**Hypothesis:** Toremifen is effective in reducing breast pain and does not increase the incidence of adverse events as a therapy for moderate to severe mastalgia.

**Design and Patients:** In a double-blind randomized controlled trial, patients with moderate to severe mastalgia received toremifen citrate, 30 mg daily, or a placebo tablet for 3 menstrual cycles and were followed up for breast pain score and adverse events. The serum levels of estradiol, progesterone, and prolactin were examined before treatment and correlated with the response rate to toremifen treatment.

**Results:** Seventy-two (69.2%) of 104 patients receiving toremifen and 29 (31.9%) of 91 receiving placebo responded to the treatment, with a reduction in breast pain score of more than 50% ($P < .001$). Among the patients with cyclical mastalgia, the response rate for toremifen was 76.7% (59/77), whereas the response rate for placebo was 34.8% (23/66; $P < .001$). In contrast, the response rate of patients with noncyclical mastalgia was 48.1% (13/27) for toremifen and 24.0% (6/25) for placebo ($P = .09$). Adverse events were observed in 44 (42.9%) of 104 patients receiving placebo and 46 (50.5%) of 91 patients receiving toremifen ($P = .45$). A positive correlation between baseline breast pain score and serum estradiol level was observed in patients with cyclical mastalgia ($r = 0.35$, $P = .003$).

**Conclusions:** Toremifen effectively relieves moderate and severe cyclical mastalgia and tends to exert a positive therapeutic effect on noncyclical mastalgia. In addition, toremifen therapy does not increase the incidence of intolerable adverse event. Therefore, it is a feasible therapy for mastalgia, especially cyclical mastalgia.

**METHODS**

**PATIENTS**

Premenopausal women with regular menstrual cycles and moderate to severe cyclical mastalgia were enrolled in the study. The patients were randomized to receive toremifen citrate, 30 mg daily, or a placebo tablet for 3 menstrual cycles. The primary outcome measures were the change in breast pain score and the incidence of adverse events. The serum levels of estradiol, progesterone, and prolactin were measured before treatment and correlated with the response to toremifen treatment.

**RESULTS**

Seventy-two (69.2%) of 104 patients receiving toremifen and 29 (31.9%) of 91 receiving placebo responded to the treatment, with a reduction in breast pain score of more than 50% ($P < .001$). Among the patients with cyclical mastalgia, the response rate for toremifen was 76.7% (59/77), whereas the response rate for placebo was 34.8% (23/66; $P < .001$). In contrast, the response rate of patients with noncyclical mastalgia was 48.1% (13/27) for toremifen and 24.0% (6/25) for placebo ($P = .09$). Adverse events were observed in 44 (42.9%) of 104 patients receiving placebo and 46 (50.5%) of 91 patients receiving toremifen ($P = .45$). A positive correlation between baseline breast pain score and serum estradiol level was observed in patients with cyclical mastalgia ($r = 0.35$, $P = .003$).

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or noncyclic mastalgia were recruited for the study. In all patients, mastalgia lasted for at least 6 consecutive menstrual cycles and more than 7 days for each cycle. To further confirm the severity and duration of mastalgia, as well as its association with menstrual cycles, we evaluated the patients using a visual analog scale (VAS) breast pain chart for 1 extra menstrual cycle and excluded those with a score of less than 4 or those with accompanying chest wall pain. Other exclusion criteria were as follows: (1) use of sex steroids (eg, oral contraceptive pill), danazol, vitamin B, or evening primrose oil within the last 3 months; (2) use of nonsteroidal anti-inflammatory drugs within the last 3 months; (3) use of hormonal therapy; (4) possible pregnancy; (5) possible noncompensated cardiac insufficiency, severe angina, or hepatic failure; (6) history of cancer and thrombus; and (7) allergy to toremifen. All these studies were approved by an academic committee in our university with informed consent of the patients.

STUDY DESIGN

The recruited patients with mastalgia were asked to record their symptoms of breast pain using a daily VAS breast pain chart, and the sum of the daily VAS within a menstrual cycle was considered the breast pain score (BPS). After a single nonmedicated menstrual cycle, designated the baseline cycle, a baseline daily score not less than 4 (VAS ≥4) verifying moderate to severe mastalgia was assigned to the participant. Qualified patients then entered a single-blind run-in phase and received placebo for 1 menstrual cycle, designated the placebo lead-in cycle, and each received a new placebo lead-in score to confirm her eligibility. Except for those with BPS decreased more than 25% after the placebo lead-in cycle, eligible participants entered the subsequent double-blind randomized controlled trial, receiving either toremifen, 30 mg daily, or placebo tablets for 3 consecutive menstrual cycles, designated the treatment cycle (Figure 1).

Clinical examination was performed at the end of the baseline period and at the end of each treatment period, and any adverse events, as well as a new BPS, was recorded at each interview. In addition, to correlate hormone levels and treatment effectiveness, we assayed serum estradiol, progesterone, and prolactin at the follicle phase just before the treatment cycle.

The randomization code was sealed and stored at the clinics individually. Before treatment, the pharmacists dispensed the tablets so that neither the physician nor the patient knew which compound had been dispensed. The codes were accessed by the investigators only when the participants dropped out of the study for the following reasons: (1) complications with life-threatening diseases, such as cancer or heart attack, that required immediate medications; (2) complications with chronic diseases that required prolonged inpatient hospitalization; (3) overdose or hypersensitivity to toremifen; or (4) unwillingness to continue therapy for personal reasons.

INTERVENTIONS

The active ingredient of a toremifen tablet was 60 mg of toremifen, and the inactive ingredients of the placebo tablets were maize starch, lactose, sodium starch glycolate, microcrystalline cellulose, colloidal anhydrous silica, and magnesium stearate. The placebo tablets were almost identical to the active tablets in size, appearance, and taste. Patients were advised to take half a tablet (30 mg of toremifen citrate or inactive ingredient in placebo) after lunch daily from the beginning of each menstrual period, and patient compliance was evaluated by means of tablet count. At the end of the study, patients without significant (P > .05) mastalgia improvement or relapse after medication received danazol, 200 mg daily, for 2 menstrual cycles.

MAIN OUTCOME MEASURES

The participants were asked to assess the severity and duration of the breast pain themselves on a daily basis and fill out the VAS breast pain chart. The severity of breast pain was scored from 0 to 10; 0 indicates no pain, and 10 indicates the worst pain. In addition, the patients were asked to record the first date of taking toremifen, all adverse events, and the reason for discontinuing therapy. Furthermore, the breast was examined clinically to check for lumpiness, tenderness, and nodularity at the end of the baseline cycle and each treatment cycle.

STATISTICS

The difference in self-assessed BPS between each treatment cycle and the placebo lead-in cycle was evaluated with the Wilcoxon rank sum test, and baseline cycle: placebo lead-in cycle; and the first, second, and third treatment cycles were compared by using repeated-measures analysis of variance. In addition, the effectiveness of toremifen treatment was defined as follows: effective rate (%) = (BPS (P) - BPS (T3))/BPS (P) × 100%, where BPS (P) indicates BPS of the placebo lead-in cycle and BPS (T3) indicates BPS at the end of the third treatment cycle. An effective rate of more than 50% was considered a clinical response to toremifen. A χ² test was used to measure the difference in clinical response rate between the toremifen and the placebo groups, with P < .05 considered statistically significant. We used a Spearman test to evaluate the correlation between treatment effectiveness and the age; types of mastalgia; baseline score; and serum levels of estradiol, progesterone, and prolactin of the patients.
RESULTS

NUMBER OF PARTICIPANTS

From September 1, 2001, through March 31, 2004, more than 7000 women attended our center at the Sun Yat-Sen Memorial Hospital for mastalgia. Among them, 988 met the criteria of moderate and severe mastalgia according to the record of the breast pain chart after 1 baseline menstrual cycle. Of these patients, only 195 had a decrease in VAS score of less than 25% after the placebo lead-in cycle and thus were assigned randomly to placebo (91 patients) or toremifen (104 patients) treatment. During the treatment months, 72 women discontinued the therapy, including 57% of patients from the placebo group because of lack of clinical response (34 patients), adverse event (2 patients), and other reasons (5 patients) and 43% from the toremifen group because of no clinical response (10 patients), adverse event (2 patients), and other reasons (19 patients). Among the patients without clinical response, 34 from the placebo group and 10 from the toremifen group switched to treatment with danazol, 200 mg daily, for 2 menstrual cycles. In addition, among the patients with positive clinical response, 13.8% (4/29) from the placebo group and 13.9% (10/72) from the toremifen group had a relapse of breast pain and switched to danazol therapy.

THERAPEUTIC EFFECT

To determine the therapeutic effect of toremifen, the percentage of reduction in BPS after 3 treatment cycles was calculated as described in the “Statistics” subsection of the “Methods” section, and 50% reduction in BPS was considered a clinical response to the treatment. As a result, clinical response was achieved in 72 (69.2%) patients from the toremifen group and in 29 (31.9%) from the placebo group ($\chi^2=27.32, P<.001$). Furthermore, for cyclical mastalgia, the response rates with toremifen and placebo were 76.7% (59/77) and 34.8% (23/66), respectively ($\chi^2=25.36, P<.001$). In contrast, for noncyclical mastalgia, the response rates with toremifen and placebo were 48.1% (13/27) and 24.0% (6/25), respectively ($\chi^2=3.26, P=.09$).

In addition, in the toremifen group, BPS reductions for the first, second, and third treatment cycles relative to the placebo lead-in cycle were 52.9% (97/104), 73.4% (78/86), and 78.9% (66/71), respectively, whereas reductions in the placebo group were 20.9% (6/91), 35.8% (56/67), and 46.2% (44/52) ($\chi^2=77.00, P<.001$) (Figure 2). As shown in Figure 3, the BPS was reduced significantly at the end of each toremifen-treated cycle as compared with the previous cycle ($P<.01$) but remained unchanged in the placebo group ($P>.05$). Furthermore, the BPS was significantly lower with toremifen treatment as compared with placebo treatment at the end of each treatment cycle ($P<.01$).

At the end of the study, patients without clinical response switched to danazol, 200 mg twice a day, for 2 menstrual cycles. Subsequently, 21 patients from the placebo group and 4 from the toremifen group responded positively. Among 14 patients with recurrent breast pain after cessation of toremifen or placebo treatment, 75% (3/4) from the placebo group and 40% (4/10) from the toremifen group responded to danazol.

ADVERSE EVENTS

During the treatment cycles in our study, the adverse events in both groups were menses disturbance, dizziness, vaginal discharge, and nausea. Overall, the incidence of adverse events in the toremifen group was not different from that of the placebo group (51.0% [53/104] vs 42.9% [39/91], $\chi^2=2.67, P=.45$). Of all these adverse events, the incidence of vaginal discharge was slightly higher in the toremifen group compared with that in the placebo group, but the difference was not statistically significant ($P=.05$).
daily16; 65% to 92% responded to danazol, 100 to 400 mg daily10,11; and 71% to 96%8-13 responded to tamoxifen citrate, 10 or 20 mg daily. Moreover, on the basis of our data, toremifen seems to be more effective for cyclical mastalgia, as it can significantly relieve moderate and severe cyclical mastalgia, with a response rate of 76.6%. Although the difference in effective rates between toremifen and placebo in the treatment of noncyclical mastalgia was not statistically significant, probably because of an insufficient number of cases of noncyclical mastalgia in our present study, toremifen tends to exert a positive therapeutic effect. Further study with more cases of noncyclical mastalgia is needed to address this issue.

Use of danazol and bromocriptine is limited because they induce severe adverse events, such as nausea and dizziness, with an incidence of 45%. In contrast, the most common adverse events of toremifen, 30 mg daily, are menstruation disturbance (27/104) and vaginal discharge (9/104), with a total incidence of 34.6%. Most important, as compared with placebo, toremifen does not increase the overall incidence of adverse event (P=.45), and only the incidence of vaginal discharge tends to be elevated (P=.05). Moreover, the incidence of hot flashes, frequently encountered in treatment with tamoxifen (25%), was tremendously reduced (5 [4.8%] of 104). In our study, only 2 patients discontinued toremifen therapy because of intolerable adverse events, with 1 case of alopecia and 1 case of vaginal discharge. Other than these, no serious adverse events were observed. Our data suggest that toremifen is effective, safe, and tolerable.

It is still controversial whether the onset of mastalgia is related to hormone levels because of mastalgia’s high response rate to hormonal therapy. Results of previous studies suggest that the cause of mastalgia is related to increased estrogen secretion, deficient progesterone, and hyperprolactinemia.17 In our study, we also investigated the relationship between severity of mastalgia and serum hormone levels. However, we found no obvious correlation between mastalgia and serum levels of progesterone and prolactin before medication; the effectiveness of toremifen therapy is not associated with sex hormone levels. Only the serum estradiol level is related to

### Table. Correlations Among Breast Pain Score, Clinical Response, Serum Hormone Levels, and Age

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Estradiol</th>
<th>Progesterone</th>
<th>Prolactin</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline breast pain score</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclical</td>
<td>Correlation coefficient</td>
<td>0.35</td>
<td>0.03</td>
<td>-0.32</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>.03</td>
<td>.87</td>
<td>.07</td>
</tr>
<tr>
<td>Noncyclical</td>
<td>Correlation coefficient</td>
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<td>0.00</td>
<td>-0.31</td>
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<tr>
<td></td>
<td>P value</td>
<td>.51</td>
<td>&gt;.99</td>
<td>.73</td>
</tr>
<tr>
<td>Clinical response to toremifen citrate</td>
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<td></td>
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<tr>
<td>Cyclical</td>
<td>T value*</td>
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<tr>
<td></td>
<td>P value</td>
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<td>.28</td>
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<tr>
<td>Noncyclical</td>
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</tr>
<tr>
<td></td>
<td>P value</td>
<td>.76</td>
<td>.46</td>
<td>.31</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

*Result of t test to compare the serum hormone level in patients with a clinical response to toremifen with those who did not respond.

### SERUM SEX HORMONE LEVELS

To further evaluate the influence of sex hormones on treatment effectiveness, we measured the serum levels of estradiol, progesterone, and prolactin in the participants before each treatment cycle. There was no mean ± SD significant difference in the serum levels of estradiol (toremifen: 115.41 ± 17.11 vs control: 93.41 ± 15.73, P > .05), progesterone (toremifen: 14.23 ± 1.04 vs control: 5.01 ± 0.65, P > .05), and prolactin (toremifen: 12.56 ± 1.41 vs control: 11.04 ± 1.30, P > .05) between patients receiving toremifen and those receiving placebo. As shown in the Table, baseline BPS correlated positively with serum estradiol (r = 0.35, P = .003) in patients with cyclical mastalgia but not in those with noncyclical mastalgia. In addition, baseline BPS was not correlated with serum progesterone or prolactin or the age of the participants (Table). Furthermore, the clinical response of toremifen treatment was not correlated with serum estradiol, progesterone, or prolactin or the age of the patients with either cyclical mastalgia or noncyclical mastalgia (Table).

## COMMENT

Toremifen, a new member of the family of selective estrogen receptor modulators, shares most of the biological activities of tamoxifen. The therapeutic effect of toremifen is comparable to that of tamoxifen as an adjuvant endocrine therapy in breast cancer and has fewer adverse events than does tamoxifen.15 We hypothesized that toremifen would be a better medication than tamoxifen for mastalgia. However, studies about toremifen therapy for benign breast diseases remain rare.

In the present study, toremifen, 30 mg daily, effectively relieved moderate and severe mastalgia, with an effective rate of 69.2%. This rate is comparable to the response rate reported elsewhere, as 65.2% of patients with mastalgia responded to bromocriptine mesylate, 5 mg daily16; 65% to 92% responded to danazol, 100 to 400 mg daily10,11; and 71% to 96%8-13 responded to tamoxifen citrate, 10 or 20 mg daily. Moreover, on the basis of our data, toremifen seems to be more effective for cyclical mastalgia, as it can significantly relieve moderate and severe cyclical mastalgia, with a response rate of 76.6%. Although the difference in effective rates between toremifen and placebo in the treatment of noncyclical mastalgia was not statistically significant, probably because of an insufficient number of cases of noncyclical mastalgia in our present study, toremifen tends to exert a positive therapeutic effect. Further study with more cases of noncyclical mastalgia is needed to address this issue.

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the baseline BPS in patients with cyclical mastalgia but not in those with noncyclical mastalgia, suggesting that we may need a more sophisticated classification of mastalgia or BPS to investigate the relationship between mastalgia and serum hormone levels.

In summary, toremifen is a feasible therapy for moderate and severe mastalgia. On the basis of our data, BPS was reduced significantly after the first treatment cycle, suggesting that toremifen can relieve mastalgia rapidly. As treatment continued, the therapeutic effect was maintained, and BPS was reduced further. However, further studies are needed to compare the therapeutic and adverse effects of toremifen therapy at different doses, for different treatment durations, and with different endocrine medicine.

Accepted for Publication: May 2, 2005.

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Author Contributions: Drs Gong and Song contributed equally to this work.

Funding/Support: This work was supported by research grants 30440021 and 30471977 from the National Natural Science Foundation of the People’s Republic of China, grants 04009402 and 19980098 from the Provincial Natural Science Foundation of Guangdong Province, and the Department of Medical Science of Sun Yat-Sen University.

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