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Chinese breast cancer patients with *CYP2D6*10* mutant genotypes have a better prognosis with toremifene than with tamoxifen

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Abstract

Purpose: To evaluate the prognosis of estrogen receptor-positive breast cancer patients with *CYP2D6*10* mutant genotypes under tamoxifen or toremifen therapy.

Methods: Estrogen receptor-positive breast cancer patients were selected and *CYP2D6*10* genotypes (C/C, C/T, and T/T) were determined by Sanger sequencing. Patients were divided into tamoxifen, toremifene, or tamoxifen + toremifene groups according to prior therapy. The correlation between *CYP2D6*10* genotype and disease-free survival was analyzed.

Results: In total, 293 estrogen receptor-positive breast cancer patients treated with tamoxifen or toremifene between 2008 and 2017 were studied. Median follow-up was 39 months (10–141). Of these, 107 (36.52%), 112 (38.23%), and 74 (25.26%) patients had C/C, C/T, and T/T genotypes, respectively. Genotype was significantly associated with disease-free survival in tamoxifen patients. Patients with C/T and T/T genotypes showed worse disease-free survival than patients with a C/C genotype. Genotype and disease-free survival in toremifene and tamoxifen+toremifene patients were not correlated. Of patients with a C/T genotype, toremifene or tamoxifen+toremifene groups showed better disease-free survival than tamoxifen patients. Although disease-free survival of patients with a T/T genotype in the three groups was not statistically different, tamoxifen patients showed worse disease-free survival. There was no correlation between different treatments and disease-free survival in patients with a C/C genotype. Cox proportional hazard analysis revealed toremifene patients had a better prognosis than tamoxifen patients; toremifene was an independent protective factoremifene for disease-free survival.

Abbreviation: 4-OH-NDM-TAM, 4-hydroxy-N-desmethyl TAM; 4-OH-TAM, 4-hydroxy TAM; ASCO, American Society of Clinical Oncology; CI, confidence interval; CPIC, Clinical Pharmacogenetics Implementation Consortium; CYP2D6, cytochrome P450 2D6; CYP3A4/5, cytochrome P450 3A4/5; DFS, disease-free survival; ER, estrogen receptor; HER, human epidermal growth factor receptor; HR, hazards ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NDM-TAM, N-desmethyl TAM; OS, overall survival; PR, progesterone receptor; RR, risk ratio; TAM, Tamoxifen; TOR, Toremifene

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Conclusions: Tamoxifen was less effective in patients with *CYP2D6*10* C/T and T/T genotypes. Estrogen receptor-positive breast cancer patients with a *CYP2D6*10* mutation genotype have a better prognosis with toremifen than tamoxifen.

KEYWORDS
breast cancer, *CYP2D6**10, tamoxifen, toremifene

1 | INTRODUCTION

Breast cancer is the most common malignant tumor in Chinese women, with more than two-thirds of breast cancer patients positive for estrogen receptors (ER+).[1] Endocrine therapy can significantly improve the local control rate and prolong the overall survival of these patients.[2,3] Tamoxifen (TAM) is currently the standard treatment for early-stage breast cancer according to evidence-based Medicine Level I, Guideline Type 1 Recommendations.[4] Toremifene (TOR) is also commonly used in clinical practice as an alternative to TAM. Results from studies indicate that patients taking TOR show similar disease-free survival (DFS) and overall survival (OS) to those under TAM therapy, but have fewer adverse reactions.[5–8]

Both TAM and TOR are chemically synthesized selective estrogen receptor modulators that exert anti-tumor biological effects by competitively antagonizing estrogen. The original TAM drug has only a weak anti-estrogenic effect, needing to be metabolized to endoxifen in the liver via hepatic cytochrome P450 3A4/5 (CYP3A4/5) and hepatic cytochrome P450 2D6 (CYP2D6) to exert its anti-estrogen effect.[9–11] TAM is demethylated by CYP3A4/5-based metabolic enzymes to form N-desmethyl TAM (NDM-TAM), and CYP2D6-based metabolic enzymes mediate hydroxylation to form 4-hydroxy TAM (4-OH-TAM). NDM-TAM is further metabolized by CYP2D6 to form the active anti-tumor component 4-hydroxy-N-desmethyl TAM, endoxifen (4-OH-NDM-TAM, endoxifen). The affinity of 4-OH-TAM and endoxifen was significantly higher than that of TAM and NDM-TAM, and the plasma concentration of endoxifen was significantly higher than 4-OH-TAM. Endoxifen has a stronger anti-estrogen effect and is the main active ingredient of TAM to exert pharmacological effects. CYP2D6 is a key enzyme that plays a decisive role in the metabolic process. However, the mutation rate of the *CYP2D6* allele is high, leading to the functional activity of enzymes encoded by different genotypes varying widely. A phenotype with reduced enzyme activity can affect the metabolism of TAM, leading to a decrease in the blood concentration of endoxifen, which, in turn, affects the efficacy of TAM.[12–14] The molecular formula of TOR is similar to that of TAM. However, because the original compound of TOR can directly exert anti-estrogen effects and the enzyme activity of its main metabolic enzyme, CYP3A, is stable, the anti-tumor biological effect of TOR is not affected by hepatocyte cytochrome enzyme.

CYP2D6 is a member of the CYP450 family. According to information provided by the Clinical Pharmacogenetics Implementation Consortium (CPIC) website(http://www.PharmVar.org), *CYP2D6* coding gene mutations, deletions, and other mutations cause more than 100 CYP2D6 subtypes and significant differences in enzyme functional activity. Genotypes without enzyme activity include *CYP2D6**3, *4, *5, *6, and *7, as well as others. Genotypes with reduced enzyme activity include *CYP2D6**10, *17, and *41, among others. Genotypes with normal or increased enzyme activity include *CYP2D6**2A, *17, and *27, and also others. When people with genotypes leading to reduced enzyme activity take TAM, the blood concentration of endoxifen is lower than in patients with normal enzyme function, which may affect the therapeutic effect of TAM. Enzyme functional activity does not affect the anti-estrogen effect of TOR. Therefore, in patients carrying the *CYP2D6**10 mutant genotype, the efficacy of TOR may be superior to that of TAM.

The distribution of *CYP2D6* genotype has marked regional differences. In Asian populations, the common *CYP2D6* genotypes are *CYP2D6**10, *CYP2D6**1, and *CYP2D6**2, including others.[15–17] Of these, the *CYP2D6**10 genotype mutation rate is the highest, which can reach more than 60% in the Chinese population, but is only 2% in Europe, America, and Africa.[18–19] People carrying the *CYP2D6**10 mutant genotype have reduced CYP2D6 metabolic enzyme activity meaning the efficacy of TOR in the Chinese population may be better than that of TAM.

2 | PATIENTS AND METHODS

2.1 | Study Participants

Patients with breast cancer at Liaoning Cancer Hospital between 2008 and 2016 were selected. All patients were pathologically confirmed as having invasive breast cancer, were ER+ (ER > 1%) and/or progesterone positive (PR+; PR ≥0%), and received regular TAM (20 mg/d) or TOR (60 mg/d) 5 to 10 years after surgery. According to National Comprehensive Cancer Network breast treatment guidelines, patients received systemic chemotherapy and radiotherapy, and other adjuvant treatment, and had no other primary tumors. The clinical and pathological characteristics of patients were collected, including age at diagnosis, postoperative stage, pathological type, histological grade, and data on ER, PR, human epidermal growth factor receptor (HER)-2, and Ki-67.

2.2 | Trial Design

Patients were divided into TAM, TOR, and TAM+TOR groups according to their previous medication. Patients in the TAM+TOR group took

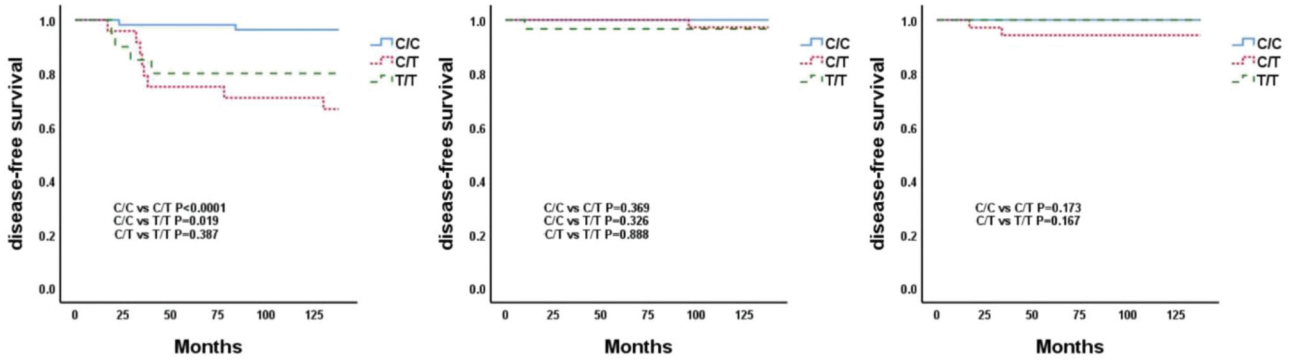

FIGURE 1 DFS of patients with different genotypes in the TAM, TOR and TAM+TOR group. *TAM* tamoxifen, *TOR* toremifene, *DFS* disease-free survival, *C/C* wild-type *CYP2D6**10, *C/T* heterozygous *CYP2D6**10, *T/T* mutant *CYP2D6**10 [Colour figure can be viewed at wileyonlinelibrary.com]

both TAM and TOR for more than 6 months. Patient *CYP2D6**10 genotype test results were obtained from the Hospital Information System. The gene test used at our hospital involved using a 5-mL peripheral blood sample from the patient and Sanger sequencing to classify the *CYP2D6**10 gene into wild-type (C/C type), heterozygous (C/T type) and mutant (T/T type) types. Patients were followed up on the phone or in the clinic. DFS was defined as the time from surgery to disease progression. What needs special explanation is that all patients in this study did not change endocrine drugs based on genetic test results.

2.3 | Statistical analysis

Data were processed using IBM SPSS 24.0 software. A $\chi 2$ test was used to compare genotypes, treatments, and clinicopathological characteristics between patient groups. The Kaplan–Meier method was used to create a survival curve, and a log-rank method was used in statistical testing. Cox regression analysis was used to determine independent predictors. A P value < .05 was considered statistically significant.

3 | RESULTS

3.1 | Study characteristics

In total, 293 patients were enrolled, including 107 C/C genotypes (36.52%), 112 C/T genotypes (38.23%), and 74 T/T genotypes (25.26%). The median follow-up time was 39 months (10–141 months). A total of 18 cases (6.14%) of disease progression occurred. A $\chi 2$ test showed no significant correlation between different treatments and *CYP2D6* genotypes, patient age, postoperative stage, pathological type, histological grade, ER, PR, HER-2, and Ki-67 (Tables 1–2).

3.2 | *CYP2D6**10 genotype correlates with DFS

A Kaplan–Meier method was used to generate a survival curve, and a log-rank method was used for statistical testing. We found that in the

TABLE 1 Relationship between different treatments and patients' characteristics

Characteristic	TAM (n = 98)	TOR (n = 95)	TAM+TOR (n = 100)	*P*
Age				.955
<50	86	84	87	
≥50	12	11	13	
T				.835
T1	50	52	59	
T2	39	36	31	
T3	5	4	4	
T4	4	3	6	
Pathological type				.909
IDCI	8	6	3	
IDCII	72	72	79	
IDCIII	9	8	10	
ILC	3	4	4	
Other	6	5	4	
ER				.900
1–10%	3	2	2	
≥10%	95	93	98	
PR				.448
0–10%	18	12	13	
≥10%	80	83	87	
HER-2				.994
No amplification	90	87	92	
Amplify	8	8	8	
Ki-67				.660
<20%	37	42	41	
≥20%	61	53	59	

TAM tamoxifen, *TOR* toremifene, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *ER* estrogen receptor, *PR* progesterone receptor, *HER* human epidermal growth factor receptor.

TABLE 2 Relationship between CYP2D6 *10 genotype and patients' characteristics

Characteristic	C/C (n = 107)	C/T (n = 112)	T/T (n = 74)	*p*
Age				.246
<50	95	94	68	
≥50	12	18	6	
T				.704
T1	55	66	40	
T2	45	35	26	
T3	4	5	4	
T4	3	6	4	
Pathological type				0.579
IDCI	10	5	2	
IDCII	75	91	57	
IDCIII	12	7	8	
ILC	4	4	3	
Other	6	5	4	
ER				0.800
1–10%	3	2	2	
≥10%	104	110	72	
PR				0.518
0–10%	19	14	10	
≥10%	88	98	64	
HER-2				0.865
No amplification	98	102	69	
Amplify	9	10	5	
Ki-67				0.865
<20%	43	48	29	
≥20%	64	64	45	

TAM tamoxifen, *TOR* toremifene, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *ER* estrogen receptor, *PR* progesterone receptor, *HER* human epidermal growth factor receptor.

TAM group, a *CYP2D6**10 genotype was significantly related to DFS. Patients with C/T (n = 24) and T/T (n = 20) genotypes showed a worse DFS than patients with a C/C genotype; the difference was statistically significant ($P<0.0001$, $P = 0.019$, respectively). However, significant differences in DFS were not noted between the three genotypes in TOR (n = 95) and TAM+TOR (n = 100) patient groups (Figure 1). Thus, *CYP2D6* genotypes determined the response to TAM and TOR. Patients with a C/C genotype were more responsive to TAM while all three genotypes were equally responsive to TOR.

3.3 | Endocrine therapy drugs are related to DFS

Significant correlations were found between different treatments and DFS in the three groups of patients. Among patients with a C/C genotype (n = 107), a statistically significant difference in DFS was not observed between the three different treatments. Among patients with a C/T type (n = 112), those taking TAM had the worst DFS. TOR and TAM+TOR group patients showed similar DFS rates that were better than the DFS of the TAM group ($P = .001$, $P = .006$, respectively). The DFS rates of patients with a T/T genotype (n = 74), who underwent the three different treatments, were not statistically different, but the survival curve showed that patients in the TAM group had a worse DFS (Figure 2). Thus, patients with a C/T and T/T genotypes showed a worse DFS when treated with TAM compared to TOR while those with a C/C genotype showed no difference.

3.4 | Endocrine therapy drugs are independent prognostic factors for DFS

A Cox proportional hazards model was used to analyze independent prognostic factors affecting patient survival. Univariate analysis showed that age, stage, pathological classification, ER, PR, HER-2, and Ki-67 had no significant effect on the 3-year DFS of patients. Therefore, only the three different treatments were included in a multivariate analysis. We found that patients taking TOR survived for longer than patients in the TAM group ($P = .002$, 95% confidence interval [CI], 2.464–48.232). Therefore, TAM is an independent prognostic factor that affects DFS, while TOR is an independent protective factor for DFS.

4 | DISCUSSION

Experts have not reached a consensus conclusion on whether a correlation exists between *CYP2D6* genotype polymorphisms and the efficacy of TAM. Some scholars believe that *CYP2D6* genotype does not affect the prognosis of TAM endocrine therapy. The 2012 Breast International Group 1–98 and the Arimidex, Tamoxifen, Alone or in Combination study showed a lack of correlation between *CYP2D6* genotype polymorphisms and breast cancer recurrence (95% CI = 0.60–1.24), although a relationship with treatment for facial flushing with consequent side effects was found.[20,21] However, some experts have questioned the choice of population, data processing, and detection methods used. Subsequently, Thompson et al. and Okishiro et al. concluded that a *CYP2D6* genotype was not associated with relapse-free survival.[22,23] In 2019, Sanchez–Spitman et al. published a multi-center prospective study report for the American Society of Clinical Oncology (ASCO), which included 667 patients with early-stage breast cancer in the Netherlands and Belgium. *CYP2D6* genotype and the endoxifen concentration in blood samples were determined by gene amplification chip and high performance liquid chromatography tandem mass spectrometry, respectively. A correlation was not found between endoxifen concentration and relapse-free survival (hazards ratio [HR]: 0.991, $P = 0.691$). A correlation between *CYP2D6* genotype and relapse-free survival (HR: 0.929, $P = .799$)[24] was also not found.

Other studies have shown that *CYP2D6* genotype polymorphisms affect the prognosis of TAM treatment. Goetz et al. analyzed patients with breast cancer from the North Central Cancer Treatment Group

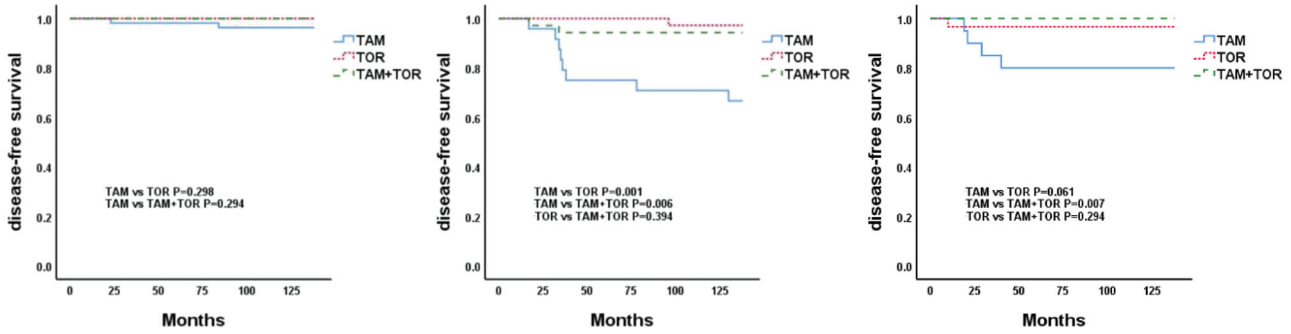

FIGURE 2 DFS in patients with a C/C, C/T and T/T genotype using different treatments. *TAM* tamoxifen, *TOR* toremifene, *DFS* disease-free survival, *C/C* wild-type *CYP2D6**10,*C/T* heterozygous *CYP2D6**10,*T/T* mutant *CYP2D6**10 [Colour figure can be viewed at wileyonlinelibrary.com]

89-30-52 trial and found that patients with the *CYP2D6**4 T/T genotype showed relapse-free survival ($P = .023$) while disease-free survival ($P = .012$) was significantly shortened.[25] Similarly, Schroth et al. performed DNA testing on 206 patients and found that patients with *CYP2D6**4, *5, *10, and*41 alleles had shorter relapse-free survival (HR: 2.24; $P = .02$).[26] In 2013, Zeng et al. conducted a meta-analysis evaluation of 11,701 patients in 20 clinical studies and found that DFS and OS rates of the slowly metabolizing *CYP2D6* gene were lower than those of the normal-functioning gene. In an Asian population subgroup analysis, DFS was found to be lower in patients with intermediate metabolism than in those with ultrafast metabolism ($P = .001$).[27] In 2018, the Union for International Cancer Control published two research reports by a group headed by a Chinese scholar, Xu et al The study included 778 patients with early-stage breast cancer. It was found that in patients receiving TAM, the 5-year DFS was significantly lower for those with a *CYP2D6**10 T/T genotype compared with C/C and C/T genotypes ($P = .007$). T/T is a significant prognostic indicator of DFS (risk ratio [RR]: 1.87, $P = .006$). Additionally, in patients with a T/T genotype, DFS in TOR-treated patients was better than that of patients in a TAM group ($P = .031$).[28,29]

However, the above clinical trials had geographical limitations to patient origin, and therefore results may not be due to differences in the geographical distribution of *CYP2D6* genotypes. It is worth noting that among the more than 100 genotypes of *CYP2D6*, only the gene distribution of *CYP2D6**10 does not conform to the genetic equilibrium state of the Hardy–Weinberg equilibrium law. For this reason, *CYP2D6* and tamoxifen treatment guidelines released by CPIC in 2018 outlined that patients with *CYP2D6**10 genotypes had significantly lower endoxifen blood concentrations when using TAM, which may affect the efficacy of TAM.[30] Sanchez–Spitman, in the 2019 ASCO report, also pointed out that patients carrying the *CYP2D6**10 genotype need special attention.[24]

The patient population in this study had a high *CYP2D6**10 gene mutation rate (66.15%), with obvious *CYP2D6* gene distributions characteristic of an Asian population. Although the duration of follow-up was short, the 3-year DFS in different groups of patients showed surprisingly significant differences (85.71% vs 97.89% vs 98%, $P = .007$). In this study, patients with *CYP2D6**10 C/T and T/T types had a poor prognosis with TAM. The efficacy of TOR in patients with *CYP2D6**10 mutations is significantly better than that of TAM. It therefore follows that in Asian populations with high *CYP2D6**10 gene mutation rates, such as in China, more than half of patients using TOR will have a better prognosis than with TAM. However, this conclusion needs to be confirmed by more large-scale clinical trials. Presently, it is recommended that genetic testing be performed on patients with breast cancer who need TAM for endocrine therapy. However, patients with a *CYP2D6**10 gene mutation should use TOR as an alternative treatment.

DATA AVAILABILITY STATEMENT

All data included in this study are available upon request by contact with the corresponding author.

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AUTHOR CONTRIBUTIONS

N.Z. designed the study, H.W. and X.M. completed the statistical analysis, and drafted the manuscript. B.Z., Y.Z., N.H., L.W., C.S., S.S., X.Z., H.G., Y.L., Y.Z., J.Z., Z.Q., and Z.L. conducted data collection. All authors read and approved the fifinal manuscript.

CONFLICTS OF INTEREST

The authors declare no competing interests.

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