Breast Cancer (2019) 26:373–377
https://doi.org/10.1007/s12282-018-00934-3

ORIGINAL ARTICLE

Neoadjuvant chemotherapy and timing of sentinel lymph node biopsy in different molecular subtypes of breast cancer with clinically negative axilla

Zhao Bi[1,2] · Jingjing Liu[3] · Peng Chen[2] · Yanbing Liu[2] · Tong Zhao[2] · Chunjian Wang[2] · Zhaopeng Zhang[2] · Xiao Sun[2] · Pengfei Qiu[2] · Binbin Cong[1,2] · Xianrang Song[2] · Yongsheng Wang[2]

Received: 23 February 2018 / Accepted: 12 November 2018 / Published online: 21 January 2019

Abstract

Purpose This study aims to determine the optimal time to perform sentinel lymph node biopsy (SLNB) for patients with clinically node-negative (cN_0) disease following neoadjuvant chemotherapy (NAC).

Method From April 2008 to April 2018, 592 patients with breast cancer underwent after NAC were included in this study. Patients with cN_0 before and ycN_0 disease after NAC received SLNB and axillary lymph node dissection (ALND) in case of positive sentinel lymph nodes (SLNs). For patients with clinically node-positive (cN_+) disease, the axillary surgery is based on the doctor's decision.

Result In general, 17.6% (104/592) of patients achieved total pathologic complete response (pCR), which was 6.9%, 33.3%, 32.3% and 15.3%, respectively, among patients with hormone receptor (HR) positive/ human epidermal growth factor receptor-2 (HER-2) negative (HR+/HER2−) subtype, triple-negative (TN) subtype, HER-2 positive (HER2+) subtype with and without targeted therapy ($p < 0.001$). Among the 525 cN_+ patients, the axillary nodal pCR (apCR) rate was 34.5%, and the apCR rate was significantly higher in patients with HER2+ (58.6% with and 28.2% without targeted therapy respectively) and TN subtype (53.2%) than that in patients with HR+/HER2−subtype (21.2%, $p < 0.001$). Among the 67 cN_0 patients, the positive rate of SLNs was 19.4% (13/67), which was 28.1% (9/32), 13.3% (2/15) and 10.0% (2/20), respectively, among patients with HR+/HER2−, TN and HER2 + subtypes.

Conclusion The pCR rates were significantly related to molecular subtype. Combining the apCR rates in different molecular subtypes of cN_+ patients and the excellent locoregional control of AOSOG Z0011 and AMAROS trials in cN_0 patients, it would be preferable to perform SLNB prior to NAC for cN_0 patients with HR+/HER2− subtype, and SLNB after NAC for those cN_0 patients with TN and HER2+ subtype to increase the chance of avoiding ALND. Among cN_0 patients, TN and HER2 + subtypes would benefit more from axillary de-escalating surgery after NAC than HR+/HER2− subtype.

Keywords Breast cancer · Neoadjuvant chemotherapy · Molecular subtype · Pathologic complete response · Sentinel lymph node biopsy

Introduction

Neoadjuvant chemotherapy (NAC) is the standard treatment for patients with locally advanced as well as some stage II or III, tripe-negative (TN) and human epidermal growth factor receptor-2 (HER-2) positive (HER2+) breast cancer; it can improve the rate of breast-conserving surgery (BCS) and offer an opportunity to evaluate the efficacy of chemotherapy on primary tumor in vivo [1]. Pathologic complete response (pCR) is an independent prognostic factor, and studies indicated that pCR was associated with molecular subtype [2]. Sentinel lymph node biopsy (SLNB) has replaced axillary

✉ Yongsheng Wang
wangysh2008@aliyun.com

1 School of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, Jinan, Shandong, People's Republic of China

2 Breast Cancer Center, Shandong Cancer Hospital Affiliated to Shandong University, Ji Yan Road 440, Jinan, Shandong Province, People's Republic of China

3 Laboratory, Qingdao Municipal Hospital, Qingdao, Shandong, People's Republic of China

lymph node dissection (ALND) as the standard axillary nodal staging technique for patients with clinically node-negative (cN_0) disease [3]. In a woman who presented with a cN_0 disease and received NAC, SLNB is appropriate to be performed. But the optimal time of SLNB in different molecular subtype breast cancer with cN_0 disease and NAC remains uncertain. The purpose of our study was to identify the rate of pCR among different molecular subtypes after NAC and determine the optimal time to perform SLNB for cN_0 patients who received NAC.

Methods

Patients

Five hundred and ninety-two female patients who had histology confirmed initial clinical staging $T_{1-4}N_{0-3}M_0$ invasive breast cancer treated at Shandong Cancer Hospital Breast Cancer Center were enrolled in this study between April 2008 and 2018. Patients diagnosed with distant metastatic disease prior to surgery or who did not have surgery at our hospital were excluded. Clinicopathologic and treatment data were collected from the patient's medical record. The study was approved by the Shandong Cancer Hospital Affiliated to Shandong University Ethics Committee (No. SDTHEC20110324). Before NAC, all patients underwent a series of evaluation by a multidisciplinary team. Suspicious positive axillary lymph nodes (ALNs) were accessed by fine needle aspiration prior to initiation of NAC. Hormone receptor (HR) was defined as positive with one percent expression rate. HER-2 receptor was considered as positive with immune-histochemical staining of 3+, or fluorescence in situ hybridization that was amplified [5]. After these evaluations, molecular subtypes could be classified into HR+/HER2−, HER2 + and TN subtypes. All patients received full course of chemotherapy regimens (taxanes combined with anthracyclines) before surgery. Breast pCR (bpCR) was defined as no residual invasive carcinoma in the breast. Patients with cN_0 disease ($n = 67$) at presentation were excluded from the axillary nodal pCR (apCR) endpoint calculation; apCR was defined as no residual carcinoma in axilla. The primary endpoint of this study was total pCR (tpCR), which means that achieved both apCR and bpCR [2].

Study procedure

For patients with cN_0 disease, SLNB would be performed when patients with ycN_0 disease after NAC, and ALND would be performed in case of positive sentinel lymph nodes (SLNs). For patients with clinically node-positive (cN_+) disease, the axillary surgery is based on the doctor's decision.

Table 1 Molecular subtypes and clinical characteristic of patients

Characteristic	No	%
Molecular subtypes		
HR+/HER2−	274	46.3
HER2+	210	35.5
TN	108	18.2
Clinical N stage		
cN_0	67	11.3
cN_1	250	42.2
cN_2	148	25.0
cN_3	127	21.5
Clinical T stage		
cT_0	59	10.0
cT_1	318	53.7
cT_2	90	15.2
cT_3	125	21.1

All patients undergoing SLNB received dual tracer injection of radiolabeled colloid (^{99m}Tc-SC) (Beijing Atomic Galactic Jinan Drug Center, Beijing, China) and blue dye (Methylene blue). ^{99m}Tc-SC (1.0 ~ 1.2 ml) was injected intraparenchymally under ultrasonographic guidance 3 ~ 18 h before surgery. Blue dye (2 ~ 4 ml) was injected subcutaneously around the tumor 10 min before surgery. Radioactive and/or blue-stained ALNs were defined as SLNs. Lymph nodes found to have any tumor, including micro-metastases and isolated tumor cells, were defined as positive.

Statistical analysis

All the statistical data were analyzed with SPSS version 22.0 software (IBM Inc., Armonk, USA). Independent-sample t test was used for continuous variables and Pearson χ^2 test or Fisher exact test was used for categorical variables. A $p < 0.05$ was considered statistically significant.

Result

Patient characteristics

Between April 2008 and April 2018, 592 patients received full course of chemotherapy regimens followed by surgery in our breast cancer center. The median age of these patients was 49 years (rang 25 to 70 years). HER2 + subtype was identified in 210 patients; due to the financial difficulty of patients, only 47.1% (99/210) of them received anti-HER-2 targeted therapy (trastuzumab) before surgery. In terms of breast surgery approach selected, 90.2% (534/592) of patients underwent mastectomy,and the other 9.8% (58/592)

of patients received BCS. All of the demographic and clinical characteristics are listed in Table 1.

Outcome associated with pCR

In general, 17.6% (104/592) of patients achieved tpCR. On multivariable analysis, after adjusting for clinicopathologic factors selected a priori, molecular subtype remained the only significant predictor of tpCR and it was 6.9%, 33.3%, 32.3% and 15.3%, respectively, among patients with HR+/HER2−, TN, HER2 + subtype with and without targeted therapy ($p < 0.001$).

One hundred and fifty-eight of 592 patients achieved bpCR, with similar bpCR rates in patients with cT_1 (47.5%), cT_2 (27.4%), cT_3 (27.8%) and cT_4 (14.4%) disease ($p = 0.592$). The bpCR was higher in TN (43.5%) and HER2 + subtype (with and without targeted therapy was 41.4% and 27.0%, respectively) compared with HR+/HER2− subtype (14.6%; $p < 0.001$).

Among the 525 cN_+ patients, apCR rate was 34.5% (181/525). Similarly, apCR was also significantly higher in patients with TN (53.2%) and HER2 + subtype (with and without targeted therapy was 58.6% and 28.2%, respectively) than in those with HR+/HER2− subtype (21.2%; $p < 0.001$) (Table 2). Our data also indicated that the apCR was not related to the clinical tumor burden in ALNs: cN_1 (38.0%), cN_2 (34.5%) and cN_3 (27.6%; $p = 0.131$).

Among the 67 cN_0 patients, 47.8% (32/67) were HR+/HER2−, 22.4% (15/67) were TN and 29.8% (20/67) were HER2 + subtype. The positive rate of SLNs after NAC was 19.4% (13/67), which was 28.1% (9/32), 13.3% (2/15) and 10.0% (2/20), respectively, among patients with HR+/HER2−, TN and HER2 + subtypes.

DISCUSSION

Molecular subtypes and pCR after NAC

It is reported that after NAC, the tpCR rate was 20% ~ 37%, bpCR rate was 27% ~ 40% and apCR rate approximately reached 30%~63% [2, 4–7] (Table 3). Judgment and classification of breast cancer by molecular subtype has improved the understanding and treatment of disease. The choice of NAC agent and patients' responses to chemotherapy were influenced by molecular subtype [8]. On multivariable analysis, after adjusting for clinicopathologic factors selected a priori, molecular subtype remained the only significant predictor of pCR. In our study, we found that tpCR after NAC was closely related to molecular subtype. The result demonstrated that it was significantly higher in HER2 + and TN subtype compared with HR+/HER2− subtype. HER2 + patients who received anti-HER2 targeted therapy in addition to chemotherapy achieved higher rates of tpCR (32.3%), similar to the 44.1% in MD Anderson Cancer Center, 44.8% in Memorial Sloan Kettering Cancer Center, and 45.4% in patients enrolled in American College of Surgeons Oncology Group (ACSOG) Z1071 trial [8–10], emphasizing the importance of optimal systemic and targeted therapy to achieve maximal treatment response.

Among the 525 cN_+ patients, the apCR rate of our study was 34.5%. Similar to bpCR and tpCR, apCR was also related to molecular subtype. The odds ratio of achieving apCR was 5.26 and 1.46 times higher for HER2 + patients with and without anti-HER2 targeted therapy than those with HR+/HER2− subtype. Among the TN patients, the odds ratio of apCR was 4.23 times higher than those with HR+/HER2− subtype (Table 4). The higher tpCR and apCR

Table 3 apCR after NAC for patients with cN_+ disease

Source	No.	apCR (%)			
		All	HR+/HER2−	TN	HER2+ (w/ anti-HER2 Tx)
Boughoy [4] 2014	525	41.1	21.1	49.4	64.7
Boileau[5], 2015	145	35.0	NA	NA	NA
Mamtani [6] 2016	195	49.0	21.0	47.0	82.1
Diego [7] 2016	30	63.0	0.0	67.0	69.0
Lori [2] 2017	321	38.0	17.0	41.0	63.0
Our study 2018	525	34.5	21.2	53.2	58.6

Table 2 tpCR, bpCR and apCR stratified by molecular subtypes

Molecular subtypes	tpCR		bpCR		apCR	
	No	%	No	%	No	%
HR+/HER2−	19	6.9	40	14.6	51	21.2
TN	36	33.3	47	43.5	50	53.2
HER2+ (w/ anti-HER2 Tx)	32	32.3	41	41.4	51	58.6
HER2+ (w/o anti-HER2 Tx)	17	15.3	30	27.0	29	28.2
All	104	17.6	158	26.7	181	34.5

tpCR total pathologic complete response, *bpCR* breast pathologic complete response, *apCR* axillary nodal pathologic complete response

Table 4 The odds radio of apCR

Molecular subtype	OR (95% CI)	*p* value
HR+/HER2−	1.00 (referent)	
HER2+ (w/ anti-HER2 Tx)	5.26 (0.28–10.24)	$p<0.001$
HER2+ (w/o anti-HER2 Tx)	1.46 (0.24–2.68)	$p=0.031$
TN	4.23 (2.80–5.66)	$p<0.001$

OR odds radio

obtained in TN and HER2 + patients after NAC reflect the improvement of the NAC treatment strategy based on molecular subtype. The apCR rate was 38.0%, 34.5% and 27.6%, respectively, in patients with cN_1, cN_2 and cN_3 disease. Although the association between apCR and axilla tumor burden was not statistically significant ($p=0.131$), there was a trend of reducing apCR with increase of tumor burden.

Optimal time to perform SLNB for cN_0 patients

As a less invasive technique, SLNB has replaced ALND as the standard treatment after NAC to evaluate the status of ALN for patients with cN_0 disease. For cN_0 patients, 2017. V1/V2 NCCN breast cancer clinical practice guidelines recommend that it is feasible to perform SLNB before and after NAC, while 2018.V1/V2 NCCN guidelines has changed that SLNB preferably be performed after NAC [11]. But there is no high level of evidence to substantiate the optimal time to perform SLNB currently. In a woman who presented with a cN_0 disease and who received NAC, the 2017 St. Gallen international expert consensus conference strongly believed SLNB to be appropriate (95.7% approved). The Panel's opinions regarding the optimal time to perform SLNB and NAC for cN_0 patients was inconsistent: 60% of the Panel approved that the biopsy should be performed after NAC, 20% of the Panel favored that SLNB should be performed prior to NAC, while 16.7% of the Panel favored that it is appropriate to perform SLNB before or after NAC [12]. A retrospective study of Pilewskie [13] showed that receipt of NAC compared with upfront BCS remained significantly associated with higher odds of ALND in the HR+/HER2− subtype (hazard ratio = 3.35; $p<0.001$), whereas NAC versus upfront mastectomy remained significantly associated with lower odds of ALND in the HER2 + and TN subtypes (hazard ratio = 0.19, $p<0.001$; hazard ratio = 0.25, $p=0.007$, respectively). This study based on the application of ACOSOG Z0011 trial criteria. Among patients with $cT_{1-2}N_0$ disease planed to receive BCS and whole breast radiation therapy, ALND was warranted for three or more positive SLNs [13, 14]. Our study showed that among patients with cN_0 disease, the rate of ALND was 28.1%, 13.3% and 10.0%, respectively, in HR+/HER2−, HER2 + and TN patients.

Since patients with cN_0 disease are unable to assess axillary status effectively and the sample size was small, we may predict the apCR of cN_0 patients after NAC by evaluating the apCR of patients with cN_+ disease. For patients with cN_+ disease, the apCR was lower in HR+/HER2− subtype after NAC, while patients with TN and HER2 + subtype achieved higher apCR. With present chemotherapy regimens, 53.2% of TN patients and 58.6% of HER2 + patients receiving targeted therapy in our study convert to apCR after NAC. Thus, we could infer that apCR was also higher in TN and HER2 + patients with cN_0 disease after NAC, and the apCR might lower in HR+/HER2− patients with cN_0 disease after NAC.

For patients who received SLNB prior to NAC, according to the results of AMAROS and ACSOG Z0011 trials, ALND could be avoided for patients with ≤ 2 positive SLNs if they would receive axilla radiotherapy [14, 15]. NSABP B-32 study and AMAROS trial found that about 30% of cN_0 patients undergoing SLNB had positive SLNs [15, 16]. And in these 30% of patients, 80% had 1 ~ 2 positive SLNs. According to the results of AMAROS and ASCOG Z0011 trial, there would be 94% of cN_0 patients who could avoid ALND (30% multiplied by 80% plus 70% was 94%).

For patients receiving SLNB after NAC, the NCCN guidelines recommend that ALND would be the standard treatment for patients with any positive SLNs after NAC, including micro-metastasis and isolated tumor cells. According to our study, the apCR rates after NAC were significantly associated with molecular subtypes. Patients with HR+/HER2− subtype achieved lower apCR rate (21.2%) than patients with TN and HER2 + subtypes. So we inferred the apCR of cN_0 patients after NAC by evaluating the apCR of patients with cN_+ disease. For patients with HR+/HER2− subtype, there would be 76.36% of cN_0 patients who could avoid ALND (30% multiplied by 21.2% plus 70% was 76.36%). The odds ratio of ALND in cN_0 patients with HR+/HER2− subtype was 3.94 times higher for SLNB after NAC than SLNB prior to NAC. On the contrary, the apCR was high in TN and HER2 + patients with cN_0 disease after NAC; those patients might have more chance to avoid ALND if performed SLNB after NAC. Among the cN_0 patients, TN and HER2 + subtypes would benefit more from axillary de-escalating surgery after NAC than HR+/HER2− subtype.

The apCR and tpCR rates after NAC were significantly associated with molecular subtypes. Patients with TN and HER2 + subtypes achieved higher apCR and tpCR than patients with HR+/HER2− subtype. The clinical nodal staging and molecular subtypes should be considered while choosing optimal time to perform SLNB following NAC. For cN_0 patients with HR+/HER2− subtype, SLNB prior to NAC would be feasible. For cN_0 patients with TN and

HER2 + subtypes, they may have more chance to avoid ALND if performed SLNB after NAC.

Acknowledgements This work was supported by National Natural Science Foundation of China (81502314) and Medical and Health Science Technology Development Program in Shandong Province (2015WS0151).

Compliance with ethical standards

Conflict of interest The authors have stated that they have no conflicts of interest in this work.

References

1. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol. 1997;15:2483–93.
2. Lori F, George P, Emily C, et al. Tumor biology predicts pathologic complete response to neoadjuvant chemotherapy in patients presenting with locally advanced breast cancer. Ann Surg Oncol. 2017;34(13):3896–902.
3. Kumar A, Puri R, Gadgil PV, et al. Sentinel lymph node biopsy in primary breast cancer: window to management of the axilla. World J Surg. 2012;36(7):1453–1459.
4. Boughey JC, McCall LM, Ballman KV, et al. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer: findings from the ACOSOG Z1071 (Alliance) prospective multicenter clinical trial. Ann Surg. 2014;260(4):608–16.
5. Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SNFNAC study. J Clin Oncol. 2015;33(3):258–64.
6. Mamtani A, Andrea V, Tari A, et al. How often does neoadjuvant chemotherapy avoid axillary dissection in patients with histologically confirmed nodal metastases? Results of a prospective study[J]. Ann Surg Oncol. 2016;23(11):3467–74.
7. Diego E, Mcauliffe P, Soran A, et al. Axillary staging after neoadjuvant chemotherapy for breast cancer: a pilot study combining sentinel lymph node biopsy with radioactive seed localization of pretreatment positive axillary lymph nodes. Ann Surg Oncol. 2016;23(5):1549–53.
8. Judy C, Linda M, Karla V, et al. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer: findings from the ACOSOG Z1071 (Alliance) prospective multicenter clinical trial. Ann Surg. 2014;260(4):608–16.
9. Bill L, Krishnamurti U, Shristi B, et al. Biomarkers predicting pathological complete response to neoadjuvant chemotherapy in breast cancer. Am J Clin Pathol. 2016;0:1–8.
10. Audree B, Wei T, Savitri K, et al. Identification of patients with documented pathologic complete response in the breast after neoadjuvant chemotherapy for omission of axillary surgery. JAMA. 2017;152(7):665–70.
11. Grasishar WJ, Anderson BO, Abraham J, et al. Breast cancer, Version 2. 2018 Featured Updates to the NCCN Guidelines. National Comprehensive Cancer Network. Available at: http://www.NCCN.org. Accessed 5 Oct 2018.
12. Curigliano G, Burstein H, Winer E, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer. Ann Oncol. 2017;28: 1700–1712.
13. Pilewskie M, Zabor E, Mamtani A, et al. The optimal treatment plan to avoid axillary lymph node dissection in early-stage breast cancer patients differs by surgical strategy and tumor subtype. Ann Surg Oncol. 2017;24(12):3527–33.
14. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011;305:569–75.
15. Mila D, Geertjan T, Marieke ES, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS):a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014;15(12):1303–10.
16. Krag DN, Anderson SJ, Julian TB. et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010; 11 (10): 908–909.