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ORIGINAL ARTICLE

Efficacy and tolerability of toremifene and tamoxifen therapy in premenopausal patients with operable breast cancer: a retrospective analysis

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ABSTRACT

Background

Given the use of tamoxifen as standard treatment for hormone receptor–positive breast cancer, the use of toremifene as an adjuvant endocrine therapy has not been widely examined. The present retrospective study compared the efficacy and safety of toremifene and tamoxifen in the treatment of operable hormone receptor–positive breast cancer in premenopausal women.

Methods

Premenopausal patients with hormone receptor–positive operable breast cancer were eligible. Enrolled patients (n = 1847) received either 60 mg toremifene (n = 396) or 20 mg tamoxifen (n = 1451) daily for a minimum of 5 years after surgery. Disease-free survival (DFS) was the primary endpoint. Overall survival (OS) and time to distant recurrence were secondary endpoints.

Results

Treatment with toremifene and tamoxifen resulted in no between-group differences in DFS (p = 0.659) or OS (p = 0.364). Mean DFS was 10.3 years for both groups. Mean OS was 11.2 years for the toremifene group and 11.1 years for tamoxifen group. The 5-year DFS rate was 87.0% in the toremifene group and 85.0% in the tamoxifen group. The 5-year survival rate was 94.3% in the toremifene group and 93.5% in the tamoxifen group. Adverse events rates were similar in the two groups, with the exception of irregular menses, which occurred at a higher rate in the tamoxifen group than in the toremifene group (10.0% vs. 6.3%, p = 0.025).

Conclusions

In this retrospective study, the efficacy and safety profiles of toremifene and tamoxifen for the treatment of operable hormone receptor–positive breast cancer in premenopausal women were similar.

KEY WORDS

Tamoxifen, toremifene, breast cancer, adjuvant endocrine therapy, premenopausal

1. INTRODUCTION

Endocrine therapy is a primary component in the management of hormone receptor–positive breast cancer. Currently available treatment options for patients who are premenopausal include ovarian ablation or suppression, and the use of selective estrogen receptor modulators such as toremifene and tamoxifen[1]. Currently, the standard endocrine therapy for premenopausal women is tamoxifen[2,3].

The benefits of tamoxifen treatment in premenopausal women with hormone receptor–positive breast cancer have been well documented. The Early Breast Cancer Trialists' Collaborative Group meta-analysis in 2000 demonstrated that, after 5 years of adjuvant tamoxifen treatment, women with hormone receptor–positive breast cancer experienced a 50% reduction in annual recurrence rate and a 31% reduction in breast cancer–related mortality rate. Both rates were lower regardless of age, nodal status, or use of chemotherapy. Furthermore, the effectiveness of tamoxifen has been demonstrated to increase over time: 5 years of therapy is more effective than 1–2 years[4].

Tamoxifen has a number of associated adverse events, including increased risk of secondary endometrial cancer, thromboembolic events, and ocular changes[4,5]. The side-effect profile of tamoxifen has driven the development of analogues, including toremifene, a chlorinated derivative with similar site-specific activity. Toremifene, like tamoxifen, is

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a nonsteroidal triphenylethylene selective estrogen receptor modulator that binds to estrogen receptors. Toremifene and tamoxifen both exert anti-estrogenic effects in breast tissue, inducing apoptosis and inhibiting entry into mitosis in human breast cancer cells[6].

In preclinical studies, toremifene has demonstrated equivalent estrogen receptor–binding and antitumour efficacy, with less estrogenic activity and DNA adduct formation in the endometrium[7]. No excess risk of endometrial cancer[8] or severe ocular toxicity[9] has been reported in patients treated with toremifene. In clinical studies, phase III results have demonstrated that 40 mg or 60 mg toremifene daily has an efficacy and safety profile similar to that of tamoxifen as first-line treatment for metastatic breast cancer in postmenopausal women. Specifically, toremifene was noninferior to tamoxifen for the treatment of advanced breast cancer in a five-study meta-analysis (1421 patients) that included three pivotal studies (the North American, Nordic, and Eastern European studies)[10].

Currently, toremifene is approved by the U.S. Food and Drug Administration for the treatment of metastatic breast cancer in postmenopausal women with estrogen receptor–positive or unknown tumours. The use of toremifene as an adjuvant endocrine therapy for premenopausal patients with breast cancer has not been widely examined. The objective of the present study was to compare the efficacy and safety of toremifene and tamoxifen in the treatment of operable hormone receptor–positive breast cancer in premenopausal women.

2. METHODS

This retrospective analysis included patients with histologically proven unilateral invasive ductal breast cancer who were treated between January 2000 and December 2009 at Sun Yat-sen University Cancer Center, Guangzhou, China. The study and all protocols were approved by the institutional review board.

Study entrants were required to have undergone either a mastectomy or breast-conserving surgical treatment, toremifene or tamoxifen treatment after chemotherapy (and radiotherapy, if indicated), a known tumour size, World Health Organization performance status 0 or 1, a complete medical record and follow-up data of at least 5 years, and regularly occurring menses throughout the data collection period (premenopausal). Toremifene or tamoxifen was chosen based on physician preference and clinical experience with both medications. Adjuvant chemotherapy regimens recommended by the National Comprehensive Cancer Network guidelines[11] and tailored by toxicities were permitted. Eligible patients received either 60 mg toremifene daily or 20 mg tamoxifen daily for a minimum of 5 years. Treatment was initiated within 3 weeks after surgery, chemotherapy, or radiotherapy, whichever was most recent. Patients receiving breast-conserving surgery, those whose tumour was larger than 5 cm, those with 4 or more positive lymph nodes, and those with a positive surgical margin received radiotherapy after surgery, with adjuvant chemotherapy. Patients with 1–3 positive lymph nodes received radiotherapy if their disease was hormone receptor–negative or showed lymphovascular invasion or overexpression of HER2 (human epidermal growth factor receptor 2).

Patients were excluded if they were perimenopausal or postmenopausal and presented with hormone receptor–negative breast cancer; with evidence of primary cancer in the contralateral breast; with a prior history of malignancies, including breast cancer; with prior treatment using toremifene or tamoxifen; or with pathologically confirmed ductal carcinoma *in situ,* lobular carcinoma *in situ,* or inflammatory breast cancer. Patients were also excluded if the type of surgery received was not indicated, or if medical records were incomplete—for example, information about hormone receptor status or follow-up was missing.

All patients were staged according to the American Joint Committee on Cancer TNM staging system for breast cancer (7th edition), evaluated before neoadjuvant therapy or surgery, whichever came first. Grading of tumours and histologic classification were based on World Health Organization criteria. Estrogen and progesterone receptor status of primary tumour was determined by immunohistochemistry, with staining of more than 10% of cells defined as positive. Patients were considered HER2-positive if the HER2 protein measured 3+ intensity when examined using immunohistochemistry or upon amplification of the HER2/*neu* gene using fluorescence *in situ* hybridization.

The primary endpoint for this retrospective analysis was disease-free survival (DFS), defined as the length of time from the date of surgery on the primary tumour to local, regional, or distant recurrence or death from any cause. The secondary endpoint was overall survival (OS), defined as the length of time from the date of surgery on the primary tumour to death from any cause or to time of last visit. Patient-reported occurrences of adverse events were also evaluated as recorded by the physician at each patient visit and were graded using the *Common Terminology Criteria for Adverse Events,* version 3.0.

Patient demographics, clinical characteristics, DFS, OS (and related outcomes), and adverse events were summarized for both the toremifene and tamoxifen treatment groups and are presented as numbers and percentages. Differences between groups were compared using the Pearson chi-square test—except for ordinal data, stage, and histologic grade, which were compared using the Mann–Whitney U-test. Time-related data stratified by group were visualized using Kaplan–Meier curves, with a log-rank test. Mean DFS and OS were summarized as means, with their respective estimated 95% confidence intervals (CIs) for the two treatment groups. Furthermore, univariate Cox regression analyses were performed,

yielding hazard ratios (HRs) with 95% CIs for the association of time-related data considering treatments, demographics, and characteristics of the patients. All statistical assessments were two-tailed and were considered significant at $p < 0.05$. Statistical analyses were performed using the SPSS statistics software (version 16.0: SPSS, Chicago, IL, U.S.A.).

3. RESULTS

Of the 1847 patients included in the our analysis, 396 received toremifene and 1451 received tamoxifen (Figure 1). Most patients in each group were more than 35 years of age (toremifene: 78.3%; tamoxifen: 79.7%). Baseline demographics and patient characteristics were balanced between the groups (Table I), except for radiotherapy (25% toremifene vs. 34% tamoxifen, $p = 0.001$).

The DFS- and OS-related outcomes were not different between the toremifene and tamoxifen treatment groups (Table II), nor were the DFS and OS times (Figure 2). During the study period, 63 patients (15.9%) receiving toremifene and 213 patients (14.7%) receiving tamoxifen died or experienced a recurrence. Mean DFS was 10.3 years for the toremifene group (95% CI: 9.9 to 10.6 years) and 10.3 years for the tamoxifen group (95% CI: 10.1 to 10.5 years). In the toremifene group, the 1-, 3-, and 5-year DFS rates were 98.7%, 90.6%, and 87.0%. In the tamoxifen group, they were 98.3%, 89.6%, and 85.0% respectively. No significant differences in DFS between the toremifene and tamoxifen groups were observed [$p = 0.659$, Figure 2(A)]. Mean OS was 11.2 years for the toremifene group (95% CI: 10.9 to 11.4 years) and 11.1 years for the tamoxifen group (95% CI: 10.9 to 11.2 years). In the toremifene group, the 1-, 3-, and 5-year survival rates were 99.7%, 97.0%, and 94.3% respectively. In the tamoxifen group, they were 99.8%, 96.9%, and 93.5%. No significant differences in OS between the groups were observed [$p = 0.364$, Figure 2(B)]. In total, 29 patients in the toremifene group (7.3%) and 105 patients in the tamoxifen group (7.2%) died (Figure 1).

Table III presents results of the univariate Cox regression analyses of DFS, OS, time to local or distant recurrence (TDR), and time to distant recurrence, considering associated factors, treatment groups, demographics, and patient characteristics. No effect by treatment group was observed for DFS, OS, TDR, or time to distant recurrence. The DFS and TDR were associated with age, surgery type, tumour size, stage, histologic grade 3, involvement of more than 1 lymph node, lymphovascular invasion, estrogen

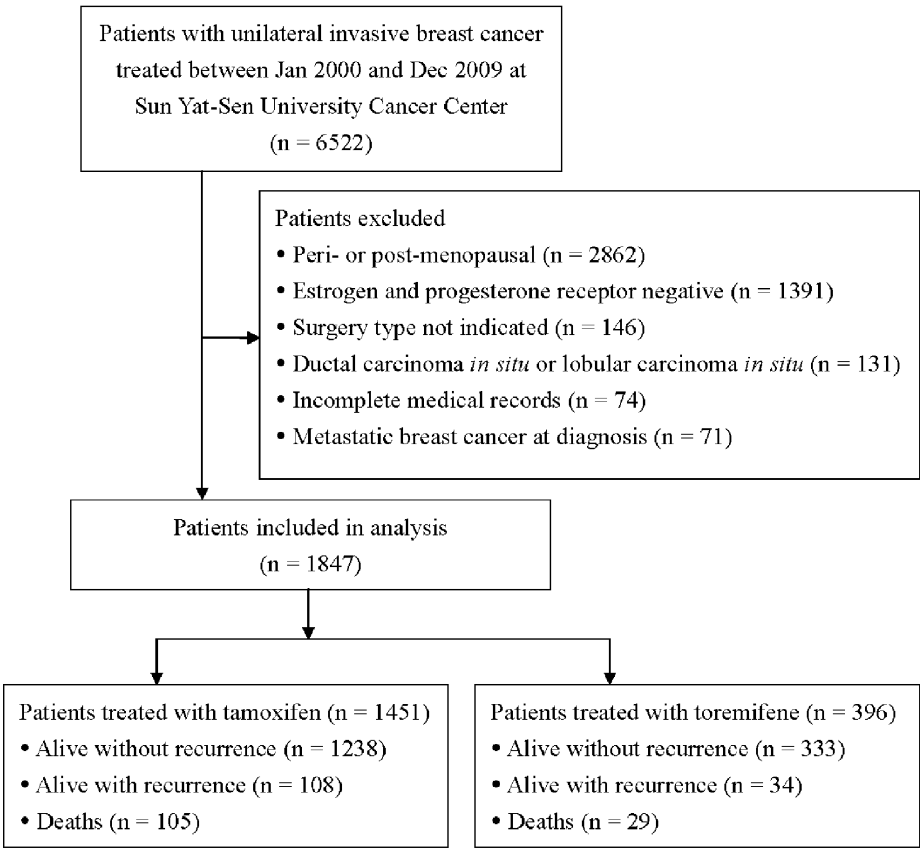

FIGURE 1 *Flow chart of patient enrollment.*

TABLE I Patient characteristics by treatment group

Variable	*Treatment group [*n *(%)]*		p *Value*[a]
	Tamoxifen	*Toremifene*	
Patients	1451	396	—
Age			0.525
≤35 Years	294 (20.3)	86 (21.7)	
>35 Years	1157 (79.7)	310 (78.3)	
Type of surgery			0.183
Mastectomy	1334 (91.9)	372 (93.9)	
Breast-conserving	117 (8.1)	24 (6.1)	
Tumour size			0.680
≤2 cm	446 (30.7)	126 (31.8)	
>2 cm	1005 (69.3)	270 (68.2)	
Stage			0.231
I	279 (19.2)	78 (19.7)	
IIA	557 (38.4)	163 (41.2)	
IIB	259 (17.8)	75 (18.9)	
IIIA	215 (14.8)	46 (11.6)	
IIIB	19 (1.3)	4 (1.0)	
IIIC	122 (8.4)	30 (7.6)	
Histologic grade[b]			0.482
1	49 (6.0)	16 (9.6)	
2	485 (59.7)	95 (56.9)	
3	278 (34.2)	56 (33.5)	
Positive lymph nodes			0.276
0	749 (51.6)	212 (53.5)	
1–3	373 (25.7)	110 (27.8)	
4–9	207 (14.3)	44 (11.1)	
≥10	122 (8.4)	30 (7.6)	
Lymphovascular invasion			0.548
Yes	41 (2.8)	9 (2.3)	
No	1410 (97.2)	387 (97.7)	
Receptor status			
Estrogen			0.691
Positive	1208 (83.3)	333 (84.1)	
Negative	243 (16.7)	63 (15.9)	
Progesterone			0.765
Positive	1351 (93.1)	367 (92.7)	
Negative	100 (6.9)	29 (7.3)	
HER2			0.924
Positive	290 (20.0)	80 (20.2)	
Negative	1161 (80.0)	316 (79.8)	
Chemotherapy			0.122
None	75 (5.2)	27 (6.8)	
Non-anthracycline, non-taxane	119 (8.2)	28 (7.1)	
Anthracycline, non-taxane	588 (40.5)	137 (34.6)	
Anthracycline–taxane combination	629 (43.3)	189 (47.7)	
Taxane only	40 (2.8)	15 (3.8)	
Radiotherapy			**0.001**
Yes	494 (34.0)	99 (25.0)	
No	957 (66.0)	297 (75.0)	
LHRH agonist therapy			0.861
Yes	63 (4.3)	18 (4.5)	
No	1388 (95.7)	378 (95.5)	

[a] Between-groups differences were assessed by chi-square test, except for the ordinal data (stage and histologic grade), which were assessed by Mann–Whitney U-test. Boldface type indicates a value of $p < 0.05$, significantly different between the treatment groups.

[b] This variable excludes 868 patients (229 in the toremifene group and 639 in the tamoxifen group) because of unknown histologic grade.

HER2 = human epidermal growth factor receptor 2; LHRH = luteinizing hormone–releasing hormone.

receptor status, progesterone receptor status, HER2 status, chemotherapy regimens, and radiotherapy (each $p < 0.05$). Furthermore, associations between OS and age, tumour size, stage, involvement of more than 1 lymph node, lymphovascular invasion, chemotherapy, and radiotherapy were also observed (each $p < 0.05$). Time to distant recurrence was found to be associated with age, surgery type, tumour size, stage, histological grade 3, involvement of more than 1 lymph node, lymphovascular invasion, progesterone receptor status, and radiotherapy (each $p < 0.05$).

All adverse events were mild or moderate. The adverse events most commonly reported after treatment (>5% in each group) were flushing, sweating, vaginal discharge, nausea, vomiting, hypertriglyceridemia, and irregular menses (Table IV). No patient reported a severe adverse event. A higher rate of irregular menses was reported by members of the tamoxifen group than by members of the toremifene group (10.0% vs. 6.3%, $p = 0.025$). Endometrial cancer developed in 1 patient in the tamoxifen group and in no patients in the toremifene group.

4. DISCUSSION

The results of the present study indicate that, in the treatment of hormone receptor–positive operable breast cancer in premenopausal women, toremifene and tamoxifen have similar efficacy and tolerability. The estimated 5-year DFS rates were not significantly different between the treatment groups. In addition, the 5-year OS and TDR were not statistically different between the groups.

The observed DFS and OS were comparable to those reported in previous studies with tamoxifen or toremifene in postmenopausal women. None of the patients in the current study received adjuvant trastuzumab. In China, trastuzumab was approved for the adjuvant therapy of HER2-positive breast cancer at the end of 2008. The present study concluded in December 2009. The cost of trastuzumab is not reimbursed by

TABLE II Comparison of patient outcomes by treatment group

Event	*Treatment group*[a]		p *Value*[b]
	Tamoxifen	*Toremifene*	
Follow-up time (years)			**<0.001**
Mean	5.6±2.9	6.9±2.6	
Range	0.1–11.9	1–11.8	
Recurrence or death			0.543
No	1238 (85.3)	333 (84.1)	
Yes	213 (14.7)	63 (15.9)	
Site of recurrence			0.294
None	1273 (87.7)	345 (87.1)	
Local or regional	26 (1.8)	12 (3.0)	
Distant	152 (10.5)	39 (9.8)	
Site of distant recurrence			
Bone	75 (5.2)	20 (5.1)	0.925
Lung	54 (3.7)	7 (1.8)	0.054
Liver	44 (3.0)	11 (2.8)	0.792
Brain	7 (0.5)	1 (0.3)	1.000
Contralateral breast	9 (0.6)	2 (0.5)	1.000
Soft tissue and skin	36 (2.5)	10 (2.5)	0.960
Pleura	12 (0.8)	4 (1.0)	0.760
Overall survival status			0.953
Alive	1346 (92.8)	367 (92.7)	
Dead	105 (7.2)	29 (7.3)	
Cause of death			0.422
Breast-cancer-related	70 (66.7)	17 (58.6)	
Non-cancer-related	35 (33.3)	12 (41.4)	

[a] Data presented as mean ± standard deviation with range (minimum to maximum) or number and percentage.

[b] Between-groups differences were assessed by Mann–Whitney U-test (follow-up times) or chi-square or Fisher exact test for any cell number less than 5. The groups showed no significant differences except in follow-up time (boldface).

China's national health insurance, and therefore very few patients (and none in the present study) received trastuzumab before 2009. Lewis *et al.*[6] examined 1813 postmenopausal women with hormone receptor–positive invasive breast cancer receiving adjuvant treatment with either tamoxifen (20 mg) or toremifene (60 mg) for 5 years. The primary treatment endpoints were 5-year DFS and OS. Consistent with our results, Lewis *et al.* demonstrated that patients treated with tamoxifen or toremifene did not differ in therapeutic response. At a mean follow-up of 59 months, no differences in DFS or OS were evident between the groups.

Rates of recurrence and distant metastasis, and also sites of recurrence, were not statistically different between the groups in the present study. That finding is also supported by Lewis *et al.,* who observed a higher, albeit nonsignificant, number of local recurrences and distant bone recurrences in women taking toremifene[6].

Another recently published study by Su *et al.,* similar to the present investigation, sought to establish

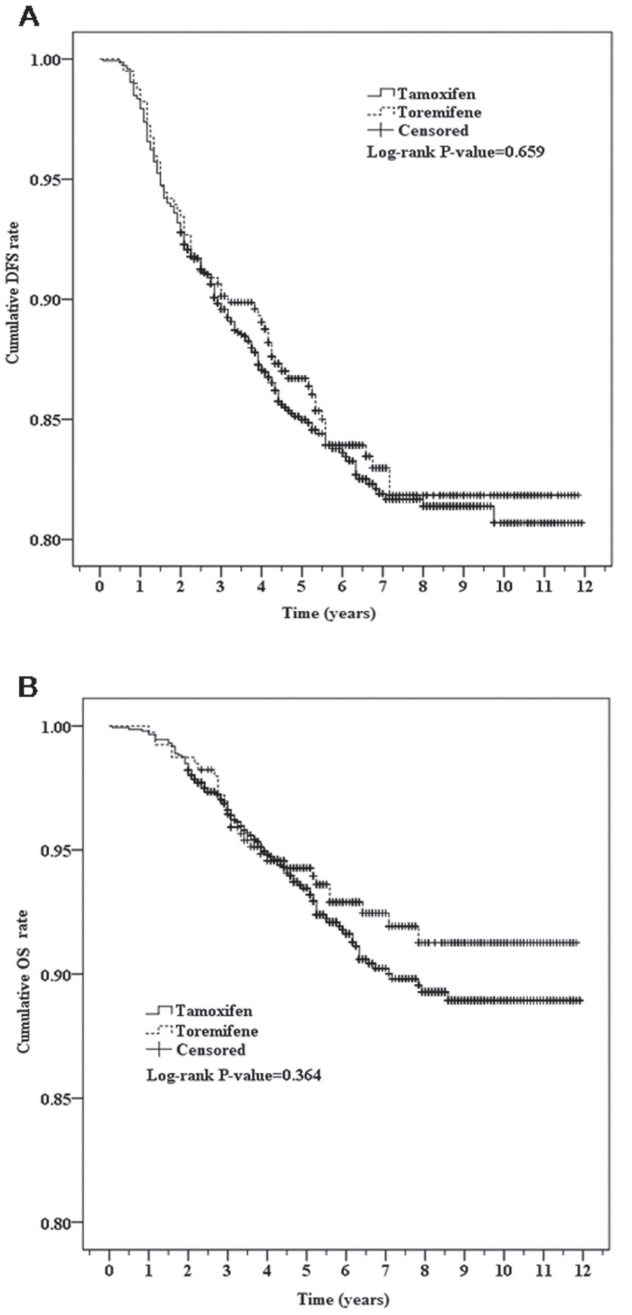

*FIGURE 2 Kaplan–Meier curves for (A) disease-free survival (DFS) and (B) overall survival (OS), by treatment group. The DFS and OS were not significantly different between the groups (*p *= 0.659 and 0.364 respectively).*

the role of toremifene as a tamoxifen alternative for endocrine therapy in premenopausal patients with estrogen or progesterone receptor–positive breast cancer. Toremifene and tamoxifen yielded similar OS values, with 5-year OS rates of 100% and 98.4% respectively ($p = 0.087$). However, recurrence-free survival was significantly better in the toremifene group than in the tamoxifen group ($p = 0.022$).

TABLE III Univariate Cox regression analysis of time to disease recurrence or death, considering treatments, demographics, and disease characteristics

Characteristic	*Disease recurrence or death*			*Death from any cause*			*Local or distant recurrence*			*Distant recurrence*		
	HR	*95% CI*	p *Value*[a]	*HR*	*95% CI*	p *Value*[a]	*HR*	*95% CI*	p *Value*[a]	*HR*	*95% CI*	p *Value*[a]
Treatment												
Tamoxifen		Reference			Reference			Reference			Reference	
Toremifene	0.9	0.7 to 1.2	0.660	0.8	0.5 to 1.2	0.365	0.9	0.7 to 1.2	0.573	0.8	0.6 to 1.2	0.237
Age												
≤35 Years		Reference			Reference			Reference			Reference	
>35 Years	0.5	0.4 to 0.6	**<0.001**	0.4	0.3 to 0.6	**<0.001**	0.5	0.4 to 0.6	**<0.001**	0.5	0.4 to 0.7	**<0.001**
Type of surgery												
Mastectomy		Reference			Reference			Reference			Reference	
Breast-conserving	0.4	0.2 to 0.8	**0.009**	0.4	0.2 to 1.1	0.084	0.4	0.2 to 0.8	**0.013**	0.3	0.1 to 0.7	**0.008**
Tumour size												
≤2 cm		Reference			Reference			Reference			Reference	
>2 cm	3.2	2.2 to 4.5	**<0.001**	4.1	2.3 to 7.3	**<0.001**	2.8	1.9 to 4.1	**<0.001**	2.4	1.7 to 3.6	**<0.001**
Stage												
I		Reference			Reference			Reference			Reference	
IIA	3.8	2.0 to 7.4	**<0.001**	7.5	1.8 to 31.2	**0.006**	3.8	2.0 to 7.4	**<0.001**	3.6	1.8 to 7.3	**<0.001**
IIB	5.0	2.5 to 10.0	**<0.001**		2.9 to 51.6	**0.001**	5.0	2.5 to 10.0	**<0.001**	4.1	2.0 to 8.6	**<0.001**
IIIA	7.3	3.7 to 14.4	**<0.001**		4.7 to 82.7	**<0.001**	7.3	3.7 to 14.5	**<0.001**	6.9	3.3 to 14.1	**<0.001**
IIIB	7.5	2.4 to 24.0	**0.001**		9.3 to 248.0	**<0.001**	7.6	2.4 to 24.3	**0.001**	8.6	2.6 to 27.9	**0.001**
IIIC		6.5 to 25.7	**<0.001**		13.4 to 228.4	**<0.001**		6.6 to 26.0	**<0.001**		6.1 to 26.1	**<0.001**
Histologic grade[b]												
I		Reference			Reference			Reference			Reference	
II	7.1	1.0 to 51.7	0.052	2.4	0.3 to 17.8	0.403	6.6	0.9 to 47.9	0.062	5.3	0.7 to 38.9	0.099
III		1.9 to 99.8	**0.009**	5.8	0.8 to 42.8	0.084		1.5 to 77.0	**0.019**	9.4	1.3 to 68.7	**0.027**
Positive lymph nodes												
0		Reference			Reference			Reference			Reference	
1–3	1.5	1.1 to 2.1	**0.023**	1.5	0.9 to 2.5	0.115	1.5	1.1 to 2.1	**0.023**	1.4	0.9 to 2.0	0.111
4–9	2.7	1.9 to 3.8	**<0.001**	3.4	2.1 to 5.5	**<0.001**	2.7	1.9 to 3.8	**<0.001**	2.8	1.9 to 4.0	**<0.001**
≥10	4.4	3.1 to 6.4	**<0.001**	8.8	5.6 to 13.7	**<0.001**	4.5	3.1 to 6.5	**<0.001**	4.6	3.1 to 6.9	**<0.001**
Lymphovascular invasion												
No		Reference			Reference			Reference			Reference	
Yes	3.3	2.1 to 5.3	**<0.001**	4.2	2.3 to 7.6	**<0.001**	3.0	1.7 to 5.1	**<0.001**	3.4	1.9 to 5.9	**<0.001**
Receptor status												
Estrogen												
Negative		Reference			Reference			Reference			Reference	
Positive	0.7	0.5 to 1.0	**0.027**	1.0	0.6 to 1.6	0.993	0.7	0.5 to 0.9	**0.011**	0.7	0.5 to 1.0	0.062

TABLE III Continued

Characteristic	*Disease recurrence or death*			*Death from any cause*			*Local or distant recurrence*			*Distant recurrence*		
	HR	*95% CI*	p *Value*[a]	*HR*	*95% CI*	p *Value*[a]	*HR*	*95% CI*	p *Value*[a]	*HR*	*95% CI*	p *Value*[a]
Receptor status (cont'd)												
Progesterone												
Negative		Reference			Reference			Reference			Reference	
Positive	0.6	0.4 to 0.8	**0.005**	0.7	0.4 to 1.2	0.145	0.6	0.4 to 0.8	**0.005**	0.5	0.3 to 0.9	**0.008**
HER2												
Negative		Reference			Reference			Reference			Reference	
Positive	1.4	1.1 to 1.8	**0.014**	1.4	1.0 to 2.1	0.081	1.5	1.1 to 2.0	**0.011**	1.3	0.9 to 1.8	0.110
Chemotherapy regimen												
None		Reference			Reference			Reference			Reference	
Non-anthracycline, non-taxane	2.9	1.2 to 7.1	**0.023**	3.3	0.7 to 15.6	0.130	2.9	1.2 to 7.1	**0.023**	3.3	1.2 to 8.9	**0.016**
Anthracycline-based, non-taxane	1.9	0.8 to 4.4	0.131	3.6	0.9 to 14.8	0.076	1.9	0.8 to 4.4	0.128	1.9	0.8 to 4.8	0.162
Anthracycline–taxane combination	2.6	1.1 to 5.8	**0.025**	4.4	1.1 to 18.0	**0.039**	2.6	1.1 to 5.8	**0.024**	2.6	1.0 to 6.3	**0.040**
Taxane only	3.1	1.1 to 8.7	**0.033**	8.2	1.7 to 38.7	**0.008**	3.1	1.1 to 8.7	**0.033**	2.5	0.8 to 8.1	0.133
Radiotherapy												
No		Reference			Reference			Reference			Reference	
Yes	1.9	1.5 to 2.4	**<0.001**	2.5	1.8 to 3.5	**<0.001**	1.8	1.4 to 2.4	**<0.001**	1.9	1.5 to 2.6	**<0.001**
LHRH agonist therapy												
No		Reference			Reference			Reference			Reference	
Yes	0.5	0.2 to 1.2	0.128	0.9	0.3 to 2.4	0.782	0.3	0.1 to 1.0	**0.050**	0.4	0.1 to 1.2	0.107

[a] Boldface type indicates a value of $p < 0.05$, significantly different between the treatment groups.
[b] This variable excludes 868 patients (229 in the toremifene group and 639 in the tamoxifen group) because of unknown histologic grade.
HER2 = human epidermal growth factor receptor 2; LHRH = luteinizing hormone–releasing hormone.

TABLE IV Adverse events, by treatment group

Adverse event[a]	*Treatment group [*n *(%)]*		
	*Tamoxifen (*n*=1451)*	*Toremifene (*n*=396)*	p *Value*[b]
Flushing	480 (33.1)	139 (35.1)	0.450
Sweating	295 (20.3)	82 (20.7)	0.869
Nausea or vomiting	213 (14.7)	57 (14.4)	0.881
Fatigue	74 (5.1)	18 (4.5)	0.653
Insomnia	62 (4.3)	14 (3.5)	0.513
Dizziness	14 (1.0)	6 (1.5)	0.408
Dry eyes	60 (4.1)	17 (4.3)	1.0
Blurred vision	40 (2.8)	9 (2.3)	0.595
Cataracts	7 (0.5)	2 (0.5)	1.0
Weight gain	68 (4.7)	17 (4.3)	0.74
Vaginal discharge	241 (16.6)	69 (17.4)	0.701
Irregular menses	145 (10)	25 (6.3)	**0.025**
Endometrial cancer	1 (0.1)	0 (0)	0.601
Ovarian cyst	20 (1.4)	4 (1.0)	0.631
Thromboembolic events	22 (1.5)	5 (1.3)	0.709
Hypertriglyceridemia	76 (5.2)	19 (4.8)	0.725
Hyper-LDL cholesterolemia	65 (4.5)	16 (4.0)	0.783
Fatty liver	64 (4.4)	13 (3.3)	0.32
Elevated AST	59 (4.1)	15 (3.8)	0.802
Elevated ALP	33 (2.3)	7 (1.8)	0.571
Hepatic cyst	29 (2.0)	6 (1.5)	0.55
Bilirubin	27 (1.9)	8 (2.0)	1.0

[a] All adverse events were mild or moderate in severity as graded by the *Common Terminology Criteria for Adverse Events*[12].

[b] Boldface type indicates a value of $p < 0.05$, significantly different between the treatment groups. Comparisons used the chi-square or Fisher exact test for any cell number less than 5.

LDL = low-density lipoprotein; AST = aspartate aminotransferase; ALP = alkaline phosphatase.

Multivariate analysis also showed that recurrence-free survival improved independently with toremifene (HR: 0.385; 95% CI: 0.154 to 0.961; $p = 0.041$)[13].

Compared with Su *et al.,* the currently reported study (although similar in scope) has distinct differences. The present study had a larger sample size, because more patients with newly diagnosed breast cancer are treated at the Sun Yat-sen University Cancer Center each year than are treated at Sun Yat-sen Memorial Hospital (the focus for Su *et al.*). Currently, a greater number of our patients undergo mastectomy; Su *et al.* reported a greater number of patients undergoing breast-conserving surgery. The present study provides further evidence supporting the efficacy and tolerability of toremifene in premenopausal patients with breast cancer.

With respect to adverse effects in the present study, irregular menses were experienced by fewer patients in the toremifene group than in the tamoxifen group. Rates of other adverse events were not significantly different between the groups. By contrast, Su *et al.* reported a greater rate of hot flashes in the toremifene group than in the tamoxifen group ($p = 0.049$); however, in accord with our results, toxicities were similar in the two treatment groups, with no women experiencing severe complications, and no patients developing endometrial cancer[13]. Tamoxifen has a number of treatment-related adverse events, particularly an increased risk of secondary endometrial cancer. Reports from previous trials demonstrated a reduced incidence of endometrial cancer with toremifene[6,14,15].

Age has an effect on the survival of patients with premenopausal breast cancer. Earlier studies have reported that the prognosis of breast cancer patients 35 years of age or younger was poorer than that of patients more than 35 years of age[16,17]. In support of those earlier reports, the HRS for disease progression, death, and recurrence were significantly lower in our patients more than 35 years of age than in those 35 years of age or younger.

It has been hypothesized that HER2-positive tumours may be less responsive to certain endocrine treatments[18]. De Laurentiis conducted a meta-analysis investigating the association between response to endocrine treatment and overexpression of HER2 in metastatic breast cancer. They found HER2-positive metastatic breast cancer to be less responsive to any type of endocrine treatment. That result is consistent with findings in the present study that patients with HER2-positive tumours had significantly higher HRS for disease recurrence and death.

Unlike tamoxifen, toremifene is not a prodrug requiring activation by CYP2D6. No drug–drug interactions are expected with agents that interfere with CYP2D6 activity, and no differences are expected in poor and fast metabolizers of CYP2D6. Kim *et al.* reported that tamoxifen, but not toremifene, is a substrate for 4-hydroxylation by CYP2D6 in human liver microsomes and that the metabolism of toremifene is not markedly affected by potent CYP2D6 inhibitors in human liver microsomes. That result is particularly relevant to our findings and suggests a potential for clinical benefit in subjects taking toremifene to treat metastatic breast cancer considering that they would not be subject to allelic variation in CYP2D6 status or affected by co-administration of CYP2D6-inhibiting medications[19].

Potential limitations to the interpretation of our results include the manner in which patients were selected for treatment with toremifene or tamoxifen (physician preference and experience). Tamoxifen is still the standard of endocrine therapy for premenopausal breast cancer, and it is prescribed for most women with premenopausal breast cancer at Sun Yat-sen University Cancer Center; however, toremifene was prescribed by some physicians based solely on personal preference. In addition, our study was not a randomized controlled trial, and the retrospective design has potential for bias. Unequal distribution

between the study groups may suggest a difficulty in making valid comparisons. Also, no severity grading of adverse events was performed. To overcome those limitations, future prospective randomized controlled trials are needed to provide further evidence for the use of toremifene in premenopausal breast cancer patients.

5. CONCLUSIONS

In premenopausal breast cancer patients, toremifene has efficacy and safety profiles similar to those for tamoxifen. Randomized controlled trials are needed to provide further support for the use of toremifene in the treatment of premenopausal women with operable hormone receptor–positive breast cancer.

6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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