Original Article

Clinicopathological Characters of Triple Negative Breast Cancer

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ABSTRACT

Objective: To study the clinicopathological characters of triple negative breast cancer (TNBC).

Methods: A total of 629 patients with breast cancer were reviewed, who were treated from 2003 to 2007 in Chongqing Cancer Institute. The comparison of clinicopathological features including TNM classification, histological type, tumor location, axillary lymphonodes status and neoadjuvant chemotherapy between TNBC and nontriple negative breast cancer (NTNBC) was performed. The overall response was evaluated by whether the patients achieve complete remission (CR) and partial remission (PR) after chemotherapy.

Results: There were 69 TNBCs in the 629 patients with breast cancer. The premenopausal patients, which was found in 49/69 of TNBCs, was more than NTNBCs. The average diameter of tumor in TNBC group was 4.1 cm, lager than NTNBC group. TNBC with axillary nodes metastasis occurred in 21 cases, and the axillary nodes metastasis rate was lower than NTNBC. The positive expression rate of p53 in TNBC was 44.9%, and the overall response (CR+PR) was 72.2%. No statistical differences were found regarding the positive expression rate of p53 and the overall response between TNBC and NTNBC.

Conclusion: TNBC were a group of primary breast cancers with triple negative, tending to occur in premenopausal women, with larger tumors, lower axillary nodes metastasis rate. TNBC had worse clinical prognosis and currently lacked effective targeted therapies.

Key words: Breast cancer; Triple negative; Prognosis

INTRODUCTION

Triple negative breast cancer (TNBC) were a group of primary breast cancers with estrogen receptor (ER)-negative (-), progesterone receptor (PR)-negative (-) and HER-2 negative (-) in immunohistochemistry (IHC). Endocrine therapy and Herceptin targeted therapy were not effective in TNBC, and TNBC had worse clinical prognosis and currently lacked effective targeted therapies. This study reviewed 629 female patients with breast cancer including 69 TNBCs, and investigated the clinicopathological characters of TNBC.

MATERIALS AND METHODS

Patients

A total of 629 female breast cancer patients underwent surgery at Chongqing Cancer Institute from 2003 to 2007. Among them, 405 cases received neoadjuvant chemotherapy, 19 cases showed CR, 253 cases had PR and overall response (CR+PR) was 67.2%. All of the patients were tested for ER, PR, HER-2 and p53 with IHC. There were 372 premenopausal patients and 257 postmenopausal patients. The average age was 48.1 y (range: 19–80 y), the average tumor size was 3.8 cm (range: 1–10 cm). The clinical TNM classification of each patients was classified according to "The Sixth Edition of the AJCC Cancer Staging Manual in 2003", 7 cases were 0, 88 cases were I, 428 cases were II, 98 cases were III, and 8 cases were IV. There were 402 cases of invasive ductal carcinoma, 55 cases of carcinoma simplex, 63 cases of medullary carcinoma and 109

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cases of other histological types. The tumors of 380 cases were located in upper outer quadrant, 78 cases located in lower outer quadrant, 66 cases located in upper inner quadrant, 52 cases located in lower inner quadrant and 53 cases located in central portion.

There were 69 TNBC in 629 female patients with breast cancer. There were 49 premenopausal patients and 20 postmenopausal patients. Thirty-six TNBCs received neoadjuvant chemotherapy, of them, 2 cases had CR, 24 cases has PR, and overall response (CR+PR) was 72.2%. The average age was 47.5 y (range: 27–79 y), the average tumor size was 4.1 cm (range: 2–10 cm). For TNM classification, 1 cases were 0, 4 cases were I, 47 cases were II and 17 cases were III. For pathology, 39 cases were invasive ductal carcinoma, 4 cases were carcinoma simplex, 14 cases were medullary carcinoma and 12 cases were other histological types. The tumor located in upper outer quadrant in 46 cases, located in lower outer quadrant in 3 cases, located in upper inner quadrant in 8 cases, located in lower inner quadrant in 5 cases and located in central portion in 7 cases.

Evaluation of Therapeutic Response in Neoadjuvant Chemotherapy

Maximum diameter and maximum perpendicular diameter of tumors were measured before and after initiation of neoadjuvant chemotherapy with use of calipers. Therapeutic response was evaluated by change of tumor size. According to WHO criteria, therapeutic response was categorized as CR (complete remission), PR (partial remission), SD (stable disease) and PD (progression of disease), and overall response was CR and PR.

Immunohistochemistry

Five-micron sections of breast cancers were deparaffined in xylene and rehydrated with a gradient alcohol series. Endogenous peroxidase activity was blocked by treatment with 3% H_2O_2. These sections were heated in citrate buffer (pH 6.0) in a microwave oven for 10 min, blocked with goat serum for 10 min, and incubated with anti-ER, anti-PR, anti-HER-2 and anti-p53 antibody at 4°C overnight, then incubated with biotinylated second antibody and streptavidin HRP conjugate for 15 min each, and the DAB-substrate solution was added on the slide at room temperature. Between each step in the staining procedures, the slides were rinsed three times in PBS. Positive tissue controls included known positive breast cancers, whereas PBS was used as negative controls to replace antibody. Cases exhibiting definitive nuclear or cytoplasmic staining in ≥10% of the cells were considered positive.

Statistical Analysis

Statistical analysis was done with the SPSS 11.0 Statistical Analysis software. Age and tumor size were compared between groups using the *t* test. The chi-square test was used to compare the clinicopathological characteristic differences between groups. *P*-value less than 0.05 was considered significant.

RESULTS

The mean age was 47.5 y in TNBCs, and the tumor average diameter was 4.1 cm. The tumor size in TNBCs was significantly different from NTNBCs ($P<0.05$, Table1). No statistical differences were found regarding age. The axillary nodes metastasis rate in TNBCs was 30.4%, which was significantly different from NTNBCs ($P<0.05$, Table2). There were 49 premenopausal patients in TNBCs, which was more than NTNBCs ($P<0.05$, Table2). The positive expression rate of p53 in TNBC was 44.9%, and the overall response (CR+PR) was 72.2%. No statistical differences were found regarding the positive expression rate of p53 and the overall response between TNBCs and NTNBCs.

DISCUSSION

Breast cancer may now be subclassified into luminal, basal, and HER2 subtypes by IHC. Basal-like phenotype did not express ER, PR and HER-2, which is called TNBC[1]. TNBC accounted for 10%–17% in all breast cancer, which were more frequent in younger premenopausal African women, African-American women, Hispanic women and women Patients with BRCA1 mutations[2–6]. TNBC lacked expression of hormone receptor and HER-2, and endocrine therapy and Herceptin targeted therapy were non-effective in TNBC. TNBC had worse clinical prognosis, had lower axillary nodes metastasis rate and had higher local recurrence rate and visceral metastasis rate[2, 4, 7]. Despite treatment with standard dose anthracycline-based chemotherapy, the clinical outcome of TN and BL cancers remains poor[8]. It

might be good choice with Carboplatin or Cisplatin-based chemotherapy[9], which might be related to BRCA-1, p53 gene mutation [10, 11].

In our study, the TNBCs were 69 cases (11%) in 629 patients with breast cancer. The tumor size in TNBCs was significantly different from NTNBCs group (P<0.05, Table1). The axillary nodes metastasis rate in TNBCs was 30.4%, which was significantly different from NTNBCs (P<0.05, Table2). There were 49 premenopausal patients in TNBCs, which was more than NTNBCs (P<0.05, Table2). Most of TNBCs were II and III, located in Upper outer quadrant, were invasive ductal carcinoma. The positive expression rate of p53 in TNBC was 44.9%, and the total effective rate of neoadjuvant chemotherapy (CR+PR) was 72.2%. Both of them were higher than the TNBCs, but no statistical differences were found.

Table 1. Comparison of age and tumor size between TNBCs and NTNBCs ($\bar{x} \pm s$)

Group	Age (years)	Tumor size (cm)
TNBC	47.5±10.1	4.1±1.7
NTNBC	48.2±10.2	3.7±1.3*

Compared with TNBCs: *P<0.05

Table 2. Comparison of clinicopathological characteristics between TNBCs and NTNBCs n (%)

Clinicopathological characteristics	Number	TNBC	NTNBC
TNM classification			
0	7	1 (1.5)	6 (1.1)
I	88	4 (5.8)	84 (15.0)
II	428	47 (68.1)	381 (68.0)
III	98	17 (24.6)	81 (14.5)
IV	8	0	8 (1.4)
Histological type			
Invasive ductal carcinoma	402	39 (56.5)	363 (64.8)
Carcinoma simplex	55	4 (5.8)	51 (9.1)
Medullary carcinoma	63	14 (20.3)	49 (8.8)
Others	109	12 (17.4)	97 (17.3)
Tumor location			
Central portion	53	7 (10.1)	46 (8.2)
Upper outer quadrant	380	46 (66.7)	334 (59.6)
Lower outer quadrant	78	3 (4.3)	75 (13.4)
Upper inner quadrant	66	8 (11.6)	58 (10.4)
Lower inner quadrant	52	5 (7.3)	47 (8.4)
Axillary nodes			
Metastasis	340	21 (30.4)	319 (57.0)*
Non-metastasis	289	48 (69.6)	241 (43.0)*
Neoadjuvant chemotherapy			
CR+PR	272	26 (72.2)	246 (66.7)
SD+PD	133	10 (27.8)	123 (33.3)
p53			
Positive	260	31 (44.9)	229(40.9)
Negative	369	38 (55.1)	331(59.1)
Menstruation status			
Premenopause	372	49 (71.0)	323 (57.7)*
Postmenopause	257	20 (29.0)	237 (42.3)*

Compared with TNBCs: *P<0.05

TNBC lacked expression of hormone receptor and HER-2, and endocrine therapy and Herceptin targeted therapy were non-effective in TNBC. TNBC currently lacked effective targeted therapies except for chemotherapy. TNBC had larger tumor size, later TNM classification, lower axillary nodes metastasis rate, but higher local recurrence rate and visceral metastasis rate.

Now most of studies on TNBC focused on prognostic markers and choice of anticancer drugs. We had found many molecule markers, such as heat shock protein alpha-basic-crystallin, CAV1 and EGFR. Heat shock protein alpha-basic-crystallin (alphaB-crystallin) was commonly expressed in basal-like tumors and predicted poor survival in breast cancer patients independently of other prognostic markers. AlphaB-Crystallin over-expression also induced EGF- and anchorage-independent growth, increased cell migration and invasion, and constitutively activated the MAPK kinase/ERK (MEK/ERK) pathway. The MEK/ERK pathway maybe acted as a potential therapeutic target for these tumors[12]. CAV1 expression in BRCA1 and BRCA2 hereditary breast cancer and identifies CAV1 as a marker associated with a basal-like-phenotype in both hereditary and sporadic breast cancer[13]. The majority of the "triple negative" patients has basal subtype tumors with high EGFR expression and that these tumors may be the subgroup of breast carcinomas that could potentially benefit the most from novel EGFR-targeted therapeutic strategies[14].

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