a randomised trial with a larger sample size and longer duration of follow-up is subsequently needed to confirm these results.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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