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Phase II Trial of Goserelin and Exemestane Combination Therapy in Premenopausal Women With Locally Advanced or Metastatic Breast Cancer

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Abstract: A promising option as the treatment of choice for premenopausal patients with locally advanced or metastatic breast cancer (MBC) could be the combination of a luteinizing hormone-releasing hormone analog and an aromatase inhibitor. However, no prospective studies on the efficacy of goserelin with exemestane in locally advanced or MBC premenopausal breast cancer patients have been reported.

We present the phase II trial of goserelin plus exemestane in a total of 44 premenopausal women with locally advanced or MBC. All patients received a subcutaneous injection of 3.6 mg goserelin every 4 weeks along with 25 mg exemestane daily. The primary end point was progression-free survival (PFS). The second end point included overall survival (OS), objective response rate (ORR), duration of response (DOR), and clinical benefit rate (CBR) based on complete response (CR), partial response (PR), or stable disease (SD) for ≥6 months.

The median PFS was 13 months (range: 2–42 months). The median DOR was 8 months (range: 2–40 months). Two patients achieved CR (4.5%), and 15 patients experienced PR (34.1%). Fifteen patients (34.1%) had SD ≥6 months. The ORR was 38.6%, and the CBR was 65.9%. Primary progressive disease occurred in 15 patients (34.1%). Five patients (11.4%) died during the study period. Because a few patients have died, the median OS has not been reached. Drug therapy was well tolerated. The most frequent grade-3 adverse events were arthralgia (18.2%), skin rash (6.8%), and myalgia (4.5%). No participants withdrew from the study due to drug toxicity.

This study suggested that goserelin and exemestane might be highly effective and well-tolerated regimens in premenopausal women with hormone-responsive, locally advanced or MBC.

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Abbreviations: AIs = aromatase inhibitors, CBR = clinical benefit rate, CR = complete response, DOR = duration of response, ER = estrogen receptor, ER+ = estrogen receptor-positive, LH-RH = luteinizing hormone-releasing hormone, MBC = metastatic breast cancer, ORR = objective response rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PgR = progesterone receptor, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease.

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INTRODUCTION

Breast cancer is one of the most common malignancies, accounting for approximately 21% of the cancer incidences worldwide from 1995 to 2009.[1,2] Previous studies have shown that the rate of breast cancer among Chinese women is lower than those in many Western countries.[3–6] However, recent studies have shown that the rate of breast cancer is rapidly increasing in China,[1,7,8] especially among women ages 20 to 45 years, and breast cancer is now the most common malignancy among Chinese women.[7,9]

Numerous case-control and cohort studies have reported that 39% to 87% of women with breast cancer have tumors expressing the estrogen receptor (ER) and/or progesterone receptor (PgR).[10] Endocrine therapies targeting the ER or estrogen synthesis have been shown to reduce breast cancer recurrence and improve survival.[11] Tamoxifen, which functions as an ER antagonist in breast tissue, has long been the first choice for endocrine therapy (ET), with or without first-line chemotherapy (CT), for hormone-responsive breast cancer in premenopausal women.[12,13] However, treatment failure occurs in a significant proportion of premenopausal women treated with tamoxifen.[11] Aromatase inhibitors (AIs), such as letrozole, anastrozole, and exemestane, inhibit the synthesis of estrogen in various nonovarian tissues, and are used to treat breast cancer in postmenopausal women with estrogen receptor-positive (ER+) tumors.[14] However, AIs do not suppress ovarian estrogen synthesis, and are therefore ineffective in premenopausal women.[15]

Luteinizing hormone-releasing hormone (LH-RH) analogs, such as goserelin and buserelin, suppress ovarian function, reducing the level of estradiol to within the postmenopausal range. Previous studies have shown that an LH-RH analog combined with an ER antagonist is a more effective breast cancer treatment than either used alone.[16–18] Combination therapy using an LH-RH and an AI has also been shown to be more effective than either treatment alone in premenopausal women with hormone-responsive, locally advanced breast cancer,[19,20] and a previous study has shown that goserelin plus anastrozole yielded clinical outcomes that were similar to those of goserelin plus tamoxifen in premenopausal women with hormone-responsive early breast cancer.[21]

Studies of the effects of goserelin combined with exemestane in premenopausal women with advanced breast cancer are scant. Therefore, whether goserelin plus exemestane is more effective for advanced or metastatic breast cancer (MBC) than goserelin plus another AI or tamoxifen is unclear. We

performed a single-center, prospective study to determine the antitumor efficacy and tolerability of goserelin plus exemestane as a second-line treatment for hormone-responsive, locally advanced or MBC in premenopausal women.

PATIENTS AND METHODS

Patients

Women admitted to our hospital for advanced breast cancer between February 2010 and November 2013 were reviewed for our study. Our phase II clinical trial was registered with the China Clinical Trials Register (registration no. ChiCTR-ONC-13003946). Our study was performed in accordance with the Declaration of Helsinki regarding the ethical principles for medical research involving human subjects, and our study protocol was approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences. Written consent was obtained from each patient before their participation in our study. Their information was collected in the hospital database and used for research purposes only.

Patients meeting the following criteria were included in our study: premenopausal woman; <60 years of age at the time of enrollment; no history of menstrual cycle abnormalities; serum levels of estradiol, follicular stimulating hormone, and luteinizing hormone within premenopausal ranges; pathologically confirmed invasive breast cancer that was unresectable, locally advanced, or metastatic; at least 1 measurable target lesion based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria; a life expectancy of >3 months; a Karnofsky performance status (WHO) of ≤2; no major organ failure; leukocyte count $\geq 4.0 \times 10^9\,L^{-1}$; neutrophil count $\geq 1.5 \times 10^9\,L^{-1}$; platelet count $\geq 100 \times 10^9\,L^{-1}$; hemoglobin ≥100 g/L; total serum bilirubin <2 times the maximum reference value; serum glutamic-pyruvic transaminase (ALT) and glutamic-oxalacetic transaminase (AST) levels ≤2.5 IU/L with no liver metastasis or ALT/AST ≤ 5 UI/L with liver metastasis; blood glucose <200 mg/dL; serum creatinine <140 mol/L; and demonstrated therapeutic compliance throughout the study period.

Following patients were excluded from our study: pregnant; breastfeeding mother; a history of exemestane treatment for recurrent or MBC; concurrent disease involving a different malignancy or a history of a malignancy other than breast cancer, except for nonmelanoma skin cancer, in situ cervical cancer, or other previously treated malignancies with no evidence of recurrence for at least 5 years; neurological disease, psychiatric disorder, or other cognitive dysfunction that might negatively influence therapeutic compliance or diminish the patient's understanding of the consent form; congestive heart failure, unstable angina, or a history of myocardial infarction within the 6-month period immediately preceding enrollment; uncontrolled hypertension or high-risk arrhythmia; uncontrolled acute infection; severe peptic ulcer, diabetes, or other condition for which adrenal corticosteroid treatment is contraindicated; previous combined use of goserelin and exemestane; or a known allergy to goserelin or exemestane.

Treatment

Treatment was initiated within 4 weeks of enrollment. Each patient received a 25-mg tablet of exemestane (Pfizer, New York) by mouth once daily. A subcutaneous injection of 3.6 mg goserelin (Zoladex, AstraZeneca, London, UK) was administered in the lower abdomen every 4 weeks. The patients were followed up, and outcomes were confirmed in June 2014. Treatment was terminated if progressive disease (PD) developed or unacceptable adverse events occurred. Progression-free survival (PFS) was considered the primary end point for our study. Objective response rate (ORR), duration of response (DOR), and clinical benefit rate (CBR) based on complete response (CR), partial response (PR), or stable disease (SD) for ≥6 months were considered secondary endpoints.

Clinical Assessment

Baseline assessments were performed within the 1-month period immediately preceding the first treatment, which included determining the ER/PgR status and the human epidermal growth factor receptor type 2 (HER2/neu) status of each patient. Following the initial treatment, tumor assessment was performed every 2 months. Tumor response was evaluated according to the RECIST 1.1 criteria. We defined Disease Free Survival (DFS) as the interval between the initial diagnosis of breast cancer and recurrence or metastasis. PFS was defined as the interval between the initial treatment using goserelin combined with exemestane and the first observation of disease progression or death from any cause.

The ORR was defined as the proportion of patients exhibiting either complete or partial response to treatment. Clinical benefit was defined as CR, PR, or SD for ≥6 months, and the CBR was defined as the proportion of patients who achieved a confirmed objective response (CR or PR) or who had SD for ≥6 months. The DOR was defined as the interval between the first confirmed objective response and disease progression and the last follow-up assessment. Overall survival (OS) was calculated as the period from the first dose of goserelin with exemestane to the date of death or the date of the last follow-up examination. At each follow-up assessment, the patients were evaluated for adverse events due to drug toxicity according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

Statistical Analysis

The patients' baseline characteristics were summarized using descriptive statistics. A Kaplan–Meier analysis was used to compare the PFS of the patients with lung metastases with that of the patients with liver metastases, and the PFS distributions were compared using the log-rank test. A logistic regression analysis was used to evaluate the effect of prior CT and endocrine treatments on PFS. Cox-proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for PFS based on the relevant risk factors, including site of metastasis, ER/PgR status, HER2/neu status, and previous CT or ET regimens for metastatic disease. The level of statistical significance was set as $P < 0.05$. All statistical analyses were performed using the SPSS, version 15.0, software (IBM, Armonk, NY).

RESULTS

Patient Characteristics

A total of 44 Han Chinese patients were included in our study. The median age was 44.0 years (range: 28–55 years), and the median body mass index was 20.6 (range: 16.8–31.3 kg/m^2). Receptor and HER2/neu status as well as World Health Organization Performance Score (WHOPS) and metastasis sites are shown in Table 1.

Efficacy

Overall Treatment Efficacy

No patients were lost to follow-up. The median DFS was 38.0 months (range: 3–144 months). Thirty-two patients had a

TABLE 1. Patients' Clinical Characteristics (N = 44)

Characteristic	n	%
Receptor status		
ER+ PgR+	32	72.7
ER+ PgR−	11	25.0
ER− PgR+	1	2.3
HER2/neu status		
HER2/neu+	5	11.4
HER2/neu−	39	88.6
WHOPS		
0	34	77.3
1	8	18.2
2	2	4.5
Metastases		
Visceral sites	32	72.7
Liver only	11	25.0
Lung only	15	34.1
Liver and lung	6	13.6
Nonvisceral sites	12	27.3

ER = estrogen receptor, HER2/neu = human epidermal growth factor receptor type 2, PgR = progesterone receptor, WHOPS = World Health Organization performance score.

DFS >24 months, among whom 11 patients had a DFS >60 months. The median PFS was 13 months (range: 2–42 months). The ORR and CBR for our breast cancer cohort were 38.6% and 65.9%. The median DOR was 8 months (range: 2–40 months). Two (4.5%) of the patients exhibited CR, and 15 (34.1%) of the patients achieved PR. Fifteen (34.1%) of the patients exhibited SD, 12 (27.2%) of whom experienced SD >6 months. Primary PD occurred in 15 (34.1%) of the patients. Five (11.4%) of the patients died as the result of disease progression before the date of the last follow-up examination, which caused the data for OS to be statistically insufficient for calculating the median OS.

Subgroup Treatment Efficacy

The CBR of the HER2/neu-positive patients (55.6%) was not significantly different from the HER2/neu-negative patients (68.6%, $P = 0.229$). The results of the subgroup analysis based on metastatic site showed that the ORR of the patients with only lung metastases (73.3%) was significantly greater than that of the patients with only liver metastases (27.3%, $P = 0.026$). On the contrary, ORR and CBR did not differ significantly between the indicated groups (Table 2). The effects of prior CT or ET on the curative effect of goserelin plus exemestane are shown in Table 3. The ORR was positively affected by no prior ET for metastasis ($P = 0.004$), no prior CT for metastasis ($P = 0.020$), and ≤1 prior CT regimen for metastasis ($P < 0.0001$), whereas the CBR was positively affected by no prior adjuvant ET ($P = 0.042$) and ≤1 prior CT regimen for metastasis ($P = 0.032$) (Table 3).

TABLE 2. Effects of Goserelin and Exemestane on Metastases

Status	ORR	CBR
Without visceral metastasis	25% (3/12)	58.3% (7/12)
With visceral metastasis	46.9% (15/32)	68.8% (22/32)
	$P = 0.121$	$P = 0.222$
Without lung metastasis	25% (3/12)	50.0% (6/12)
With lung metastasis	60% (12/20)	80.0% (16/20)
	$P = 0.059$	$P = 0.085$
Lung metastasis only	27.3% (3/11)	54.5% (6/11)
Liver metastasis only	73.3% (11/15)	80.0% (12/15)
	$P = 0.026$	$P = 0.169$

CBR = clinical benefit rate, ORR = objective response rate.

TABLE 3. Effects of Prior Chemotherapy (CT) or Endocrine Therapy (ET) on the Curative Effect of Second-Line Treatment with Goserelin and Exemestane

Status	ORR	CBR
No prior adjuvant ET	55.6% (10/18)	83.3% (15/18)
Prior adjuvant ET	30.8% (8/26)	53.8% (14/26)
	$P = 0.091$	$P = 0.042$
No prior ET for metastasis	57.1% (16/28)	75.0% (21/28)
Prior ET for metastasis	12.5% (2/16)	50.0% (8/16)
	$P = 0.004$	$P = 0.066$
No prior CT for metastasis	60.0% (12/20)	75.0% (15/20)
Prior CT for metastasis	25.0% (6/24)	58.3% (14/24)
	$P = 0.020$	$P = 0.120$
≤1 prior CT regimen for metastasis	60.0% (18/30)	76.7% (23/30)
≥2 prior CT regimens for metastasis	0% (0/14)	42.9% (6/14)
	$P < 0.0001$	$P = 0.032$

CBR = clinical benefit rate, ORR = objective response rate.

As shown in Figure 1, a representative metastatic lesion in the lung of a breast cancer patient was clearly shrunken after 9 months of goserelin and exemestane treatment, which also reflected in the Kaplan–Meier analysis (Figure 2), which showed that the goserelin and exemestane medication delayed disease progression significantly longer in patients with lung metastases than in those with liver metastases (median PFS: 20 months vs 10 months; $P = 0.037$). The logistic regression analysis showed that the relationship between PFS and the goserelin and exemestane treatment was not affected by the type or number of previous CT or ET regimens ($P = 0.359$). The Cox proportional hazards model showed that no history of adjuvant tamoxifen ET (HR: 0.421, 95% CI: 0.216–0.820) and <2CT regimens for metastatic disease (HR: 0.428, 95% CI: 0.2165–0.851) were associated with longer PFS, compared with the other risk factors, including ER/PgR status, HER2/neu status, metastatic site, and the type or number of previous anticancer therapy regimens.

Drug Toxicity

The frequency and grade of the adverse events are shown in Table 4. The most frequent adverse events were hot flashes (54.5%), arthralgia (52.3%), and fatigue (38.6%). No grade-4 adverse events were observed. The most frequent grade-3 adverse events were arthralgia (18.2%), skin rash (6.8%), and myalgia (4.5%). No participants were withdrawn from our study due to drug toxicity.

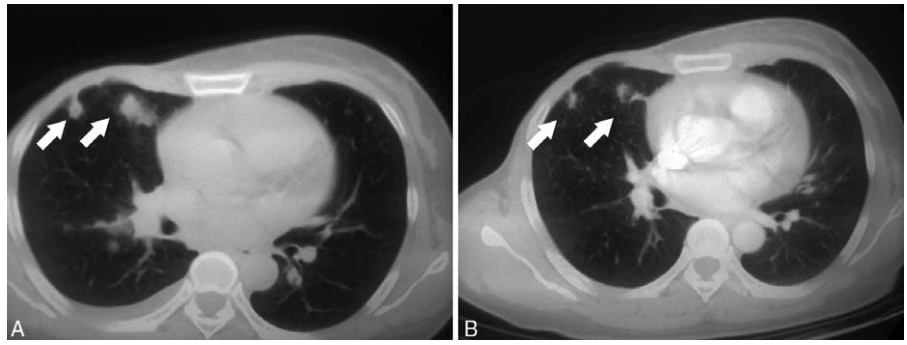

FIGURE 1. CT images of a 9-month goserelin plus exemestane treatment outcome for lung metastasis. (A) CT image showing a chest CT scan of a breast cancer patient (female, 42 years old) 4 years after surgery, who developed lung metastases and started goserelin plus exemestane treatment. (B) CT image showing the same patient 9 months after goserelin plus exemestane treatment (arrows are indicating the metastatic lesions).

DISCUSSION

Recent studies have shown that the rate of breast cancer among Chinese women is rapidly increasing.[1,7–9] The current peak age range of breast cancer incidences in China is 44 to 54 years, indicating that the proportion of premenopausal women with breast cancer is also increasing.[7] Therefore, the use of ET for premenopausal breast cancer in China has also increased. Studies of the use of goserelin in combination with exemestane in premenopausal women with local advanced or MBC are scant. From our 44 patients, 38 patients had been treated with tamoxifen before this study, including 26 patients for adjuvant ET, from which 20 developed recurrence or metastasis within 5 years and in all 12 metastasis patients the tamoxifen treatment failed because of PD. Aromatase inhibitors have become a standard ET, after the failure of tamoxifen in postmenopausal women with advanced breast cancer.[22] However, for premenopausal breast cancer patients only aromatase inhibitor treatments are not applicable. In order to render premenopausal breast cancer patients in a postmenopausal state, medicinal ovarian function suppression using GnRH-analogs like goserelin has been developed leading to ORRs and duration of remission comparable to those seen following oophorectomy.[23]

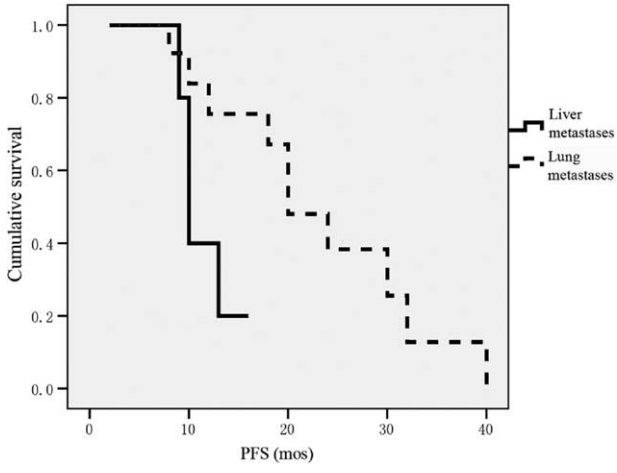

FIGURE 2. Kaplan–Meier analysis of progression-free survival (PFS) among breast cancer patients with lung or liver metastasis ($P = 0.037$).

In our study, the ORR was 38.6% and higher than previously reported rates of 30%[24] and 33%[25] in patients only treated with GnRH-analogs. Our CBR was 65.9% and also higher than 48% with only goserelin medication in premenopausal advanced breast cancer patients,[25] which indicates that the clinical efficacy of goserelin combined with exemestane therapy in premenopausal women with local advanced or MBC is superior than goserelin medication alone. In addition, no grade-4 toxicities were observed, and those that did occur were consistent with the use of a single-agent AI treatment in postmenopausal women with breast cancer.[26–28] Various studies have reported similar results regarding the efficacy of aromatase inhibitors combined with goserelin as a first-line treatment in premenopausal women with hormone-responsive, locally advanced or MBC.[29–31] Cheung et al[29] studied the efficacy of goserelin plus anastrozole, and observed a CBR and ORR of 67% and 36%, respectively, with a time to progression of 12 months. Carlson et al[30] also investigated the efficacy of goserelin combined with anastrozole, and reported a CBR and ORR of 71.9% and 37.5%, respectively, with a median time to progression of 8.3 months. Park et al[31] investigated the efficacy of goserelin plus letrozole, and reported a CBR and ORR of 77% and 46%, respectively, with a median time to progression of 9.5 months. The results of our investigation of the efficacy of goserelin plus exemestane are consistent with the findings of these previous studies. Comparisons of the various endocrine therapies used to treat

TABLE 4. Adverse Events in Patients Receiving Goserelin and Exemestane Combination Therapy

Adverse Event	Grade 1 (n)	Grade 2 (n)	Grade 3 (n)	Total (%)
Hot flashes	15	6	3	54.5
Arthralgia	12	3	8	52.3
Myalgia	6	1	2	20.5
Fatigue	15	2		38.6
Headache	6			13.6
Alopecia	2			4.5
Vaginal dryness	4	2		13.6
Vaginal spotting	4	2		13.6
Dry skin	7			15.9
Rash	2		3	11.4

breast cancer are problematic because the majority of such studies have used relatively small cohorts of breast cancer patients. However, the high level of efficacy that goserelin plus exemestane demonstrated in our study support the use of this regimen for ET in premenopausal women with hormone receptor-positive breast cancer. Previous studies have shown that various endocrine therapies for breast cancer have demonstrated low efficacy for visceral metastasis, but higher efficacies have been reported for bone or soft tissue metastases.[32–36] The results of our study showed that patients with lung metastases responded more favorably to goserelin and exemestane combination therapy than those without lung metastases (ORR: 60% vs 25%, $P = 0.059$), and patients with only lung metastases had a significantly more favorable prognosis than those with only liver metastases (ORR: 73.3% vs 27.3%, $P = 0.026$). A limitation of our study was the small sample size and that it was a single-arm study.

CONCLUSIONS

In our study, goserelin and exemestane combination therapy was a highly efficacious ET for hormone receptor-positive locally advanced or MBC in premenopausal women, and was significantly more efficacious in patients with lung metastases than in those with liver metastases. Future studies are warranted to identify the antitumor mechanism by which goserelin and exemestane act upon lung metastases. Large, randomized clinical trials investigating the efficacy of goserelin plus exemestane for locally advanced and MBC in premenopausal women are also warranted to confirm our overall findings.

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