中国临床研究 Chin J Clin Res, March 2024, Vol.37, No.3
Cite as: Duan S, Aisimutula D, Wang HY, et al. Influencing factors of pathological complete remission in triple-negative breast cancer with neoadjuvant chemotherapy [J]. Chin J Clin Res, 2024,37(3):354-358.
DOI: 10.13429/j.cnki.cjcr.2024.03.006

Influencing factors of pathological complete remission in triple-negative breast cancer with neoadjuvant chemotherapy

DUAN Shuai, Dilimulati Aisimutula, WANG Haiyan, GUO Chenming

Department of Breast Surgery, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang 830054, China

Corresponding author: *GUO Chenming*, E-mail: gcm_xjmu@yeah.net

Abstract: Objective To analyze the clinical and pathological factors affecting pathological complete response (pCR) of triple-negative breast cancer (TNBC) with neoadjuvant chemotherapy (NAC). **Methods** A retrospective analysis was conducted in 78 TNBC patients treated with NAC and surgery in The First Affiliated Hospital of Xinjiang Medical University from January 2018 to September 2023. The patients were divided into pCR group (n=28) and non-pCR group (n=50) based on whether they had achieved pCR or not. Logistic regression analysis was used to investigate the clinical and pathological factors affecting pCR. The pCR rate and incidence of adverse reactions after NAC between TP regimen (taxane + platinum) and TAC regimen (taxane + anthracycline + cyclophosphamide) were compared. **Results** The overall pCR rate was 35.9%. There were statistically significant differences between the two groups of patients in tumor diameter, chemotherapy cycle, chemotherapy regimen, paclitaxel type, human epidermal growth factor receptor 2 (HER-2) expression, Ki-67 expression, and androgen receptor (AR) positive expression (P>0.05). Multivariate logistic regression analysis showed that tumor diameter ≤ 3cm was an independent favorable factor of pCR (OR=4.191, *95%CI*:1.246-14.094, P=0.021), and AR positive expression was an independent unfavorable factor of pCR (OR=0.124, *95%CI*:0.020-0.784, P=0.027). In addition, the pCR rate of the TP regimen was significantly better than that of the TAC regimen [54.8% (17/31) *vs* 28.1% (9/32), χ^2=4.636, P=0.031], and there was no significant difference in the incidence of adverse reactions between two groups (P>0.05). **Conclusion** TP or TAC regimen and albumin bound paclitaxel in NAC for TNBC is beneficial for achieving pCR status, but the pCR rate of TP regimen is better than that of TAC regimen, and the incidence of adverse reactions is comparable. The pCR rate is higher for tumors ≤ 3cm, while low expression of Her-2, Ki-67, or AR indicates a lower pCR rate. AR positive expression is an independent negative predictor of pCR.

Keywords: Triple-negative breast cancer; Neoadjuvant chemotherapy; Pathological complete response; Clinical pathological features; Paclitaxel; Androgen receptors; Human epidermal growth factor receptor 2
Fund Program: National Natural Science Foundation of China Regional Program (32260186)

Triple negative breast cancer (TNBC) is a heterogeneous tumor characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) amplification. It accounts for approximately 15% to 20% of all breast cancers. TNBC tumors are typically larger, have higher histological grades, and often involve lymph nodes, making them biologically more aggressive. Compared with other subtypes, TNBC has a shorter response duration to treatment, a higher risk of local and distant recurrence, faster progression, and the worst survival outcomes. Currently, in order to improve long-term efficacy, effective treatment strategies for TNBC focus on neoadjuvant chemotherapy (NAC) to achieve down-staging and assess chemotherapy response. Pathological complete response (pCR) is still considered an important alternative marker for good treatment response, lower tumor recurrence or metastasis, and higher overall survival rate [1]. However, only 30% to 50% of TNBC achieve pCR after receiving NAC, leaving a significant portion of patients who endure toxicities associated with standard chemotherapy without achieving favorable treatment outcomes [2]. Therefore, it is crucial to predict NAC efficacy based on clinical characteristics and preoperative pathological information to guide the selection of initial treatment regimens for stage II-III TNBC. However, there are limited reports on related studies. In this study, we retrospectively collected and analyzed clinical and pathological characteristics, treatment regimens, and other relevant information of TNBC patients who underwent NAC and surgical treatment, to identify factors influencing pCR and provide reference for the selection of initial treatment regimens for TNBC.

1 Materials and Methods

1.1 General Data

Clinical pathological data, and treatment plans were collected from TNBC patients who underwent NAC and surgical treatment at the Breast Surgery Department of The First Affiliated Hospital of Xinjiang Medical University from January 2018 to September 2023.

1.1.1 Inclusion criteria

(1) Age ≥ 18 years old;

(2) Diagnosed as invasive ductal carcinoma of the breast by fine-needle aspiration biopsy;

(3) No amplified expression of ER, PR, and HER-2 confirmed by immunohistochemistry (IHC);

(4) NAC with a chemotherapy cycle of ≥ 4 cycles;

(5) Underwent standardized surgical treatment after NAC;

(6) Completed clinical and pathological data.

1.1.2 Exclusion criteria

(1) Non TNBC or metastatic breast cancer;

(2) NAC<4 cycles;

(3) Incomplete clinical and pathological data.

ER and PR non-amplification were defined as IHC<1% nuclear staining. HER-2 non-amplification was defined as IHC0, IHC1+, and IHC2+, or negative *in situ* hybridization detection. pCR was defined as the absence of invasive carcinoma or only *in situ* carcinoma with negative regional lymph nodes in the primary breast lesion. According to the inclusion and exclusion criteria, a total of 78 TNBC patients were included in this study. After NAC, 28 patients reached pCR and were divided into the pCR group, with a pCR rate of 35.9% (28/78). Fifty patients did not reach pCR and were divided into the non pCR group. Among the 28 patients with pCR, 17 patients (60.7%) were treated with TP regimen, 9 patients (32.2%) were treated with TAC regimen, and 2 patients (7.1%) were treated with other regimens. This study was approved by the hospital ethics committee (Ethics approval number: 230714-07)

1.2 Treatment method

First, the patients were diagnosed as breast cancer by imaging and physical examination. Then, IHC status was determined by fine-needle aspiration and core needle biopsy. If there was abnormal enlargement of axillary lymph nodes, fine-needle aspiration should be performed. At the same time, metal titanium clips should be placed in the breast tumor lesion and suspected positive axillary lymph nodes to mark them. After being diagnosed with TNBC, systemic examination should be performed to determine the presence of distant organ metastasis. Patients with locally advanced stage, tumor size>2cm, lymph node metastasis, breast conserving intention, or other high-risk factors should be included for NAC treatment. According to the guidelines, TP regimen (taxane+platinum) or TAC regimen (taxane+anthracycline+cyclophosphamide) was the primary choice for chemotherapy regimen, and other regimens should be selected based on patient adaptability, drug accessibility, and specific circumstances. During the NAC process, the chemotherapy effect is evaluated every 2 cycles according to the RECIST evaluation criteria. After 4 cycles, if the chemotherapy effect was still poor, surgical treatment should be implemented after multidisciplinary discussions on breast tumors. If the chemotherapy effect was significant, surgery should be performed after 6 cycles of chemotherapy. IHC was conducted on postoperative pathological specimens and relevant information of this study was recorded.

1.3 Observation indicators

(1) General clinical indicators: patient's age, body mass index (BMI), menstrual status, chemotherapy regimen, paclitaxel type, chemotherapy cycle, tumor size, and axillary lymph node status at initial diagnosis.

(2) Pathological indicators: histological grading, neurovascular invasion, expression status of HER-2, Ki-67, androgen receptor (AR), GATA3, CK5/6, and whether pCR has been achieved.

(3) pCR rate.

(4) Adverse reaction indicators: bone marrow suppression, liver and kidney dysfunction, and myocardial enzyme abnormalities after NAC.

1.4 Statistical methods

SPSS 26.0 was used for statistical analysis. Normal distribution measurement data was represented by $\bar{x} \pm s$, and *t*-test was used to compare between two groups. Count data was represented as case (%), and chi-square test or corrected chi-square test was used to compare the differences between two groups. Multivariate analysis was conducted using binary logistic regression analysis. Significance level: α=0.05, two-sided test.

2 Results

2.1 Univariate analysis

Tumor diameter ≤ 3cm, TP or TAC regimen, albumin bound paclitaxel and 6-cycle NAC were significantly correlated with achieving pCR status (P<0.05). The low expression of HER-2, low expression of Ki-67, or positive expression of AR were significantly correlated with non pCR status (P<0.05). However, there was no significant correlation between age, BMI, menstrual status, histological grading, axillary lymph node status at initial diagnosis, neurovascular invasion, GATA3 and CK5/6 expression status, and whether pCR status was achieved after NAC (P>0.05). **See Table 1.**

2.2 The pCR rate and incidence of adverse reactions in TP and TAC

NAC patients with TP regimen had a higher pCR rate than that in patients with TAC regimen (54.8% *vs* 28.1%, P<0.05). However, there was no statistically significant difference in the incidence of adverse reactions such as bone marrow suppression, liver and kidney dysfunction, and myocardial enzyme abnormalities between the two regimens (P>0.05). **See Table 2.**

2.3 Multivariate analysis

Tumor diameter ≤ 3cm was an independent favorable factor for achieving pCR status after NAC (*P*=0.021), while AR positive expression was an independent unfavorable for pCR after NAC (*P*=0.027). **See Table 3.**

Tab.1 Univariate analysis of pCR after NAC in 78 cases of TNBC [case(%)]

Item	pCR group (*n*=28)	non-pCR group (*n*=50)	*t*/*χ2* value	*P* value
Age (year, $\bar{x}\pm s$)	48.9±7.1	50.0±10.3	0.515	0.608
BMI (kg/m², $\bar{x}\pm s$)	27.5±5.1	26.8±4.6	0.639	0.525
Menstrual Status			0.509	0.475
Menopause	10(35.7)	22(44.0)		
Non-menopause	18(64.3)	28(56.0)		
Tumor Diameter			4.237	0.040
≤3 cm	10(35.7)	20(40.0)		
>3 cm	18(64.3)	30(60.0)		
Organizational Classification			0.446	0.504
Ⅱ	8(28.6)	18(36.0)		
Ⅲ	20(71.4)	32(64.0)		
Axillary Lymph			1.454	0.228
Positive	14(50.0)	32(64.0)		
Negative	14(50.0)	18(36.0)		
Neurovascular Invasion	2(7.1)	7(14.0)	0.291	0.589[a]
Chemotherapy Regimen			4.109	0.043
TAC/TP	26(92.9)	37(74.0)		
Others	2(7.1)	13(26.0)		
Type of Paclitaxel			3.974	0.046
Albumin bound type	22(78.6)	28(56.0)		
Others	6(21.4)	22(44.0)		
Chemotherapy Cycle			5.354	0.021
6	22(78.6)	26(52.0)		
4 or 5	6(21.4)	24(48.0)		
HER-2 Low Expression	9(32.1)	30(60.0)	5.571	0.018
Ki-67 Expression			4.789	0.029
≤30%	2(7.1)	14(28.0)		
>30%	26(92.9)	36(72.0)		
AR+	2(7.1)	18(36.0)	7.839	0.005
GATA3+	14(50.0)	22(44.0)	0.260	0.610
CK5/6+	11(39.3)	21(42.0)	0.055	0.815

Tab.2 pCR and adverse reactions after NAC of TP or TAC [case (%)]

Note:[a] represents corrected chi-square test

Item	TP(n=31)	TAC(n=32)	$t/\chi 2$ value	P value
Age (year, $\bar{x}\pm s$)	48.9±6.8	47.8±11.4	0.478	0.635
BMI (kg/m^2, $\bar{x}\pm s$)	27.4±5.4	26.1±4.5	1.036	0.304
Menstrual Status			0.176	0.674
Menopause	11(35.5)	13(40.6)		
Non-menopause	20(64.5)	19(59.4)		
Type of Paclitaxel			0.130	0.718
Albumin bound type	22(71)	24(75)		
Others	9(29)	8(25)		
Chemotherapy Cycle				
6	23(74.2)	22(68.8)	0.229	0.633
4 or 5	8(25.8)	10(21.2)		
pCR Status			4.636	0.031
pCR	17(54.8)	9(28.1)		
non-pCR	14(45.2)	23(71.8)		
Adverse Reaction				
Bone marrow suppression	6(19.4)	8(25.0)	0.290	0.590
Abnormal liver and kidney function	7(22.6)	10(31.3)	0.601	0.438
Abnormal myocardial enzymes	4(12.9)	6(18.8)	0.084	0.772[a]

Tab.3 Multivariate analysis of neoadjuvant chemotherapy pCR in 78 cases of TNBC

Item	*B*	*SE*	*Wald*	*P*	*OR*	*95%CI*
Tumor Diameter≤3cm	1.433	0.619	5.362	0.021	4.191	1.246-14.094
TP/TAC	0.729	0.945	0.596	0.440	2.074	0.326-13.211
Albumin Bound Paclitaxel	0.945	0.700	1.823	0.177	2.573	0.653-10.142
6 Chemotherapy Cycles	1.140	0.660	2.983	0.084	3.126	0.858-11.393
HER-2 Low Expression	-0.693	0.606	1.309	0.253	0.500	0.153-1.639
Ki-67 Low Expression	-0.676	0.921	0.538	0.463	0.509	0.084-3.094
AR+	-2.089	0.942	4.919	0.027	0.124	0.020-0.784

3 Discussion

Currently, anthracycline-based and taxane-based regimens remain the standard chemotherapy for TNBC, with only 30% to 50% of TNBC patients achieving pCR [3]. However, recent studies using platinum-based chemotherapy challenge the standard regimens and suggest that incorporating platinum agents into the chemotherapy regimen can significantly improve the pCR rate, especially for TNBC with BRCA mutations [4]. Studies have also shown that the TP combination of paclitaxel and carboplatin also achieve good pCR in NAC for patients with TNBC [5]. Therefore, based on clinical practice, exploring the actual clinical effects of different chemotherapy regimens is of great significance for optimizing NAC regimens to further improve pCR rates and improve the long-term prognosis of TNBC.

The pCR rate of this study was 35.9%, with 92.9% of NAC regimens using TP and TAC, and 78.6% using albumin bound paclitaxel. Moreover, pCR patients mainly came from the TP group, who used albumin bound paclitaxel combined with platinum, accounting for 60.7%, indicating that the pCR rate of the TP regimen was significantly better than that of the TAC regimen (54.8% *vs* 28.1%). Similar findings were observed in the NeoCART trial, where the combination of nab-paclitaxel

and carboplatin demonstrated a higher pCR rate compared to doxorubicin+ cyclophosphamide + nab-paclitaxel (61.4% *vs* 38.6%) [6]. Additionally, this study also confirmed the significant role of albumin-bound paclitaxel in increasing the pCR rate in NAC. Therefore, compared to the regimen of standard paclitaxel combined with anthracycline drugs without platinum, albumin bound paclitaxel combined with platinum without anthracycline drugs may be a promising alternative, especially for TNBC with contraindications to anthracycline drugs [7]. Furthermore, based on this study's results, for TNBC patients with relatively small breast volume, tumor size of approximately 2-3 cm, and axillary lymph node metastasis at initial diagnosis, who also desire breast conservation, the placement of titanium clips during initial biopsy for marking the tumor and evaluating the effect of NAC can help improve and optimize the surgical approach, which is important for increasing breast-conserving rates and reducing physical and psychological trauma for patients. In terms of chemotherapy adverse reactions, studies such as the (CALGB) 40603 [8], BRIGHTNess [9], GeparSixto [2], and meta-analysis [10] have all demonstrated the significant role of adding platinum agents to standard regimens in improving the pCR rate. It is believed that adding platinum drugs in anthracycline and paclitaxel-based regimens should be considered the preferred backbone of NAC. However, the addition of platinum usually leads to an increased risk of hematological toxicity, and the increased pCR rate often comes at the cost of more adverse reactions, affecting the safety and orderliness of chemotherapy. TP regimen not only has a significant effect on improving the pCR rate, but also has a similar incidence of adverse reactions to the TAC regimen. Therefore, the relative low toxicity of the TP regimen may be another significant advantage that it can eliminate anthracycline chemotherapy drugs.

In addition, this study used 30% as the cutoff value for Ki-67 high expression. Univariate analysis showed that pCR group had higher rate of Ki-67>30%, and Ki-67<30% indicated poor pCR effects. Therefore, low Ki-67 expression is considered a negative predictive indicator of pCR. Many studies have validated these findings [11-16], although some studies have reported no statistically significant difference in Ki-67 expression between pCR and non-pCR groups [17]. On the one hand, different studies have used different criteria as the threshold for high expression of Ki-67, but the main reason may be that using Ki-67 alone is not sufficient to predict pCR, and other markers are needed for robust prediction models [14]. Based on this, this study also found that low expression of HER-2 was not conducive to achieving pCR status. Relevant studies [14] reported the predictive effect of low expression of HER-2 was significant in the TP regimen of albumin bound paclitaxel combined with platinum, and the conclusion was similar to this study. The reason may be that the immune response of the HER-2 low expression subgroup resulted in a significant decrease in pCR rate [14,18]. Besides, it was reported that the expression rate of AR in TNBC is about 10% to 50% [19], with a probability of 25.6% in this study. However, the AR positive expression rate was only 7.1% in the pCR group and 36% in the non pCR group, with significant differences. In the multivariate analysis, AR positive expression was an independent negative predictive indicator of pCR, indicating that AR positive expression reduced the opportunity to achieve pCR. Studies have found that AR positive TNBC has a reduced response to NAC [20-21] and is significantly associated with lower pCR rates [1,22-23]. The reason may be chemotherapy resistance caused by lower proliferation rates [23], and AR may be involved in tumor cell immune evasion, leading to lower immune responses and thus reducing the chance of achieving pCR [24].

In summary, the combination of albumin bound paclitaxel and platinum-based TP regimen significantly improved the pCR rate of TNBC, which may be a promising alternative to NAC that eliminates anthracycline drugs and has relatively low toxicity. Especially for TNBC with relatively small breast volume, clear breast conserving intention, tumor diameter of 2-3 cm and positive axillary lymph nodes, it can improve the surgical approach. In addition, low expression of Her-2, Ki-67, or AR positive expression all indicate a lower pCR rate. The combined evaluation of the three indicators is more effective in predicting pCR than a single indicator, and has certain significance for the selection of initial TNBC plans. However, the sample size of this study is small, and the single center pathological review mechanism and retrospective study nature have caused bias in the results, requiring more research to verify.

Conflict of interest: None

References

[1] Lee EG, Lee DE, Kim HH, et al. Androgen receptor as a predictive marker for pathologic complete response in hormone receptor–positive and HER-2–negative breast cancer with neoadjuvant chemotherapy[J]. Cancer Res Treat, 2023, 55(2): 542-550.

[2] Li ZY, Zhang Z, Cao XZ, et al. Platinum-based neoadjuvant chemotherapy for triple-negative breast cancer: a systematic review and meta-analysis[J]. J Int Med Res, 2020, 48(10): 030006052096434.

[3] Lee JS, Yost SE, Yuan Y. Neoadjuvant treatment for triple negative breast cancer: recent progresses and challenges[J]. Cancers, 2020, 12(6): 1404.

[4] Byrski T, Huzarski T, Dent R, et al. Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients[J]. Breast Cancer Res Treat, 2014, 147(2): 401-405.

[5] Holanek M, Selingerova I, Bilek O, et al. Neoadjuvant chemotherapy of triple-negative breast cancer: evaluation of early clinical response, pathological complete response rates, and addition of platinum salts benefit based on real-world evidence[J]. Cancers, 2021, 13(7): 1586.

[6] Zhang LL, Wu ZY, Li J, et al. Neoadjuvant docetaxel plus carboplatin vs epirubicin plus cyclophosphamide followed by docetaxel in triple-negative, early-stage breast cancer (NeoCART): results from a multicenter, randomized controlled, open-label phase II trial[J]. Int J Cancer, 2022, 150(4): 654-662.

[7] Yu YS, Zhang J, Lin YX, et al. Efficacy and safety of neoadjuvant therapy for triple-negative breast cancer: a Bayesian network meta-analysis[J]. Expert Rev Anticancer Ther, 2022, 22(10): 1141-1151.

[8] Shepherd JH, Ballman K, Polley MY C, et al. CALGB 40603 (alliance): long-term outcomes and genomic correlates of response and survival after neoadjuvant chemotherapy with or without carboplatin and bevacizumab in triple-negative breast cancer[J]. J Clin Oncol, 2022, 40(12): 1323-1334.

[9] Geyer CE, Sikov WM, Huober J, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial[J]. Ann Oncol, 2022, 33(4): 384-394.
[10] Poggio F, Tagliamento M, Ceppi M, et al. Adding a platinum agent to neoadjuvant chemotherapy for triple-negative breast cancer: the end of the debate[J]. Ann Oncol, 2022, 33(3): 347-349.
[11] Nakashoji A, Matsui A, Nagayama A, et al. Clinical predictors of pathological complete response to neoadjuvant chemotherapy in triple-negative breast cancer[J]. Oncol Lett, 2017, 14(4): 4135-4141.
[12] Sivina E, Blumberga L, Purkalne G, et al. Pathological complete response to neoadjuvant chemotherapy in triple negative breast cancer - single hospital experience[J]. Hered Cancer Clin Pract, 2023, 21(1): 4.
[13] Guestini F, Ono K, Miyashita M, et al. Impact of Topoisomerase IIα, PTEN, ABCC1/MRP1, and KI67 on triple-negative breast cancer patients treated with neoadjuvant chemotherapy[J]. Breast Cancer Res Treat, 2019, 173(2): 275-288.
[14] Gluz O, Kolberg-Liedtke C, Prat A, et al. Efficacy of deescalated chemotherapy according to PAM50 subtypes, immune and proliferation genes in triple-negative early breast cancer: primary translational analysis of the WSG-ADAPT-TN trial[J]. Int J Cancer, 2020, 146(1): 262-271.
[15] Zuo K, Yuan XY, Liang XZ, et al. qRT-PCR-based DNA homologous recombination-associated 4-gene score predicts pathologic complete response to platinum-based neoadjuvant chemotherapy in triple-negative breast cancer[J]. Breast Cancer Res Treat, 2022, 191(2): 335-344.
[16] Toss A, Venturelli M, Civallero M, et al. Predictive factors for relapse in triple-negative breast cancer patients without pathological complete response after neoadjuvant chemotherapy[J]. Front Oncol, 2022, 12: 1016295.
[17] Van Bockstal MR, Noel F, Guiot Y, et al. Predictive markers for pathological complete response after neo-adjuvant chemotherapy in triple-negative breast cancer[J]. Ann Diagn Pathol, 2020, 49: 151634.
[18] van den Ende NS, Smid M, Timmermans A, et al. HER2-low breast cancer shows a lower immune response compared to HER2-negative cases[J]. Sci Rep, 2022, 12(1): 12974.
[19] Gerratana L, Basile D, Buono G, et al. Androgen receptor in triple negative breast cancer: a potential target for the targetless subtype[J]. Cancer Treat Rev, 2018, 68: 102-110.
[20] Echavarria I, López-Tarruella S, Picornell A, et al. Pathological response in a triple-negative breast cancer cohort treated with neoadjuvant carboplatin and docetaxel according to lehmann's refined classification[J]. Clin Cancer Res, 2018, 24(8): 1845-1852.
[21] Santonja A, Sánchez-Muñoz A, Lluch A, et al. Triple negative breast cancer subtypes and pathologic complete response rate to neoadjuvant chemotherapy[J]. Oncotarget, 2018, 9(41): 26406-26416.
[22] Witzel I, Loibl S, Wirtz R, et al. Androgen receptor expression and response to chemotherapy in breast cancer patients treated in the neoadjuvant TECHNO and PREPARE trial[J]. Br J Cancer, 2019, 121(12): 1009-1015.
[23] Mohammed AA, Elsayed FM, Algazar M, et al. Neoadjuvant chemotherapy in triple negative breast cancer: correlation between androgen receptor expression and pathological response[J]. Asian Pac J Cancer Prev, 2020, 21(2): 563-568.
[24] Wang Y, Li JJ, Li JJ, et al. An enhancer-based analysis revealed a new function of androgen receptor in tumor cell immune evasion[J]. Front Genet, 2020, 11: 595550.

Submission received: 2023-12-07 / **Revised:**2024-01-29

·论　著·

三阴性乳腺癌新辅助化疗病理完全缓解的影响因素

段帅，　地力木拉提·艾斯木吐拉，　王海燕，　郭晨明
新疆医科大学第一附属医院乳腺外科，新疆 乌鲁木齐 830054

摘要：目的　分析影响三阴性乳腺癌（TNBC）新辅助化疗（NAC）后病理完全缓解（pCR）的临床与病理因素。**方法**　收集 2018 年 1 月至 2023 年 9 月于新疆医科大学第一附属医院行 NAC 及手术治疗的 78 例 TNBC 患者的临床与病理资料行回顾性分析，按其是否达到 pCR 分为 pCR 组（$n=28$）和 non-pCR 组（$n=50$），采用 logistic 回归分析影响 pCR 的临床与病理因素，并比较 TP 方案（紫杉类+铂类）与 TAC 方案（紫杉类+蒽环类+环磷酰胺）NAC 后 pCR 率和不良反应发生率。**结果**　总体 pCR 率为 35.9%，两组患者在瘤体直径、化疗周期、化疗方案、紫杉醇类型、人类表皮生长因子受体 2（HER-2）表达、Ki-67 表达及雄激素受体（AR）阳性表达方面差异均具有统计学意义（$P<0.05$）。多因素分析显示，瘤体直径≤3 cm 是 pCR 的独立有利因素（$OR=4.191$，95%CI：1.246～14.094，$P=0.021$），AR 阳性表达是 pCR 的独立不利因素（$OR=0.124$，95%CI：0.020～0.784，$P=0.027$）。另外，TP 方案的 pCR 率显著优于 TAC 方案[54.8%（17/31）*vs* 28.1%（9/32），$\chi^2=4.636$，$P=0.031$]，且两者的不良反应发生率差异无统计学意义（$P>0.05$）。**结论**　TNBC 新辅助化疗采用 TP 或 TAC 方案并选用白蛋白结合型紫杉醇均有利于达到 pCR 状态，但 TP 方案的 pCR 率优于 TAC 方案，且不良反应发生率相当。而瘤体直径≤3 cm 的 pCR 率更高，HER-2 低表达，或 Ki-67 低表达，或 AR 阳性表达均预示较低的 pCR 率，且 AR 阳性表达是 pCR 的独立不利影响因素。

关键词：三阴性乳腺癌；新辅助化疗；病理完全缓解；临床病理特征；紫杉醇；雄激素受体；人类表皮生长因子受体 2
中图分类号：R737.9　**文献标识码：**A　**文章编号：**1674-8182(2024)03-0354-05

Influencing factors of pathological complete response in triple-negative breast cancer with neoadjuvant chemotherapy

DUAN Shuai, Dilimulati Aisimutula, WANG Haiyan, GUO Chenming
Department of Breast Surgery, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang 830054, China
Corresponding author: GUO Chenming, E-mail: gcm_xjmu@yeah.net

Abstract: Objective　To analyze the clinical and pathological factors affecting pathological complete response (pCR) of triple-negative breast cancer (TNBC) after neoadjuvant chemotherapy (NAC). **Methods**　A retrospective analysis was conducted in 78 TNBC patients treated with NAC and surgery in The First Affiliated Hospital of Xinjiang Medical University from January 2018 to September 2023. The patients were divided into pCR group ($n=28$) and non-pCR group ($n=50$) based on whether they had achieved pCR or not. Logistic regression analysis was used to investigate the clinical and pathological factors affecting pCR. The pCR rate and incidence of adverse reactions after NAC between TP regimen (taxane+platinum) and TAC regimen (taxane+anthracycline+cyclophosphamide) were compared. **Results**　The overall pCR rate was 35.9%. There were statistically significant differences between the two groups of patients in tumor diameter, chemotherapy cycle, chemotherapy regimen, paclitaxel type, human epidermal growth factor receptor 2 (HER-2) expression, Ki-67 expression, and androgen receptor (AR) positive expression ($P>0.05$). Multivariate logistic regression analysis showed that tumor diameter ≤ 3 cm was an independent favorable factor of pCR ($OR=4.191$, 95%CI: 1.246-14.094, $P=0.021$), and AR positive expression was an independent unfavorable factor of pCR ($OR=0.124$, 95%CI: 0.020-0.784, $P=0.027$). In addition, the pCR rate of the TP regimen was significantly better than that

DOI: 10.13429/j.cnki.cjcr.2024.03.006
基金项目：国家自然科学基金地区项目（32260186）
通信作者：郭晨明，E-mail：gcm_xjmu@yeah.net
出版日期：2024-03-20

QR code for English version

of the TAC regimen [54.8%(17/31) *vs* 28.1%(9/32), χ^2=4.636, P=0.031], and there was no significant difference in the incidence of adverse reactions between two groups (P>0.05). **Conclusion** TP or TAC regimen and albumin bound paclitaxel in NAC for TNBC is beneficial for achieving pCR status, but the pCR rate of TP regimen is better than that of TAC regimen, and the incidence of adverse reactions is comparable. The pCR rate is higher for tumor diameter≤3 cm, while low expression of HER-2, Ki-67, or AR indicates a lower pCR rate. AR positive expression is an independent unfavorable factor of pCR.

Keywords: Triple-negative breast cancer; Neoadjuvant chemotherapy; Pathological complete response; Clinical pathological features; Paclitaxel; Androgen receptors; Human epidermal growth factor receptor 2

Fund program: Regional Program of National Natural Science Foundation of China (32260186)

三阴性乳腺癌(triple-negative breast cancer, TNBC)是缺乏雌激素受体(estrogen receptor, ER)、孕激素受体(progesterone recrptor, PR)和人表皮生长因子受体 2(human epidermal growth factor receptor 2, HER-2)扩增的异质性肿瘤集合,约占所有乳腺癌的 15%~20%。TNBC 瘤体通常较大,组织学分级较高,多合并淋巴结受累,生物学上更具侵袭性。与其他亚型相比,对治疗的反应持续时间短,局部和远处复发的风险更高,进展更快,生存结果最差。目前,为降期缩瘤、提升手术方式和获取化疗反应信息制定有效治疗方案以改善远期疗效,在术前行新辅助化疗(neoadjuvant chemotherapy, NAC)是 TNBC 常见的治疗策略。病理完全缓解(pathological complete response, pCR)目前依然被认为是对治疗反应良好,肿瘤较少复发、转移和总生存率较高的重要替代标志[1],但只有 30%~50%的 TNBC 在接受 NAC 治疗后能实现 pCR,仍有大部分患者必须忍受与标准化疗相关的毒性却无法获得良好的疗效[2]。因此,通过临床特征和术前穿刺所得的病理信息去预测 NAC 疗效,对指导Ⅱ~Ⅲ期 TNBC 初始治疗方案的选择具有重要的意义。目前相关研究报道较少,本研究通过回顾性收集并分析既往纳入 NAC 和手术治疗的 TNBC 患者的临床与病理特征、治疗方案等信息以明确影响 pCR 的相关因素,为 TNBC 初始治疗方案的选择提供一定参考。

1　资料与方法

1.1　一般资料　收集 2018 年 1 月至 2023 年 9 月就诊于新疆医科大学第一附属医院乳腺外科行 NAC 和手术治疗的 TNBC 患者的临床与病理资料,以及治疗方案等信息。

1.1.1　纳入标准　(1) 年龄≥18 岁;(2) 经空心针穿刺明确诊断为乳腺浸润性导管癌;(3) ER、PR、HER-2 经免疫组化证实均无扩增表达;(4) 行 NAC 且化疗周期≥4 个周期;(5) NAC 后行规范手术治疗;(6) 临床与病理资料完整。

1.1.2　排除标准　(1) 非 TNBC 或转移性乳腺癌;(2) NAC<4 个周期;(3) 临床与病理资料不完整。

ER 和 PR 无扩增定义为免疫组织化学检测(immunohistochemistry, IHC)<1%细胞核着色。HER-2 无扩增定义为 IHC0、IHC1+、IHC2+/原位杂交检测阴性。pCR 定义为乳腺原发灶无浸润性癌或仅有原位癌且区域淋巴结阴性。依据纳入与排除标准本研究共计纳入符合标准的 TNBC 患者 78 例,NAC 后有 28 例达到 pCR 状态,pCR 率为 35.9%(28/78),划分为 pCR 组;未达到 pCR 50 例,划分为 non-pCR 组。28 例 pCR 患者中采用 TP 方案 17 例,占比 60.7%(17/28),采用 TAC 方案 9 例,占比 32.2%(9/28),采用其他方案 2 例,占比 7.1%(2/28)。本研究经医院伦理委员会批准通过(伦理审批号:230714-07)

1.2　治疗方法　影像学及体格检查初步诊断为乳腺癌者,行细针穿刺定性和空心针穿刺明确 IHC 状态,如合并腋窝淋巴结异常肿大一并行细针穿刺定性,同时于乳腺肿瘤病灶和可疑阳性腋窝淋巴结置入金属钛夹予以标记。穿刺确诊为 TNBC 后完善全身检查明确有无远处脏器转移,并将局部晚期,或瘤体直径>2 cm、或合并淋巴结转移、或有保乳意愿、或合并其他高危因素的患者纳入 NAC。依据指南共识化疗方案,以 TAC(紫杉类+蒽环类+环磷酰胺)或 TP(紫杉类+铂类)方案为首要选择,并结合患者适应性、药物可及性和具体情况选择其他方案。NAC 过程中依据 RECIST 评价标准每 2 个周期评估化疗效果,4 个周期后化疗效果仍不佳者经乳腺肿瘤多学科讨论后实施手术治疗;如化疗效果显著则至化疗 6 个周期后实施手术。术后病理标本行免疫组化检测并记录本研究相关信息。

1.3　观察指标　包括患者的年龄、身体质量指数(body mass index, BMI)、月经状态、化疗方案、选用紫杉醇类型、化疗周期、瘤体大小、初诊穿刺腋窝淋巴结状态等一般临床指标;组织学分级、神经脉管侵袭情况、HER-2、Ki-67、雄激素受体(androgen receptor, AR)、GATA3、CK5/6 表达状态,以及是否达到 pCR

等病理指标;并比较 TP 方案与 TAC 方案 NAC 后的 pCR 率和骨髓抑制、肝肾功能异常、心肌酶异常等不良反应指标。

1.4　统计学方法　使用的统计软件为 SPSS 26.0。符合正态分布的计量资料以 $\bar{x}\pm s$ 表示,两组间比较采用成组 t 检验。计数资料以例(%)表示,两组间差异采用 χ^2 检验,不满足条件的采用校正 χ^2 检验。多因素分析采用二元 logistic 回归分析。研究整体选取检验水准 α 为双侧的 0.05。

2　结　果

2.1　单因素分析结果　瘤体直径≤3 cm、采用 TP 或 TAC 化疗方案、选用白蛋白结合型紫杉醇及 6 周期 NAC,均与达到 pCR 显著相关(P<0.05);HER-2 低表达、或 Ki-67 低表达、或 AR 阳性表达,均与未达到 PCR 相关(P<0.05)。而年龄、BMI、月经状态、组织学分级、初诊穿刺腋窝淋巴结状态、神经脉管侵犯情况、GATA3 和 CK5/6 表达状态,与 NAC 后是否达到 pCR 无显著相关性,差异无统计学意义(P>0.05)。详见表 1。

表 1　78 例 TNBC 患者 NAC 后 pCR 的单因素分析　[例(%)]

Tab. 1　Univariate analysis of pCR after NAC in 78 cases of TNBC　[case(%)]

项目	pCR 组 (n=28)	non-pCR 组 (n=50)	t/χ^2 值	P 值
年龄(岁, $\bar{x}\pm s$)	48.9±7.1	50.0±10.3	0.515	0.608
BMI(kg/m^2, $\bar{x}\pm s$)	27.5±5.1	26.8±4.6	0.639	0.525
月经状态				
绝经	10(35.7)	22(44.0)	0.509	0.475
未绝经	18(64.3)	28(56.0)		
瘤体直径				
≤3 cm	10(35.7)	20(40.0)	4.237	0.040
>3 cm	18(64.3)	30(60.0)		
组织学分级				
Ⅱ级	8(28.6)	18(36.0)	0.446	0.504
Ⅲ级	20(71.4)	32(64.0)		
穿刺腋窝淋巴结状态				
阳性	14(50.0)	32(64.0)	1.454	0.228
阴性	14(50.0)	18(36.0)		
神经脉管侵犯	2(7.1)	7(14.0)	0.291	0.589[a]
化疗方案				
TAC/TP	26(92.9)	37(74.0)	4.109	0.043
其他方案	2(7.1)	13(26.0)		
紫杉醇类型				
白蛋白结合型	22(78.6)	28(56.0)	3.974	0.046
其他类型	6(21.4)	22(44.0)		
化疗周期				
6	22(78.6)	26(52.0)	5.354	0.021
4 或 5	6(21.4)	24(48.0)		
HER-2 低表达	9(32.1)	30(60.0)	5.571	0.018
Ki-67 表达状态				
≤30%	2(7.1)	14(28.0)	4.789	0.029
>30%	26(92.9)	36(72.0)		
AR 阳性	2(7.1)	18(36.0)	7.839	0.005
GATA3 阳性	14(50.0)	22(44.0)	0.260	0.610
CK5/6 阳性	11(39.3)	21(42.0)	0.055	0.815

注:[a] 表示连续校正 χ^2 检验。

2.2　TP 和 TAC 的 pCR 率和不良反应发生情况　NAC 采用 TP 方案的患者 pCR 率显著优于 TAC 方案(54.8% *vs* 28.1%),差异有统计学意义(P<0.05)。而两种方案在骨髓抑制、肝肾功能异常及心肌酶异常等不良反应发生率方面差异无统计学意义(P>0.05)。见表 2。

2.3　多因素 logistic 分析结果　瘤体直径≤3 cm 是 NAC 后达到 pCR 的独立有利因素(P=0.021),AR 阳性表达是 NAC 后达到 pCR 的独立不利因素(P=0.027)。见表 3。

表 2　TP 和 TAC 方案 NAC 后 pCR 和不良反应情况　[例(%)]

Tab. 2　pCR and adverse reactions after NAC of TP or TAC　[case(%)]

项目	TP 方案 (n=31)	TAC 方案 (n=32)	t/χ^2 值	P 值
年龄(岁, $\bar{x}\pm s$)	48.9±6.8	47.8±11.4	0.478	0.635
BMI(kg/m^2, $\bar{x}\pm s$)	27.4±5.4	26.1±4.5	1.036	0.304
月经状态				
绝经	11(35.5)	13(40.6)	0.176	0.674
未绝经	20(64.5)	19(59.4)		
紫杉醇类型				
白蛋白结合型	22(70.0)	24(75.0)	0.130	0.718
其他类型	9(29.0)	8(25.0)		
化疗周期				
6	23(74.2)	22(68.8)	0.229	0.633
4 或 5	8(25.8)	10(21.2)		
pCR 情况				
pCR	17(54.8)	9(28.1)	4.636	0.031
non-pCR	14(45.2)	23(71.8)		
不良反应				
骨髓抑制	6(19.4)	8(25.0)	0.290	0.590
肝肾功能异常	7(22.6)	10(31.3)	0.601	0.438
心肌酶异常	4(12.9)	6(18.8)	0.084	0.772[a]

注:[a] 表示连续校正 χ^2 检验。

表 3　78 例 TNBC 患者 NAC 后 pCR 的多因素 logistic 分析

Tab. 3　Multivariate logistic analysis of pCR after NAC in 78 cases of TNBC

变量	B	SE	$Wald$	P 值	OR	95%CI
瘤体直径≤3 cm	1.433	0.619	5.362	0.021	4.191	1.246~14.094
TP/TAC 化疗方案	0.729	0.945	0.596	0.440	2.074	0.326~13.211
白蛋白结合型紫杉醇	0.945	0.700	1.823	0.177	2.573	0.653~10.142
化疗 6 周期	1.140	0.660	2.983	0.084	3.126	0.858~11.393
HER-2 低表达	−0.693	0.606	1.309	0.253	0.500	0.153~1.639
Ki-67≤30%	−0.676	0.921	0.538	0.463	0.509	0.084~3.094
AR 阳性表达	−2.089	0.942	4.919	0.027	0.124	0.020~0.784

3　讨　论

目前,以蒽环类和紫杉醇为基础的方案仍然是 TNBC 的标准化疗方案,但只有 30%~50% 的 TNBC 实现了 pCR[3]。而且,最新的以铂类为化疗用药基础的相关研究对标准方案提出了挑战,认为在化疗方

案中以铂类为基础或额外加入铂类能够显著提升 pCR 率,尤其是对于存在 BRCA 突变的 TNBC[4]。并有研究将紫杉醇与卡铂的 TP 组合应用于 TNBC 的 NAC 同样获得了良好的 pCR 效果[5]。因此,以临床实践为基础,探讨不同化疗方案的实际临床效果对优化 NAC 方案以进一步提升 pCR 率从而改善 TNBC 的长期预后具有重要意义。

本研究总体的 pCR 率为 35.9%,92.9%的 NAC 方案为 TP 和 TAC,78.6%的方案使用了白蛋白结合型紫杉醇。并且,pCR 患者主要来源于使用白蛋白结合型紫杉醇联合铂类的 TP 组,占比达 60.7%,表明 TP 方案的 pCR 率显著优于 TAC 方案(54.8% *vs* 28.1%)。NeoCART 试验显示,采用 TP 方案(其中紫杉醇为非白蛋白结合型)比 TAC 方案的 NAC 疗效显著增高(61.4% *vs* 38.6%)[6]。本研究结果与其相似,不同的是,本研究同时也证实了白蛋白结合型紫杉醇在 NAC 中对提升 pCR 率的显著作用。因此,与不含铂类的标准紫杉醇联合蒽环类药物的方案相比,白蛋白结合型紫杉醇联合铂类并省去蒽环类药物可能是一种有前途的替代方法,特别是对于有蒽环类药物治疗禁忌的 TNBC[7]。另外,根据本研究结果,针对乳房体积相对较小、瘤体直径 2~3 cm、初诊穿刺合并腋窝淋巴结转移,且具有保乳意愿的 TNBC,通过初诊穿刺时在乳腺肿瘤病灶和可疑阳性腋窝淋巴结中放置金属钛夹有助于标记瘤床和评估 NAC 后效果,从而改善和提升手术方式,对提升保乳率和减少患者身心创伤具有重要的意义。在化疗不良反应方面,诸如 CALGB 40603 试验[8]、BrighTNess 试验[9]、GeparSixto 试验[2]和荟萃分析[10]等均证明了在标准方案中增加铂类对改善 pCR 率方面的显著作用,认为在以蒽环类和紫杉醇为基础的方案中加入铂类药物应被视为首选的 NAC 主干。但是,额外增加铂类通常会导致血液学毒性风险的增加,增益的 pCR 率多以更多的不良反应为代价,影响化疗的安全性和有序性。然而,不同于在标准方案上增加铂类带来的额外副作用,TP 方案不仅在提升 pCR 率方面效果显著,且不良反应发生率与 TAC 方案相当。因此,TP 方案的相对低毒性可能是其可以省去蒽环类化疗药物的另一显著优势。

另外,本研究以 30%作为 Ki-67 高表达的临界值,单因素分析显示,在 pCR 组中 Ki-67>30%的比例显著上升,Ki-67≤30%则预示着不良的 pCR 效果,因此认为 Ki-67 低表达是 pCR 的阴性预测指标,此结果与诸多研究[11-16]结论一致,但也有研究认为 pCR 组和 non-pCR 组之间的 Ki-67 表达水平没有统计学差异[17]。一方面在于不同的研究使用了不同的标准作为 Ki-67 高表达的临界值,但主要原因可能是仅仅使用 Ki-67 不足以预测 pCR,稳健的预测模型还需要其他标记物[14]。基于此,本研究亦发现 HER-2 低表达同样不利于达到 pCR 状态,相关研究[14]报道了类似结果,并发现 HER-2 低表达可预测接受白蛋白结合型紫杉醇联合铂类的 TP 方案患者的 pCR,本研究与其结论相似。原因可能是 HER-2 低表达亚群较低的免疫反应导致了 pCR 率的显著减低[14,18]。此外,有研究报道 AR 在 TNBC 的表达率约 10%~50%[19],本研究这一概率为 25.6%。但在 pCR 组中 AR 阳性表达率仅为 7.1%,non-pCR 组为 36.0%,差异有统计学意义,并在多因素分析中 AR 阳性表达为 pCR 的独立不利因素,这表明 AR 阳性表达降低了实现 pCR 的机会。有研究发现 AR 阳性 TNBC 对 NAC 的反应降低[20-21],并与较低的 pCR 率显著相关[1,22-23],其原因可能是由较低的增殖率导致的化疗耐药[23],以及 AR 可能参与肿瘤细胞免疫逃避,导致较低的免疫应答,从而降低实现 pCR 的机会[24]。

综上所述,以白蛋白结合型紫杉醇联合铂类的 TP 方案显著提升了 TNBC 的 pCR 率,可能是一种既能省去蒽环类药物又相对低毒性的有前途的 NAC 替代方案,尤其针对乳房体积相对较小、有明确保乳意愿、瘤体直径 2~3 cm 合并腋窝淋巴结阳性的 TNBC,能够改善手术方式。另外,HER-2 低表达,或 Ki-67 低表达,或 AR 阳性表达均预示较低的 pCR 率,三者的联合评估比单一指标更能有效预测 pCR 情况,对 TNBC 初始方案的选择具有一定的意义。但本研究样本量小,单中心的病理审核机制及回顾性研究性质均对结果造成了偏倚,需要更多研究去验证。

利益冲突　无

参考文献

[1] Lee EG, Lee DE, Kim HH, et al. Androgen receptor as a predictive marker for pathologic complete response in hormone receptor - positive and HER-2-negative breast cancer with neoadjuvant chemotherapy[J]. Cancer Res Treat, 2023, 55(2): 542-550.

[2] Poggio F, Bruzzone M, Ceppi M, et al. Platinum-based neoadjuvant chemotherapy for triple-negative breast cancer: a systematic review and meta-analysis[J]. Ann Oncol, 2018, 29(7): 1497-1508.

[3] Lee JS, Yost SE, Yuan Y. Neoadjuvant treatment for triple negative breast cancer: recent progresses and challenges[J]. Cancers, 2020, 12(6): 1404.

[4] Byrski T, Huzarski T, Dent R, et al. Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients

[J]. Breast Cancer Res Treat, 2014, 147(2): 401-405.

[5] Holanek M, Selingerova I, Bilek O, et al. Neoadjuvant chemotherapy of triple-negative breast cancer: evaluation of early clinical response, pathological complete response rates, and addition of platinum salts benefit based on real-world evidence[J]. Cancers, 2021, 13(7): 1586.

[6] Zhang LL, Wu ZY, Li J, et al. Neoadjuvant docetaxel plus carboplatin vs epirubicin plus cyclophosphamide followed by docetaxel in triple-negative, early-stage breast cancer (NeoCART): results from a multicenter, randomized controlled, open-label phase II trial[J]. Int J Cancer, 2022, 150(4): 654-662.

[7] Yu YS, Zhang J, Lin YX, et al. Efficacy and safety of neoadjuvant therapy for triple-negative breast cancer: a Bayesian network meta-analysis[J]. Expert Rev Anticancer Ther, 2022, 22(10): 1141-1151.

[8] Shepherd JH, Ballman K, Polley MY C, et al. CALGB 40603 (alliance): long-term outcomes and genomic correlates of response and survival after neoadjuvant chemotherapy with or without carboplatin and bevacizumab in triple-negative breast cancer[J]. J Clin Oncol, 2022, 40(12): 1323-1334.

[9] Geyer CE, Sikov WM, Huober J, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial[J]. Ann Oncol, 2022, 33(4): 384-394.

[10] Poggio F, Tagliamento M, Ceppi M, et al. Adding a platinum agent to neoadjuvant chemotherapy for triple-negative breast cancer: the end of the debate[J]. Ann Oncol, 2022, 33(3): 347-349.

[11] Nakashoji A, Matsui A, Nagayama A, et al. Clinical predictors of pathological complete response to neoadjuvant chemotherapy in triple-negative breast cancer[J]. Oncol Lett, 2017, 14(4): 4135-4141.

[12] Sivina E, Blumberga L, Purkalne G, et al. Pathological complete response to neoadjuvant chemotherapy in triple negative breast cancer-single hospital experience[J]. Hered Cancer Clin Pract, 2023, 21(1): 4.

[13] Guestini F, Ono K, Miyashita M, et al. Impact of Topoisomerase Ⅱα, PTEN, ABCC1/MRP1, and KI67 on triple-negative breast cancer patients treated with neoadjuvant chemotherapy[J]. Breast Cancer Res Treat, 2019, 173(2): 275-288.

[14] Gluz O, Kolberg-Liedtke C, Prat A, et al. Efficacy of deescalated chemotherapy according to PAM50 subtypes, immune and proliferation genes in triple-negative early breast cancer: primary translational analysis of the WSG-ADAPT-TN trial[J]. Int J Cancer, 2020, 146(1): 262-271.

[15] Zuo K, Yuan XY, Liang XZ, et al. qRT-PCR-based DNA homologous recombination-associated 4-gene score predicts pathologic complete response to platinum-based neoadjuvant chemotherapy in triple-negative breast cancer[J]. Breast Cancer Res Treat, 2022, 191(2): 335-344.

[16] Toss A, Venturelli M, Civallero M, et al. Predictive factors for relapse in triple-negative breast cancer patients without pathological complete response after neoadjuvant chemotherapy[J]. Front Oncol, 2022, 12: 1016295.

[17] Van Bockstal MR, Noel F, Guiot Y, et al. Predictive markers for pathological complete response after neo-adjuvant chemotherapy in triple-negative breast cancer[J]. Ann Diagn Pathol, 2020, 49: 151634.

[18] van den Ende NS, Smid M, Timmermans A, et al. HER2-low breast cancer shows a lower immune response compared to HER2-negative cases[J]. Sci Rep, 2022, 12(1): 12974.

[19] Gerratana L, Basile D, Buono G, et al. Androgen receptor in triple negative breast cancer: a potential target for the targetless subtype[J]. Cancer Treat Rev, 2018, 68: 102-110.

[20] Echavarria I, López-Tarruella S, Picornell A, et al. Pathological response in a triple-negative breast cancer cohort treated with neoadjuvant carboplatin and docetaxel according to lehmann's refined classification[J]. Clin Cancer Res, 2018, 24(8): 1845-1852.

[21] Santonja A, Sánchez-Muñoz A, Lluch A, et al. Triple negative breast cancer subtypes and pathologic complete response rate to neoadjuvant chemotherapy[J]. Oncotarget, 2018, 9(41): 26406-26416.

[22] Witzel I, Loibl S, Wirtz R, et al. Androgen receptor expression and response to chemotherapy in breast cancer patients treated in the neoadjuvant TECHNO and PREPARE trial[J]. Br J Cancer, 2019, 121(12): 1009-1015.

[23] Mohammed AA, Elsayed FM, Algazar M, et al. Neoadjuvant chemotherapy in triple negative breast cancer: correlation between androgen receptor expression and pathological response[J]. Asian Pac J Cancer Prev, 2020, 21(2): 563-568.

[24] Wang Y, Li JJ, Li JJ, et al. An enhancer-based analysis revealed a new function of androgen receptor in tumor cell immune evasion[J]. Front Genet, 2020, 11: 595550.

收稿日期:2024-01-17　**修回日期**:2024-02-06　**编辑**:叶小舟