

RESEARCH COMMUNICATION

Predictive Role of Molecular Subtypes in Response to Neoadjuvant Chemotherapy in Breast Cancer Patients in Northeast China

Minhao Lv¹, Beibei Li², Yongfeng Li¹, Xiaoyun Mao¹, Fan Yao¹, Feng Jin^{1*}

Abstract

Introduction: Breast cancer is increasingly regarded as a heterogeneous disease which can be classified into distinct molecular subtypes with prognostic significance. **Materials and methods:** ER, PR, HER2 and ki-67 were used to divided 102 breast cancers treated with neoadjuvant chemotherapy (NCT) into 4 subtypes: luminal A (ER+,PR+,HER2-, and ki-67 \leq 14%), luminal B (ER+, PR+,HER2- and ki-67>14% ; ER+ and/or PR+, HER2+), HER2-overexpression (ER-, PR- and HER2+) and triple-negative (ER-, PR-,and HER2-). **Results:** Among 102 patients, a pCR was seen in 16 (15.7%) patients. The pathologic complete remission (pC) rates according to different subtypes are as follows: luminal A, 0 of 20 (0.0%), luminal B, 2 of 23 (8.7%), HER2-overexpression 4 of 18 (22.2%), and triple-negative, 10 of 41 (24.4%) (p=0.041). In triple-negative subtype patients, the rates of pCR differed significantly among the 3 chemotherapy regimens with 5.6% (1/18) for CEF (cyclophosphamide, epirubicin and flurouracil), 20.0% (1/5) for TE (docetaxel and epirubicin) and 44.4% (8/18) for TCb (docetaxel and carboplatin) (p=0.024). In locally advanced breast cancer patients, the rates of pCR seem to differ among the 3 chemotherapy regimens with 6.7% (2/30) for CEF, 0.0% (0/8) for TE and 23.1% (6/26) for TCb, but this did not attain statistical significance (p>0.05). **Conclusions:** Molecular subtypes are good predictors for response to NCT in breast cancer patients in Northeast China. Compared with luminal A tumors, HER2-overexpression and triple-negative subtypes are more sensitive to NCT. For triple-negative breast cancer, we concluded that the TCb combination is a promising NCT regimen. Our results also indicated that the TCb combination is promising for the treatment of locally advanced breast cancer.

Keywords: Breast cancer - molecular subtype - predictive factor - chemotherapy - pathologic complete remission

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Introduction

Neoadjuvant chemotherapy (NCT) is becoming the standard of care for patients with locally advanced breast cancer (LABC) and is increasingly being used in the treatment of patients with large operable breast cancer or proven lymph node metastasis (Fisher et al., 1997). The aim of NCT is to downstage the tumor load to increase the rate of breast-conserving surgery and to gain information on drug response by in-breast assessment [(Mieog et al., 2007). Moreover, NCT provides the opportunity to discover predictive markers of chemotherapy. Several researches had demonstrated that patients achieved pathologic complete remission (pCR) had better prognosis than those that did not (van der Hage et al., 2001; Rastogi et al., 2008). The prediction of the possibility of pCR before starting NCT can be used to maximize the treatment and minimize unnecessary toxicity (Kim et al., 2010).

We all know that breast cancer is a heterogeneous

disease, therefore, tumor with the same clinicalpathological characteristics may be diverse in disease behavior, response to therapy and prognostic (Carey et al., 2006). Gene expression profiling studies have identified at least four categories of breast cancer: luminal A, luminal B, HER2-overexpression, and basal-like subtype. But large-scale subtyping using gene expression profiling from formalin-fixed, paraffin-embedded samples is not currently feasible. Therefore, immunohistochemistry surrogate panels of estrogen receptor (ER), progesterone receptor (PR), HER2 and ki-67 have been proposed to potentially discriminate the subtype as a substitution of gene expression profiling (Nielsen et al., 2004; Livasy et al., 2006; Carey et al 2007; Hugh et al., 2007; Cheang et al., 2008). We hypothesized that the distinct molecular subtype might have a different response to NCT in breast cancer patients in Northeast China. The aim of our study is to investigate whether these different molecular subtypes of breast cancer also response differently to NCT.

¹Department of Surgical Oncology, Department of Breast Surgery, The First Affiliated Hospital of China Medical University, ²Department of Obstetrics and Gynecology, The Affiliated Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China *For correspondence: jinfeng66cn@hotmail.com

Materials and Methods

Study Population

This study was approved by the Ethics Committee of China Medical University, Shenyang, China, and written informed consent was obtained from all participants. One hundred and two patients who were initially diagnosed between July 1, 2006 and May 5, 2011 by core needle biopsy and treated with NCT followed by definitive surgical resection were retrieved from the First Affiliated Hospital, China Medical University, Shenyang, China. The inclusion criteria were as follows: (1) receipt of at least one cycle of chemotherapy; (2) availability of complete information on clinical (cTNM at diagnosis) and pathologic stage (pTNM after NCT); (3) known response to treatment; and (4) known ER, PR, HER2, and ki-67 status. Patients were excluded from the analysis if they had received trastuzumab. Patients presenting with stage IV disease or with inflammatory breast cancer (T4d) were also excluded. The tumor size was assessed with ultrasound, mammography, and MRI. Prior to NCT, 14-gauge biopsies of the breast tumor were taken under ultrasound guidance to determine the histological subtype, hormone receptor, HER2, and ki-67 status. The surgical specimens were entirely submitted for routine pathologic evaluation. An overview of patient and clinicopathologic characteristics is given in Table 1.

Chemotherapy regimens

NCT regimens contained cyclophosphamide, epirubicin and fluorouracil (CEF, C 500 mg/m² iv d1, E 70 mg/m² iv d1, and F 500 mg/m² iv d1, repeated every 21 days); docetaxel plus carboplatin (TCb, T 75 mg/m² iv d1, Cb AUC=6 iv d1, repeated every 21 days); and docetaxel plus epirubicin (TE, T 75 mg/m² iv d1, E 70 mg/m² iv d1, repeated every 21 days).

Response evaluation

The response to treatment at the time of surgery was taken as an end point. Both pathology and clinical findings were used for response evaluation. After two cycles of chemotherapy, we evaluate the treatment outcome by using Ultrasound or MRI, patients with favorably responding tumors continued their initial chemotherapy to four cycles or more, and patients with minimal response or stable disease were switched to the alternative chemotherapy regimen or immediate surgical operation. According to the diameter of primary tumor and the axillary lymph node status, the clinical response was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the RECIST criteria [12]. In the final analysis, patients were classified into two groups: the objective response group (OR), containing patients classified as CR or PR, and the Non-response group (NR), containing patients classified as SD or PD.

Pathology assessment

The cut-off values for ER and PR positivity was defined as $\geq 1\%$ tumor cells with nuclear staining. The IHC staining for HER2 was scored according to standard

criteria as 0, 1+, 2+, or 3+. Scores of 0 and 1+ were considered of negative and 3+ was considered positive. When a score of 2+ was found, additional FISH testing was done to establish HER2 gene amplification status. The tumor grade was assessed using the Elston and Ellis method. TNM stages were diagnosed according to the American Joint Committee on Cancer Staging Manual (6th edition). The pCR was defined as no residual invasive cancer in the excised tumor or lymph nodes after completion of neoadjuvant chemotherapy. Patients with residual ductal carcinoma in situ were also considered as pCR.

Molecular subtyping

Luminal A tumors were defined as ER+, PR+, HER2-, and ki-67 $\leq 14\%$. Luminal B tumors were defined as ER+, PR+, HER2-ki-67 $> 14\%$; ER+ and/or PR+, HER2+, HER2-overexpression tumors were defined as ER-, PR-, and HER2+. Triple-negative tumors were defined as ER-, PR-, and HER2-.

Study endpoint and Statistics

The primary endpoint of this study was the pCR rate according to molecular subtypes. All data were analyzed with SPSS statistics software (Version 13.0, Chicago, IL, USA). The Chi-square test or Fisher exact test was used to assess the relationship between the different subtype groupings and the pCR rate. For the univariate analyses, Chi-square test or Fisher exact test was used. For the multivariate analyses, logistic regression was used. All statistical tests were two-sided, and P-value < 0.05 was considered statistically significant.

Results

Patient Characteristics and Distribution of Molecular Subtypes

Patient characteristics and distribution of molecular subtypes are reported in Table 1. A total of 102 patients were eligible for final analysis. The mean age was 49.0 years. The positive rate of ER, PR and HER2 was 39.2%, 34.3% and 23.5% respectively. Twenty (19.6%) patients were luminal A, 23 (22.5%) were luminal B, 18 (17.6%) were HER2-overexpression, 41 (40.2%) were triple-negative. The majority of patients were T2 (44.1%) or T3 (34.3%), and 41.2% patients were node-negative. Fifty-one patients (50.0%) were diagnosed with stage II disease and 51 patients (50.0%) were diagnosed with stage III disease. Ninety-eight carcinomas (96.1%) were diagnosed as invasive ductal carcinoma, 4 as invasive lobular carcinoma (3.9%). Ten carcinomas were grade 1 (9.8%), 81 were grade 2 (79.4%) and 11 were grade 3 (10.8%).

Neoadjuvant chemotherapy

Patients in our study were treated with a variety of chemotherapy regimens (Table 1). Forty-four patients (43.1%) received a regimen containing cyclophosphamide, epirubicin and fluorouracil (CEF); 13 patients (12.7%) received a regimen containing docetaxel and epirubicin (TE); 45 patients (44.1%) received a regimen containing

Table 1. Patient Characteristics

	Luminal A (n=20)	Luminal B (n=23)	HER2 (n=18)	Triple-negative (n=41)	All (n=102)
Age at menarche(y)					
≤13	5(25.0%)	7(30.4%)	4(22.2%)	3(7.3%)	19(18.6%)
>13	15(75.0%)	16(69.6%)	14(77.8%)	38(92.7%)	83(81.4%)
Menopausal status					
Premenopause	11(55.0%)	9(39.1%)	6(33.3%)	20(48.8%)	46(45.1%)
Postmenopause	9(45.0%)	14(60.9%)	12(66.7%)	21(51.2%)	56(54.9%)
Age(year)					
≤35	3(15.0%)	3(13.0%)	6(33.3%)	3(7.3%)	15(14.7%)
36-50	8(40.0%)	7(30.4%)	4(22.2%)	20(48.8%)	39(38.2%)
≥51	9(45.0%)	13(56.5%)	8(44.4%)	18(43.9%)	48(47.1%)
Median age	47.8	52.0	45.6	48.4	49.0
Pre-T Stage					
T2	9(45.0%)	13(56.5%)	6(33.3%)	17(41.5%)	45(44.1%)
T3	6(30.0%)	5(21.7%)	8(44.4%)	16(39.0%)	35(34.3%)
T4	5(25.0%)	5(21.7%)	4(22.2%)	8(19.5%)	22(21.6%)
Pre-N Stage					
N0	13(65.0%)	7(30.4%)	12(66.7%)	10(24.4%)	42(41.2%)
N1	6(30.0%)	10(43.5%)	3(16.7%)	19(46.3%)	38(37.3%)
N2	1(5.0%)	6(26.1%)	1(5.6%)	10(24.4%)	18(17.6%)
N3	0(0.0%)	0(0.0%)	2(11.1%)	2(4.9%)	4(3.9%)
AJCC stage					
IIA	7(35.0%)	5(21.7%)	6(33.3%)	5(12.2%)	23(22.5%)
IIB	5(25.0%)	7(30.4%)	4(22.2%)	12(29.3%)	28(27.5%)
IIIA	3(15.0%)	6(26.1%)	3(16.7%)	15(36.6%)	27(26.5%)
IIIB	5(25.0%)	5(21.7%)	3(16.7%)	7(17.1%)	20(19.6%)
IIIC	0(0.0%)	0(0.0%)	2(11.1%)	2(4.9%)	4(3.9%)
Histology					
Invasive ductal	18(90.0%)	22(95.7%)	18(100.0%)	40(97.6%)	98(96.1%)
Invasive lobular	2(10.0%)	1(4.3%)	0(0.0%)	1(2.4%)	4(3.9%)
Tumor grade					
I	4(20.0%)	0(0.0%)	0(0.0%)	6(14.6%)	10(9.8%)
II	16(80.0%)	23(100.0%)	16(88.9%)	26(63.4%)	81(79.4%)
III	0(0.0%)	0(0.0%)	2(11.1)	9(22.0%)	11(10.8%)
Chemotherapy regimen					
TCb	9(45.0%)	12(52.2%)	6(33.3%)	18(43.9%)	45(44.1%)
CEF	7(35.0%)	9(39.1%)	10(55.6%)	18(43.9%)	44(43.1%)
TE	4(20.0%)	2(8.7%)	2(11.1%)	5(12.2%)	13(12.7%)
Chemotherapy cycles					
1-2	7(35.0%)	6(26.1%)	4(22.2%)	12(29.3%)	29(28.4%)
3-4	13(65.0%)	16(69.6%)	12(66.7%)	24(58.5%)	65(63.7%)
>4	0(0.0%)	1(4.3%)	2(11.1%)	5(12.2%)	8(7.8%)
median cycle	3.1	3.3	3.2	3.3	3.3
Recist					
CR	3(15.0%)	5(21.7%)	0(0.0%)	5(12.2%)	13(12.7%)
PR	12(60.0%)	14(57.1%)	8(44.4%)	27(65.9%)	61(59.8%)
SD	5(25.0%)	3(13.0%)	9(50.0%)	8(19.5%)	25(24.5%)
PD	0(0.0%)	1(4.3%)	1(5.6%)	1(2.4%)	3(2.9%)
Surgery					
BCT	0(0.0%)	2(8.7%)	1(5.6%)	4(9.8%)	7(6.9%)
Mastectomy	20(100.0%)	21(91.3%)	17(94.4%)	37(90.2%)	95(93.1%)

docetaxel and carboplatin (TCb) (Table.1).

pCR rate according to breast cancer subtypes

Of the 102 patients analyzed, 16 patients achieved pCR; thus, the pCR rate was 15.7%. The rates of pCR differed significantly among the 4 molecular subtypes with 0.0% (0/20) for luminal A, 8.7% (2/23) for luminal B, 22.2% (4/18) for HER2-overexpression and 24.4% (10/41) for triple-negative (p=0.041) (Table.2). The greatest difference of the pCR rate was observed between the triple-negative and luminal A subtypes.

In the univariate analyses, only the molecular subtype

and ER-status were found to be significant predictors of a pCR (P = 0.004, and 0.041, respectively). In the multivariate analysis (logistic regression), menopausal status, pre-N Stage, molecular subtype and chemotherapy regimen were found to be significantly predictive of a pCR (P = 0.032, 0.015, 0.002, and 0.010, respectively) (Table 2). To perform a conclusive multivariate analysis, more samples will be needed.

In luminal A subtype tumors, the pCR rate is 0. But the OR (cCR/cPR) rate reached up to 75.0% (15/20) and 15.0% (3/20) patients met the criteria for breast-conserving surgery but all refused.

Table 2. Univariate Analysis and Multivariate Analysis of Factors Associated with pCR

Characteristic	Pathological response		Univariate analysis P-value	Multivariate analysis	
	pCR (n=16)	Non-pCR (n=86)		OR(95%CI)	p-value
Age at menarche (y)			1.000*	0.14(0.017-1.13)	0.065
≤13	3(15.8%)	16(84.2%)			
>13	13(15.7%)	70(84.3%)			
Menopausal status			0.280	7.249(1.185-44.348)	0.032
Premenopause	5(10.9%)	41(89.1%)			
Postmenopause	11(19.6%)	45(80.4%)			
Age at diagnosis(y)			0.455*	1.208(0.085-17.188)	0.889
≤35	1(6.7%)	14(93.3%)			
>35	15(17.2%)	72(82.8%)			
Pre-T Stage			0.169	0.364(0.093-1.420)	0.146
T2	10(22.2%)	35(77.8%)			
T3-4	6(10.5%)	51(89.5%)			
Pre-N Stage			0.268	0.15(0.033-0.687)	0.015
N0	9(21.4%)	33(78.6%)			
N1-3	7(11.7%)	53(88.3%)			
AJCC stage			0.054	–	–
II	12(23.5%)	39(76.5%)			
III	4(7.8%)	47(92.2%)			
Histology			1.000*	–	–
Invasive ductal	16(16.3%)	82(83.7%)			
Invasive lobular	0(0.0%)	4(100.0%)			
Tumor grade			0.356*	–	–
I	0(0.0%)	10(100.0%)			
II-III	16(17.4%)	76(82.6%)			
ER status			0.004	–	–
Positive	1(2.5%)	39(97.5%)			
Negative	15(24.2%)	47(75.8%)			
PR status			0.251	–	–
Positive	3(8.6%)	32(91.4%)			
Negative	13(19.4%)	54(80.6%)			
HER2 status			1.000*	–	–
Positive	4(16.7%)	20(83.3%)			
Negative	12(15.4%)	66(84.6%)			
Molecular subtype			0.041*	4.513(1.772-11.493)	0.002
Luminal A	0(0.0%)	20(100.0%)			
Luminal B	2(8.7%)	21(91.3%)			
HER2-overexpression	4(22.2%)	14(77.8%)			
Triple-negative	10(24.4%)	31(75.6%)			
Chemotherapy regimen			0.062*	3.228(1.321-7.889)	0.010
TCb	11(24.4%)	34(75.6%)			
TE	2(15.4%)	11(84.6%)			
CEF	3(6.8%)	41(93.2%)			
Chemotherapy cycles			0.547*	1.371(0.246-7.646)	0.719
1-2	3(10.3%)	26(89.7%)			
≥3	13(17.8%)	60(82.2%)			

*Fisher’s exact test

Table 3. Triple-negative Breast Cancer (n=41) Treated with Different Chemotherapy Regimens

Therapy	Pathological response			P-value
	pCR (%)	Non-pCR(%)	Total	
TCb	8 (44.4)	10(55.6)	18	0.024*
TE	1 (20.0)	4 (80.0)	5	
CEF	1 (5.6)	17(94.4)	18	

*Fisher’s exact test

In Triple-negative subtype patients, we analysed the pCR rate according to different chemotherapy regimens. The rates of pCR differed significantly among the 3 chemotherapy regimens with 5.6% (1/18) for CEF (cyclophosphamide, epirubicin and flurouracil), 20.0%

Table 4. The pCR Rate of TCb Regimen According to Different Molecular Subtypes

molecular subtype	Pathological response			P-value
	pCR (%)	Non-pCR(%)	Total	
Luminal A	0(0.0)	9(100.0)	9	0.025*
Luminal B	1(8.3)	11(91.7)	12	
HER2-overexpression	2(33.3)	4(66.7)	6	
Triple-negative	8(44.4)	10(55.6)	18	

*Fisher’s exact test

(1/5) for TE(docetaxel and epirubicin) and 44.4% (8/18) for TCb(docetaxel and carboplatin) (p=0.024) (Table.3). The pCR rate of TCb regimen also differed significantly among different molecular subtypes with 0.0% (0/9)

Table 5. LABC (n=64) Treated with Different Chemotherapy Regimen

Chemotherapy regimen	Clinical evaluation			Pathological response		
	OR(%)	NR(%)	P-value	pCR(%)	Non-pCR(%)	P-value
TCb	19(73.1)	7(26.9)	0.617*	6(23.1)	20(76.9)	0.127*
TE	6(75.0)	2(25.0)		0(0.0)	8(100.0)	
CEF	18(60.0)	12(40.0)		2(6.7)	28(93.3)	
Total	43(67.2)	21(32.8)		8(12.5)	56(87.5)	

*Fisher's exact test

for luminal A, 8.3% (1/12) for luminal B, 33.3% (2/6) for HER2-overexpression and 44.4% (8/18) for triple-negative subtypes (p=0.025)(Table 4).

We also test the the pCR rate according to different chemotherapy regimens in locally advanced breast cancer patients (T3-4, N2-3). The rates of pCR seem to differed significantly among the 3 chemotherapy regimens with 6.7% (2/30) for CEF (cyclophosphamide, epirubicin and flurouracil), 0.0% (0/8) for TE(docetaxel and epirubicin) and 23.1% (6/26) for TCb (docetaxel and carboplatin), but it did not show statistical significance(p=0.127) (Table 5).

Discussion

Breast cancer is now regarded as a heterogeneous disease classified into distinct molecular subtypes with prognostic significance. As far as we know, these subtypes are luminal A, luminal B, HER2-overexpression, basal-like and normal breast-like subtypes (Perou et al., 2000). However, it is not clear that whether the normal breast-like subtype represents a true subtype. Peppercorn et al (2000) have suggested that this subtype might potentially be owing to normal tissue contamination based on its adipose tissue-enriched expression pattern. The golden standard for molecular subtyping is the cDNA microarrays analysis. The use of a gene classification system, however, seems to fail to offer a better prediction of neoadjuvant therapy response than a simpler routine IHC/FISH based method (de Ronde et al., 2010). Thus, in this study, reference to the 2011 St Gallen consensus, we divided breast carcinomas based on IHC into luminal A (ER+, PR+, HER2-, and ki-67 ≤14%), luminal B (ER+, PR+, HER2-,and ki-67>14%; ER+and/or PR+, HER2+), HER2-overexpression(ER-, PR-,and HER2+) and triple-negative (ER-, PR-,and HER2-). We look forward to use this newly IHC classification criteria to better represent the biological characteristics of breast tumor. It is well accepted that various subtypes of breast cancer show different sensitivities to NCT (Bhargava et al., 2010; Huober et al., 2010; Straver et al., 2010). Nevertheless, there is little known about the relevance between molecular subtypes and NCT sensitivities in the Chinese population. Our study is aimed to evaluate the role of molecular subtypes in predicting the response to NCT among breast cancer patients in Northeast China.

In our study, the rate of luminal A subtype was 19.6%, 22.5% for luminal B, 17.6% for the HER2-overexpression, and 40.2% for the triple-negative subtype. The incidence of HER2-overexpression subtype was similar to what was

previously reported in western countries. Surprisingly, the incidence of triple-negative subtype was much higher than the previous reports (40% vs 15-20%) which could possibly be explained by the advanced stage of disease and the relative small number of samples. A large number of clinical trials had revealed that pCR was related to good treatment outcomes and could be used as a surrogate marker of better survival (Fisher et al., 1998; Carey et al., 2005; Rastogi et al., 2008). Among total 102 patients, the pCR rate of luminal A, luminal B, HER2-overexpression and triple-negative was 0.0%, 8.7%, 22.2% and 24.4%, respectively (p=0.041). In this study, we added evidence to previous observations that HER2-overexpression and triple-negative subtypes are more sensitive to NCT.

As high expression of the hormone receptors and low expression of Ki67, luminal A tumors are considered to be less chemotherapy responsive, and someone even believe that luminal A tumors should receive endocrine therapy only and should avoid NCT (Parker et al., 2009; Blows et al., 2010; Rodenhuis et al., 2010). However, we implemented NCT in breast cancer patients not only to achieve pCR but also to change the choice of surgery. In our study, for luminal A tumors treated with NCT, although none achieved a pCR, the OR (cCR/cPR) rate reached up to 75.0%, and 15.0% patients met the criteria for breast-conserving surgery but all refused. Clearly, this article will not end the discussion whether luminal A tumors should receive NCT. Our recommendation is similar to previous reports reports (Kim et al., 2005; Peintinger et al., 2006; Thomas et al., 2006), that is treatment of luminal A tumors with NCT can allow breast-conserving surgery to take place and as such can be an effective treatment option for this group.

Triple-negative breast cancer (TNBC) accounts for at least 15–20% of all breast cancers. TNBC is not amenable to conventional therapies for breast cancer such as endocrine therapy or anti-HER2 therapy, leaving only chemotherapy in the therapeutic armamentarium. However, despite their poor prognosis, TNBC are sensitive to conventional chemotherapy. Recent reports demonstrated that TNBC tumors were highly responsive to NCT containing carboplatin (Chang et al., 2010; Staudacher et al., 2011). Our study also indicated that, for triple-negative subtype, the rates of pCR differed significantly among the three chemotherapy regimens with 5.6% for CEF, 20.0% for TE and 44.4% for TCb regimen (p=0.024). Therefore, we concluded that the TCb combination is a promising NCT regimen for TNBC. Meanwhile, other molecular subtypes of breast cancer patients also treated with TCb regimen in our study. Surprisingly, the rates of pCR also differed significantly among the four molecular subtypes with 0.0% for luminal A, 8.3% for luminal B, 33.3% for HER2 and 44.4% for triple-negative(p=0.025). We all know that TCH regimen is an alternative for HER2+ patients. Surprisingly, even though we did not add Herceptin, pCR rate of HER2-overexpression patients also reached up to 33.3%. Therefore, we have reason to believe that TCb regimen will be an effective choice for HER2-overexpression subtype patients if they have poor cardiac function and can not afford Herceptin.

In recent years, an increasing number of patients had been diagnosed with earlier stages of breast cancer, whereas, locally advanced breast cancer (LABC) remains a major clinical problem in many parts of China. The main rationale for NCT in LABC is to improve surgical option by shrinking the primary tumor and controlling axillary lymph node metastasis. To our knowledge, there were relative few studies focused on NCT regimen containing carboplatin in the treatment of LABC in China. Our study indicated that the pCR rate of TCb regimen (23.1%) is significantly higher than that of TE regimen (0.0%) and CEF regimen (6.7%), but it did not show statistical significance ($p=0.127$). We speculated that if we increase the number of sample, the result may show statistical significance. Our result is similar to other reports. Gogas et al. (2010) examined the pCR rate to NCT containing paclitaxel and carboplatin in LABC. They observed a high pCR rate (9.5%) and the chemotherapy was well tolerated. Therefore, it is convincible that the combination of paclitaxel and carboplatin is an effective regimen for patients with LABC.

There are several limitations in this study. One limitation is the relative small number of patients enrolled in this trial. Another limitation is that patients received different regimens of chemotherapy which may cause confusion when we analyze the final results. However, the different regimens are not restricted to or overrepresented in specific subtypes and since other studies that used the same regimen across all subtypes reported similar results, so we consider the overall conclusions to be valid (Goldstein et al., 2007; Andre et al., 2008)..

In conclusion, molecular subtypes based on ER, PR, HER2 and ki-67 can predict the pathological response of Chinese breast cancer patients treated with NCT. Compared with luminal A subtype, HER2-overexpression and triple-negative subtypes of breast cancer are more sensitive to NCT. Considering triple-negative breast cancer, the TCb combination is a promising neoadjuvant chemotherapy regimen. Our results also indicated that the TCb combination is promising for the treatment of LABC.

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