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Original article

Prognostic and predictive value of TFF1 for adjuvant endocrine therapy in Chinese women with early ER positive breast cancer: Comparing aromatase inhibitors with tamoxifen

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ABSTRACT

Factors that predict in favor of an aromatase inhibitors (AIs) over tamoxifen (TAM) in estrogen receptor (ER) breast cancer remains to be identified. We compared progesterone receptor (PR) and trefoil factor 1 (TTF1) status (+ve versus −ve) as predictive of superior effect of AI's over tamoxifen among a total of 1973 Chinese women with early ER+ breast cancer. The expression of TFF1 was independently associated with ER and PR. However, there was no correlation with TFF1 and HER-2 expression. Treatment effect was more pronounced in the ER+/TFF1+ postmenopausal patients with a hazard ratio favoring AIs (HR = 0.397, 95%CI 0.183–0.860), but not in the PR positive cohorts (HR = 0.466, 95%CI 0.186–1.164). We suggested that AIs was better than TAM especially in the postmenopausal patients with ER+/TFF1+ breast cancer; however the clinical application of this observation still requires further prospective studies.

Introduction

Endocrine therapy plays an important role in adjuvant treatment in early stage breast cancer. Steroid sex hormone receptors, estrogen receptor (ER) and progesterone receptor (PR), are regarded as powerful predictive markers for benefit to endocrine therapy. Previous studies have reported that Western patients with ER+/PR+ tumor have a better outcome and benefit more from adjuvant tamoxifen (TAM) therapy than those who with ER+/PR− tumors.[1] In 2005 the St Gallen expert consensus conference defined tumors with low levels or lacking either ER or PR as endocrine responsive uncertain cancer.[2]

Recent clinical trials[3,4] have demonstrated superior clinical outcomes for aromatase inhibitors AIs over TAM in postmenopausal ER+ breast cancer. However predictive markers of AI benefit remain to be identified. It has previously been shown that HER-2 status[5] or Oncotype Dx Recurrence score[6] do not identify patients with differential benefits from AIs over TAM. However in the BIG1-98 clinical trial comparison of AI versus TAM showed a high ki-67 labeling index as a way to identify patients that benefit preferentially from letrozole.[7]

PR was originally considered to predictive value for response to endocrine therapy thought due to the fact that PR is an estrogen-regulated gene. However, an increasing literature has suggested that the nonfunctional ER theory was not sufficient to explain the loss of PR in ER-positive tumors. The ER+/PR− subset also indicated active growth factor signaling via the PI3K/Akt/mTOR pathway.[8] However, whether PR is predictive of benefit from AIs remains controversial. Results from the ATAC trial suggested that AIs improved outcome in PR negative cases, but the Trans-ATAC and TEAM analyses did not confirm this. Benefit from AIs seemed to be more pronounced in the PR positive group in the BIG1-98.[9] Because mobidity and hormone levels are lower in breast cancer patients in China than in western women,[10] we examined the characteristics of Chinese women with breast cancer to find reasons why PR has no predictive and prognostic value.

Trefoil factor 1 (TFF1, formerly pS2), a peptide consisting of 60 amino acids, is a member of the trefoil factor family and also considered to be an indicator of ER functionality.[11] The TFF1 gene has a composite promoter with an estrogen-responsive element and a TPA-responsive element, and it has been reported that its activation can be regulated by growth factors, hormones, and phorbol esters.[12] Growth factors such as IGF-I are able to elicit estrogenic responses in target tissues in the absence of estradiol, and the expression of TFF1 is increased by IGF-I while IGF-I sharply lowers PR levels and activity.[13] This suggests that although TFF1 is

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regulated by estrogen acting through ER, it is somewhat different from PR. Many authors agree that it might be possible to use TFF1 expression to define a subset of ER-positive tumor that is more likely to respond to TAM treatment.[11,14] However the value of TFF1 in combination with ER for predicting clinical benefit from AI therapy in the adjuvant setting has not been studied.

We hypothesize that TFF1 is different from PR in some estrogen-independent signal modulating mechanisms which might allow TFF1 levels to predict benefit from AIs versus TAM in post-menopausal women with ER + breast cancer. We investigated the influence of PR and TFF1 expression in Chinese women with ER positive breast cancer on disease-free survival (DFS), as well as the predictive value of PR and TFF1 for AIs treatment benefit.

Patients and methods

Study population

Information about 1973 patients with early ER+ breast cancer who were diagnosed and treated between 2000 and 2005 were obtained from the database established by the Cancer hospital of Fudan University, Shanghai, China. Steroid receptor assays and histological diagnoses were performed by the pathology department of Shanghai Cancer Hospital. All female patients who had complete data for ER and PR were analyzed: 1431 (72.5%) patients had PR positive tumors and 1277 (64.7%) TFF1 positive. Those who had at least three months of clinical follow-up were included in the disease-free survival (DFS) analysis. The median follow-up time was 32 months (range, 3–96 months).

Among these patients, there were 991 postmenopausal women with different adjuvant endocrine therapy, 503 (50.76%) patients received TAM treatment and 204 (20.59%) patients received adjuvant therapy containing AIs (anastrozole, letrozole or exemastine), upfront use (177) or sequentially after initial TAM treatment (27). A total of 284 (28.66%) patients did not receive adjuvant endocrine therapy or received other therapy such as ovarian ablation or function suppression or received unknown regiment.

Prognostic and predictive factors

Bloom-Richardson grading of tumors was employed.[15] ER, PR and TFF1 and all other biomarkers were determined by routine clinical testing using immunohistochemistry. Scoring was as follows: Score 0: not stained; Score 1: stained cells ≤25%; Score 2: stained cells >25% but ≤50%; Score 3: stained cells >50% but ≤75%; and Score 4: stained cells >75%. The intensity score, according to the staining intensity, was interpreted as follows: Score 0: negative; Score 1: weak; Score 2: intermediate; and Score 3:strong. Thereby, the two scores are combined, and the total score gauged from 0 to 12. The total assessment scores are determined and presented as follows: negative (−): Score 0; weak positive (+): Score 1–4; intermediate positive (++): Score 5–8; and strong positive (+++): Score 9–12. All scorings of biomarkers were performed according to these criteria. HER-2 was defined as negative for scores of 0–8 (namely,0,1+ and 2+ in the DAKO scoring system) and positive for strong membranous staining with scores of 9–12 (namely DAKO score 3+). Biomarkers including TFF1 and PR were defined as positive (1+, 2+ and 3+) and negative (0). Staining results were assessed by at least two pathologists, and discrepancies were resolved under multiheaded microscope.

Statistical methods

Tumors were stratified into two groups according to their PR or TFF1 status respectively. Associations of PR, TFF1 and other tumor features including HER-2 status were evaluated using chi-square tests and the multivariate analyses were carried out by logistic regression. DFS was defined as time from first diagnosis to the earliest time of invasive recurrence; the contralateral breast cancer; or death from any cause. Survival curves were derived from Kaplan–Meier estimates and the curves were compared by log-rank tests. The influence of receptor status, adjusted for other prognostic factors, was assessed in multivariate analyses by Cox proportional hazards models. DFS hazard ratios (HRs) were used to compare the efficacy of AIs versus TAM for subgroups defined by PR and TFF1 status.[9]

All statistical tests were two-sided, and a P value<0.05 was considered statistically significant. All statistical analyses were carried out with Stata statistical software package (SE10.0; Stata Corporation, College Satation, TX, USA) for Windows. Survival rates and hazard ratio were presented with their 95% confidence intervals (CIs).

Results

Differences in clinical and biologic characteristics between ER+/PR+ and ER+/PR− tumors

Characteristics for the patients were listed in Table 1. The majority of patients in the ER+/PR− group (>50ys: 58.3%) were older than the ER+/PR+ group (>50ys: 49.2%, $P < 0.001$). Grade 3 (27.3% vs 19.0%, $P = 0.001$) and larger size (>2 cm, 60.6% vs 51.7%, $P = 0.001$) tumors were more common in ER+/PR−. In addition, ER+/PR− tumors trended to be associated with more lymph node metastasis (52.9% vs 48.1%, $P = 0.084$).

Table 1
Characteristics of 1973 ER+ patients.

	n	%
Total	1973	
Age		
≤35	94	4.76
35–50	859	43.54
>50	1020	51.70
Grade		
I	40	2.0
II	1062	53.8
III	299	15.2
Unknown	572	29.0
Size (cm)		
≤2	810	41.1
2–5	878	44.5
>5	78	4.0
Unknown	207	10.5
Nodal status		
0	831	42.1
1–3	468	23.7
≥4	344	17.4
Unknown	330	16.7
Level of ER		
+	1251	63.4
++	328	16.6
+++	394	20.0
PR		
Negative	542	27.5
Positive	1431	72.5
HER-2		
−,+,++	1611	81.7
+++	344	17.4
Unknown	18	0.9
TFF1		
Negative	506	25.6
Positive	1277	64.7
Unknown	190	9.6

Abbreviation: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor; TFF1, trefoil factor 1.