Journal of Zhejiang University SCIENCE B
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
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HER2 over-expression and response to different chemotherapy regimens in breast cancer

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Received Dec. 3, 2007; revision accepted Dec. 10, 2007

Abstract: Purpose: To exam the relationship between HER2 over-expression and different adjuvant chemotherapies in breast cancer. Patients and Methods: A total of 1625 primary breast cancer patients who received post-surgery adjuvant chemotherapy in Tianjin Cancer Hospital, China, from July 2002 to November 2005 were included in the study. Among them, 600 patients were given CMF (CTX+MTX+5-Fu) regimen, 600 given CEF (CTX+E-ADM+5-Fu) regimen, and 425 given anthracyclines plus taxanes regimen, with mean follow-up time of 42 months. Results: In CMF treatment group, the 3-year disease free survival (DFS) in HER2 over-expressed patients was lower than that of the HER2-negative ones (89.80% vs 91.24%, P=0.0348); in node-positive subgroup, the 3-year DFS was 84.72% in HER2 over-expressed patients, and 90.18% in the HER-2-negative ones (P=0.0271). Compared to CMF regimen, anthracyclines and anthracyclines plus taxanes regimens are more effective (P<0.05) in node-positive HER2 over-expression than those in the node-negative. Conclusion: HER2 over-expression is an independent index for predicting poor prognosis and short DFS for breast cancer patients. HER2 over-expressed patients are resistant to CMF regimen chemotherapy, but sensitive to anthracyclines-based or anthracyclines plus taxanes regimen. HER2 expression can be taken as a marker for therapies in breast cancer.

Key words: Breast cancer, HER2, Chemotherapy
doi:10.1631/jzus.B073003 **Document code:** A **CLC number:** R737; R730.54

INTRODUCTION

Breast cancer threatens women all over the world, and has become the second cause for female deaths. In China, the incidence of breast cancer has been increasing and has become the most common female malignant tumor (Shen and Shao, 2002). HER2/neu is a member of the erbB-like oncogene family, and is related to, but distinct from, the epidermal growth factor receptor.

This oncogene has been shown to be amplified in human breast cancer cell lines. Many studies show a close correlation between the expression of HER2/neu and prognosis in breast cancer (Ferretti *et al*., 2007; Révillion *et al*., 2007). HER2 has become the independent prognostic factor for tumor relapse and total survival time. Being HER2 positive indicates a poor prognosis, i.e., shorter overall survival time, poorer outcome in node-negative patients when combined with St. Gallen classification, poorer outcome in node-positive patients, earlier relapse after adjuvant chemotherapy and so on (Pritchard *et al*., 2006).

In this study, we analysed 1625 primary breast cancer patients who received adjuvant chemotherapy after operation during July 2002 to November 2005, reporting the correlation between HER2 over-expression and the response to different adjuvant therapy in breast cancer.

PATIENTS AND METHODS

Study population

A total of 1625 primary breast cancer patients who received adjuvant chemotherapy after operation were included in the study. Among them, 600 patients aged from 27 to 89 years, with mean age of 50 years, were given CMF regimen (C: 600 mg/m^2 IV on Day 1,

M: 40 mg/m^2 IV on Day 1, F: 500 mg/m^2 IV on Day 1, q3w×6), and 56 cases had relapse and metastasis and 10 died. Another 600 cases with age range of 23 to 75 years and mean age of 49 years were given CEF regimen (C: 600 mg/m^2 IV on Day 1, E: 75~90 mg/m^2 IV on Day 1, F: 500 mg/m^2 IV on Day 1, q3w×6), and 40 cases relapsed and metastasized and 2 died. The remaining 425 cases, aged from 22~89 years with mean age of 49 years, were given anthracyclines plus taxanes regimen (TE or TEC 6 circles, or EC-P 8 circles; T: 75 mg/m^2 IV on Day 1, E: 60 mg/m^2 IV on Day 1, q3w×6; P: 175 mg/m^2 IV on Day 1, q3w×4), and 31 relapsed or developed metastasis and 3 died. Mean follow-up time was 42 months.

Materials and statistical analysis

All of the cases were confirmed by IHC SP method. HER2 was previously tested for protein over-expression by HercepTest (grouped into Hercep 0, 1+, 2+ and 3+).

Disease free survival (DFS) rate of patients was described by DFS curve by Kaplan-Meier method, and log-rank was applied to observe whether statistical difference of DFS existed between HER2-positive and HER2-negative subgroups. The statistical analysis was carried out using SPSS 12.0 statistical analysis software.

RESULTS

Response to CMF regimen in HER2 over-expressed patients

In CMF treatment group, HER2 over-expressed patients had a 3-year DFS of 89.80%, whereas the 3-year DFS was 91.24% in HER2-negative patients (P=0.0348, Fig.1). It probably suggests that HER2 over-expressed patients were resistant to CMF regimen therapy. In node-negative subgroup (377 cases), the 3-year DFS in HER2 over-expressed patients was 91.40%, whereas 92.70% in HER2-negative ones (P=0.9351). In node-positive subgroup (223 cases), the 3-year DFS in HER2 over-expressed patients was 84.72%, but 90.18% in HER2-negative ones (P= 0.0271, Fig.2). These results indicate that HER2 over-expressed patients were resistant to CMF regimen, and the node-negative HER2 over-expression patients were not resistant to CMF regimen, but only node-positive HER2 over-expressed patients were resistant to CMF regimen.

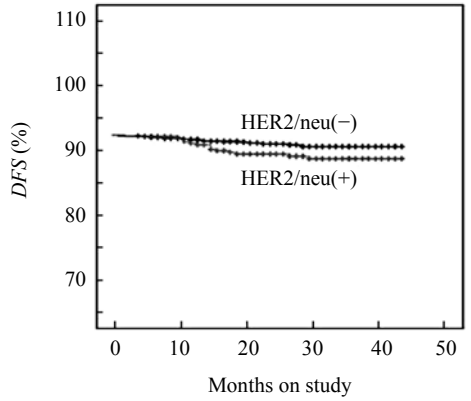

Fig.1 Disease free survival (DFS) curve diagram in HER2 over-expressed or HER2-negative patients given CMF

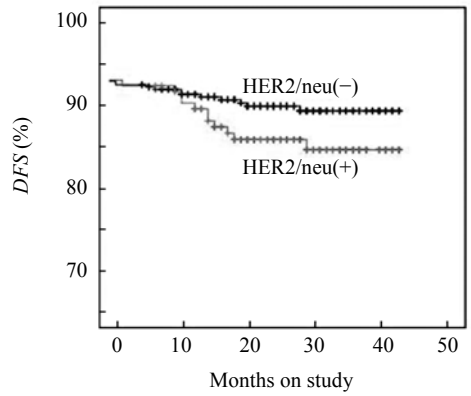

Fig.2 Disease free survival (DFS) curve diagram in node-positive patients

Response to CEF regimen in HER2 over-expressed patients

In CEF therapy group, the 3-year DFS in HER2 over-expressed patients was 90.10%, and 91.23% in HER2-negative patients (P=0.3010). In node-negative subgroup (290 cases), the 3-year DFS in HER2 over-expressed patients was 92.71%, and 93.84% in HER2-negative ones (P=0.7835). In node-positive subgroup (310 cases), the 3-year DFS in HER2 over-expressed patients was 90.10%, and 91.23% in HER2-negative ones (P=0.2555). The results show that there was no difference of 3-year DFS between HER2 over-expressed and HER2-negative patients with CEF regimen. This may indicate that HER2 over-expressed patients were susceptive to anthracyclines-based regimen.

Response to anthracyclines plus taxanes regimen in HER2 over-expressed patients

In anthracyclines plus taxanes therapy group, the 3-year DFS in HER2 over-expressed patients was 91.04%, and 92.03% in HER2-negative ones (P=0.0715). In node-negative subgroup (104 cases), the 3-year DFS in HER2 over-expressed patients was 91.72%, and 92.26% in HER2-negative ones (P=0.4326). In node-positive subgroup (321 cases), the 3-year DFS in HER2 over-expressed patients was 89.85%, and 90.24% in HER2-negative ones (P=0.9614). These results suggest no difference of 3-year DFS between HER2 over-expressed and HER2-negative patients given anthracyclines plus taxanes regimen. It indicates that HER2 over-expressed patients were susceptive to anthracyclines plus taxanes regimen.

Comparison of response to different chemotherapy regimens in HER2 over-expressed patients

In HER2 over-expressed patients (425 cases, features listed in Table 1), the 3-year DFS in CMF therapy was 89.41%, in CEF treatment was 92.67%, and in anthracyclines plus taxanes regimen was 91.53%. The 3-year DFS in CMF regimen was lower than that of anthracyclines and anthracyclines plus taxanes regimens (P=0.045, Fig.3), suggesting that anthracyclines-based and anthracyclines plus taxanes regimens were more effective than CMF for HER2 over-expressed patients. No difference between anthracyclines-based and anthracyclines plus taxanes regimens for HER2 over-expressed patients was observed (P=0.786).

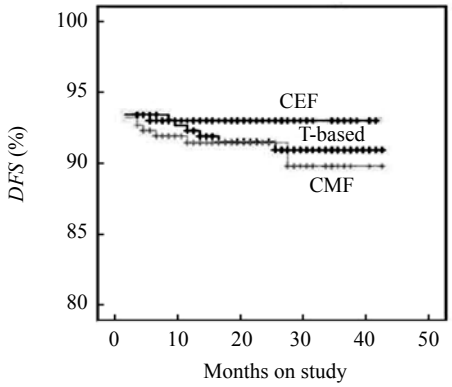

Fig.3 Disease free survival (DFS) curve in HER2 over-expressed patients treated by different chemotherapy regimens
T-based: Anthracyclines plus taxanes regimen

In node-positive HER2 over-expressed subgroup (235 cases, patients features listed in Table 2), the 3-year DFS in CMF treatment was 84.70%, in CEF treatment was 90.76%, and in anthracyclines plus taxanes treatment was 89.74%. Compared to CMF regimen, anthracyclines and taxanes were more effective (P=0.031, Fig.4). No difference between anthracyclines-based and anthracyclines plus taxanes regimens for HER2 over-expressed patients (P=0.843) was observed. These results suggest that anthracyclines-based and anthracyclines plus taxanes regimens were more effective than CMF in HER2 over-expressed patients with node-positive. No difference between anthracyclines-based and anthracyclines plus taxanes regimens in HER2 over-expressed patients with node-positive was observed.

Table 1 Features of 425 HER2 over-expressed patients

	CMF (183)	CEF (121)	T-based (121)
Age (median age)	30~80 (50)	26~73 (49)	28~73 (49)
Pre-menopausal (%)	55.7	54.5	57.0
ER+ (%)	52.5	51.1	49.8
PR+ (%)	45.3	47.9	50.1
Nodes 1~3	25.7	19.0	27.3
Node >4	13.7	37.2	72.7
Grade I (%)	2.1	1.0	1.0
Grade II (%)	82.3	79.6	64.6
Grade III (%)	15.6	19.4	34.4
Pathological type	All are invasive non-special type		

T-based: Anthracyclines plus taxanes regimen

Table 2 Features of 235 HER2 over-expressed patients with node-positive

	CMF (72)	CEF (68)	T-based (95)
Age (median age)	30~74 (50)	26~73 (50)	28~73 (50)
Pre-menopausal (%)	54.2	60.3	56.8
ER+ (%)	50.7	27.3	45.3
PR+ (%)	42.3	28.1	35.8
Nodes 1~3	65.3	33.8	28.4
Node >4	34.7	66.2	71.6
Grade I (%)	3.2	1.7	0
Grade II (%)	82.3	72.1	62.7
Grade III (%)	14.5	26.2	37.3
Pathological type	All are invasive non-special type		

T-based: Anthracyclines plus taxanes regimen

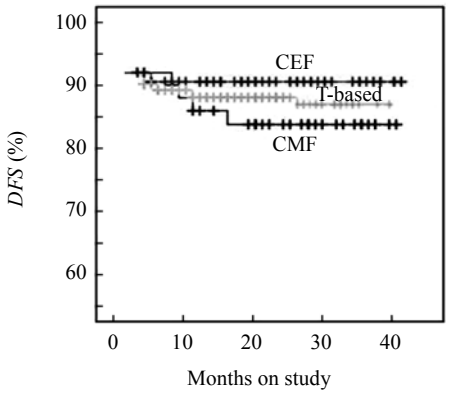

Fig.4 Disease free survival (DFS) curve of HER2 over-expressed patients with node-positive treated by different chemotherapy regimens
T-based: Anthracyclines plus taxanes regimen

DISCUSSION

HER2 is a member of the type I receptor tyrosine kinase family, which consists of four closely related family members, HER2 (neu/ErbB2), epidermal growth factor receptor (EGFR, ErbB1), HER3 (ErbB3) and HER4 (ErbB4). Aberrant signaling through these receptors is believed to play a direct role in malignant transformation and/or progression (Di Fiore *et al*., 1987). HER2 amplification results in a 50 to 100-fold increase in the number of surface HER2 receptors on cancer cells compared to the normal mammary epithelium. Evidence obtained in model systems supports the premise that progression of HER2-amplified breast cancers is driven by HER2 gene activity. When the level of engineered HER2 expression in tumor cell lines mimics the disease state, important phenotypic changes are observed, including increased growth in vitro, decreased anti-estrogen response, increased production of angiogenic factors, as well as increased tumorigenicity and metastatic potential in vivo. These changes parallel the observed aggressive clinical behavior of human tumors that contain an amplified HER2 gene.

Amplification of the HER2 gene has been reported in many human cancers, including breast (Berns *et al*., 1992), ovaries, lung, pancreas and gastral cancers. Research of amplification of HER2 gene in breast cancer is the most, and it has become the early event in tumor development (Chong *et al*., 1999). In every development stage of breast cancer, HER2 expression could keep stable. HER2 over-expression is detected in approximately range from 15% to 30% (Shin *et al*., 2006; Leong and Leong, 2006); in our study, HER2 over-expression is 26.6%.

Chemotherapy regimens commonly used after operation for breast cancer include CMF and anthracyclines-based regimens. Some studies showed that HER2 over-expressed patients are probably resistant to CMF regimen. Allered conducted a randomized study on 306 patients treated with CMFP (CTX+MTX+5-Fu+PDN) after surgery, and found that the DFS of HER2-negative patients was longer than that of patients not given chemotherapy, and the DFS of HER2 over-expressed patients had no difference between chemotherapy and non-chemotherapy. In our study, the DFS of HER2 over-expressed patients was lower than that of HER2-negative ones (P<0.05); similarly, in node-positive subgroup, the DFS of the HER2 over-expressed was significantly lower than that of the HER2-negative (P=0.0271).

NSABP (National Surgical Adjuvant Breast and Bowel Project) B11 trial has proved that anthracyclines has made HER2 over-expressed patients get similar survival time as that of HER2-negative ones, suggesting that HER2 over-expression may be a sensitive marker indicating the optimal dose of anthracyclines chemotherapy. In this study, for patients given CEF regimen, no difference of the 3-year DFS was observed between the HER2 over-expressed and the HER2-negative. This suggests that anthracyclines chemotherapy is effective for HER2 over-expressed patients and improves DFS.

Taxanes have been applied widely into adjuvant chemotherapy after operation and advanced breast cancer (Hayes *et al*., 2007), and a clinical trial in Memorial Sloan-Kettering Tumor Centre (NY, USA) indicated that the response to taxanes is higher in HER2 over-expressed patients (65%) than that in HER2-negative ones (36%). In our study, for patients treated with anthracyclines plus taxanes regimen, the 3-year DFS of HER2 over-expressed patients is similar to that of HER2-negative ones, suggesting taxanes are effective for HER2 over-expressed patients.

Recently, many cooperative studies indicated that anthracyclines-based regimen is superior to CMF regimen. NSABP B23 trial reported that effect of

4-circle AC (anthracyclines and CTX) regimen is as same as that of the 6-circle CMF. Results from trial of EBCTCG (Early Breast Cancer Trialists' Collaborative Group) also showed, compared to CMF regimen, anthracyclines regimen could decrease relapse and death risk rate by 11% and 16%, respectively, and decrease the 5-year and 10-year death rate by 3.5% and 4.6%, respectively. In our study, we found that DFS of HER2 over-expressed patients given anthracyclines or taxanes regimen was both higher than that of patients given CMF regimen. And in node-positive and HER2 over-expressed subgroup, the 3-year DFS of patients given CMF regimen was lower by 5% than that of patients given anthracyclines or taxanes regimen. It suggests anthracyclines and taxanes regimens are both superior to CMF regimen.

Subgroup analysis in this study also showed, HER2 expression has no influence on DFS of node-negative patients. And it has suggested axillary lymph nodes status is still the optimal index for predicting therapy effects and prognosis, and most reliable factor to divide risk category.

We, therefore, conclude that HER2 expression can serve as the reference index to select and estimate the adjuvant chemotherapy regimens. HER2 over-expression may suggest that patients will be resistant to CMF regimen, but sensitive to anthracyclines-based or anthracyclines plus taxanes regimen. Compared to CMF regimen, anthracyclines-based and anthracyclines plus taxanes regimens are more effective in HER2 over-expressed patients, especially the node-positive ones. However, HER2 over-expressed patients, even though node-positive, will probably respond to anthracyclines-based and anthracyclines plus taxanes regimens with similar sensitivity.

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