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Prognostic value of pathologic complete response and the alteration of breast cancer immunohistochemical biomarkers after neoadjuvant chemotherapy

Yanjie Shuai, Li Ma*

Hebei Medical University, Fourth Affiliated Hospital, Hebei Province Tumor Hospital, China

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ABSTRACT

Neoadjuvant chemotherapy(NCT) has become the standard treatment for breast cancer. The information about the tumor's sensitivity to chemotherapy and prognostic significance based on response to therapy can be provided after individualized neoadjuvant treatment. The biomarkers are key factors in the decision-making process regarding treatment as well as important prognostic indicators. Studies have shown that patients who achieve pathological complete response(pCR) after NCT have a better prognosis. For patients who do not achieve pCR, the pathological characteristics of the residual tumor can make an effect on the survival. Furthermore, the immunohistochemical (IHC) markers of the residual diseases after primary systemic therapy might be different from the primary tumor. Estrogen receptor (ER), progesterone receptor (PR), and Ki67 can usually change after NCT, while human epidermal growth factor receptor 2(HER2) seems to be more stable. The relationship between changes in breast cancer molecular biomarkers and the prognosis after neoadjuvant therapy is not yet clear. The article will make a review about it.

1. Introduction

Breast cancer is one of the most common malignancy affecting women in the world. With the development of cognition of breast cancer, the current treatment of breast cancer has evolved from a surgical-based treatment model to a multidisciplinary treatment of surgery, chemotherapy, endocrine therapy, radiotherapy, targeted therapy, and biological therapy. Neoadjuvant chemotherapy(NCT), as one of the systemic treatment of breast cancer, could be employed for downstaging of tumors, improving the rate of breast-conserving, providing information about the tumor's sensitivity to chemotherapy and assessing individualized prognostic significance based on response to therapy [1]. Before the initiation of NCT, a core needle biopsy (CNB) is commonly performed to confirm the diagnosis and determine the presence of immunohistochemical (IHC) markers, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2(HER2) and Ki67, which are key factors in the decision-making process regarding neoadjuvant therapy as well as important prognostic indicators.

Recently, a series of studies have associated NCT-induced pathological complete response (pCR) with better prognosis for patients with breast cancer. Conversely, patients with residual disease after NCT have been associated with a poor survival [2]. In addition, researchers have indicated that the characteristic of the residual tumor may have influence on the prognosis of the patients, such as the size of the residual tumor, the shrink pattern of breast cancer, and the molecular subtype of the disease after NCT. Currently, the effect of treatment on hormone receptor(HR), HER-2, and Ki-67 expression in tumor tissue is unclear. Figuring out the association between the alterations in receptor status after NCT and long-term survival outcomes, could help us make accurate individual adjuvant treatment for breast cancer patients.

2. Pathologic complete response after NCT

Since many researchers use pCR as a primary endpoint to assess prognosis for patient accepted NCT, discordance exists in the definition of pCR in the literature. Some studies have reported pCR in the breast only, while others have defined pCR as complete response in the breast and axillary nodes. The CTNeoBC trial [3] definition of pCR as ypT0 ypN0 (ie, absence of invasive cancer and in-situ cancer in the breast and axillary nodes) or ypT0/is ypN0 (ie, absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ) is currently accepted.

Previous studies have reported that NCT can decrease the tumor

* Corresponding author.
E-mail address: mlsyj2015@163.com (L. Ma).

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burden of axillary lymph node metastases in breast cancer patients, and nearly 23% of patients converted from clinically node positive to pathologically node negative after chemotherapy [4]. Patients who achieve pCR in the primary tumor are more likely to get negative pathologic axillary nodal status. Similarly, a study have found that patients with axillary and breast pCR after NCT have superior long-term survival outcomes than breast pCR alone or axillary pCR alone [5], and patients with a pCR in the axilla but residual disease in the breast had better survival than patients with a pCR in the breast but residual disease in the axilla, in agreement with findings from the previous study [6]. Therefore, evaluating the response and status of axillary lymph nodes after NCT could help better predict long-term survival. Although most of current clinical studies have confirmed that pCR is associated with improved overall survival(OS), there are also a small percentage of patients who achieve pCR will develop disease recurrence and distant disease in the short term. Gonzalez-Angulo et al.[7] reported that factors related to distant metastasis after pCR included: stage IIIB or higher clinical stage at the time of initial diagnosis, premenopausal status and $\leq$ 10 lymph nodes examined.

Factors associated with increased pCR rate included age $<$ 40 years, smaller tumors ($<$ 2.0 cm), ductal histology, high nuclear grade tumors, high expression of Ki67, ER negative, triple negative(TN) subtype and HER2-positive disease. A meta-analysis of thirty studies involved in 11,695 showed that the pCR rate after NCT for all breast cancer patients was 19.2%, except for the patients with unknown molecular subtypes [8]. And it found that the pCR rate is strongly related to the molecular substype of breast cancer, the pCR rate were 8.3% in the HR positive/HER2 negative subtype, 18.7% in the HER2 positive/HR positive subtype, 38.9% in the HER2 positive/HR negative subtype and 31.1% in TNBC.

Since NSABP B-18 and NSABP B-27 [9] have shown that patients who achieved pCR have a longer OS and disease-free survival(DFS) compared with patients who did not, more and more researchers are working on the relationship between pCR and prognosis. The CTNeoBC trial [3] also found that patients with aggressive breast cancer subtypes (TN, HER2 positive/HR negative, HR positive/HER2 negative and histological grade 3) could get benefit survival from pCR, while the prognosis of patients with Luminal A subtype achieved pCR after NCT could not be improved. TN and HER2-positive tumors showed a good pathological response to NCT compared with other molecular subtypes, especially when the patients with HER2-positive tumors treated with trastuzumab [3,10]. Similarly, the EORTC10994/BIG1 -00 trial[11] also indicated that TNBC and HER2 positive could be more sensitive to NCT. As for the reason why HER2 positive tumor show a good pathologic response to the NCT, it may be related that the HER2 positive tumor cells were more likely to be eliminated by chemotherapy[12].

As the NOAH trial [13] showed trastuzumab could improve the pCR rate of patients with locally advanced or inflammatory breast cancer, and the patients who experienced pCR could get sustained benefit in event-free survival(EFS) from trastuzumab-containing NCT followed by adjuvant trastuzumab. Recently, a lot of studies focus on the dual HER2 blockade with a combination of two anti-HER2 targeted treatmeng for patients with HER2 positive breast cancer. The NeoSphere trial [13], investigating the addition of pertuzumab to trastuzumab with or without docetaxel, found that patients with chemotherapy combined with dual-targeted therapy had a higher pCR rate compared with chemotherapy combined with trastuzumab alone (45.8% vs. 29%). However, it is notable that the pCR rate of the group receiving dual-targeted anti-HER2 therapy without any chemotherapy was 16.8%, suggesting that some patients may benefit from anti-HER2 therapy alone. However, The NeoALTTO trial [14] indicated that pCR rate was higher in double-targeted anti-HER2 combined with paclitaxel group than in the lapatinib or trastuzumab combined with paclitaxel groups (51.3% vs. 24.7% vs. 29.5%), even though the patients who achieved pCR got longer EFS and OS, there is no proof confirming that the increased pCR rate could convert to long-term survival benefits. Therefore, it is still unclear whether the increase in pCR rate could convert to survival benefits. The results might be related to the discordance in the patient's heterogeneity, treatment regimen, and the objectives of the studies.

It is inappropriate to use pCR to replace DFS and OS as an accurate prognostic surrogate endpoint to evaluate the survival benefit of patients. In the study of NSABP B-27 [15], the result did not show improvement in OS, even though the pCR rate was high. The invasive lobular carcinoma has a good prognosis despite lower pCR rate compared with invasive ductal carcinoma. Therefore, analyzing the prognostic significance of pCR should combine the biological properties of the tumor itself. For example, it seems not advisable for the patients with HR positive, HER2 negative or invasive lobular carcinoma to overly pursue pCR by NCT, because these patients may benefit more from the endocrine therapy.

In current clinical trials and clinical practice, pCR is still one of the main indicators to observe, but large amounts of data show that the pCR rates after neoadjuvant treatment range from 3% to 48%, rarely more than 1/3, more breast cancer patients have different degrees of residual disease after neoadjuvant therapy. Studies have confirmed that residual cancer burden(RCB) was related to EFS and OS. Symmans WF et al. [16] classified the RCB by continuous index combining pathologic measurements of primary tumor (size and cellularity) and nodal metastases (number and size), finding 5-year distant relapse rate of 2.4% in patients with minimal residual tumor(RCB-I) and 53.6% in extensive residual tumor(RCB-III) after NCT. In addition, the 5-year prognosis in patients with minimal or no detectable residual disease (RCB-0 or RCB-I) was similar to those with pCR[16]. The Neo-Bioscore model [17], a comprehensive scoring system built by MD Anderson Cancer Center investigators for the prediction of long-term survival after NCT, is a more accurate method to evaluate the prognosis compared with pCR.

3. Ki67 expression pre- and post-neoadjuvant systemic chemotherapy

As the most commonly used marker of tumor cell proliferation, high Ki-67 expression usually indicates poor prognosis[18]. Ki67 expression was positively correlated with nuclear grade, lymph node status, mitosis, and HER2 status. Studies have reported that tumors with high Ki67 expression can benefit more from NCT compared with low Ki67 expression [19], patients with high Ki67 level were more likely to respond to NCT, even in ER/PR positive patients who were considered to be less chemosensitive[20].

It is demonstrated that the expression of pre-treatment Ki67 was also a pCR predictor to NCT[21]. Alba E et al.[22] found that basal Ki67 index $>$ 50% could be considered as an independent predictive factor for pCR. Whereas Balmativola et al.[23] reported that the theroid of Ki-67 $\geq$ 18% could get pCR or partial remission response(pPR). To discriminate the pCR group and pNR(pathologic no response) group, the most relevant Ki-67 cutoff value was 20% in the two groups. Considering OS, the most relevant Ki-67 cutoff value was 15% [24]. These results indicated that cell proliferation is closely related to chemosensitivity. Sueta et al.[20] reported that the pCR rate was high in the luminal type disease with high basal expression of Ki67, but there was no association between the expression of Ki67 and pCR rate in patients with HER2 positive or TNBC, which might be related to the chemosensitivity of HER2 positive or TNBC. Qi-Xing Tan et al. [25] concluded that HR negative patients with high pre-treatment expression of Ki67 showed significantly improved pCR rates after NCT, being consistent with several other studies [21,26].

Ki67 levels of residual diseases after NCT may also provide independent prognostic information for patients, most notably in HR positive patients[28]. High Ki67 expression of the residual tumors was considered to be associated with poorer DFS and OS regardless of the molecular subtype[29], and patients with high Ki67 index of residual diseases are more likely to experience the early distant metastases. Similarly, studies have shown that Ki67 levels of residual tumors are

more predictive of long-term outcomes than the levels before or the alteration after NCT [27,28]. In contrast, Von Minckwitz et al.[27] reported that patients with decreased Ki67 expression had a better prognosis. Patients with no change or an increase change in Ki67 value had the worst prognosis, especially in ER negative patients.

One clinical trial indicated that Ki67 levels in residual diseases decreased to < 20% was related to better both DFS and OS[29]. Considering tumor heterogeneity, it is not only the expression of Ki67 before and after NCT, but also any change of Ki67 levels through NCT may provide prognostic information for patients. Overall, patients with high posttreatment Ki67 levels are candidates for innovative post-neoadjuvant treatment concepts.

4. Evalution of ER and PR before and after NCT

ER and PR expression usually are positive in well-differentiated, less malignant breast cancer patients, acting as a favorable prognostic factor. At present, a majority of researchers viewed that HR status and Ki67 expression could usually change after primary systemic chemotherapy, whereas HER2 amplification appeared to be more stable but might be modified when trastuzumab was added to NCT. Systematic reviews revealed that HR and HER2 status change occured in 51% and 43% of patients who received chemotherapy and trastuzumab-contained therapy, respectively[30], the rates reported in the article were higher than that reported in many other literatures. Xian et al.[31] reported the median alteration rate of molecular markers before and after NCT was 13% for ER, 21% for PR, and 12% for HER2. A prospective observational study [32] discovered that 18.4% of HR status changed after NCT, and the change was mainly from HR positive to HR negative (13.0%), the same as a study which reported changes in HR status in patients from 8% to 33% after NCT[30]. Wen-kai Ge et al. [33] concluded that the loss of HR positivity was an independent prognostic factor for worse DFS and worse OS.

The magnitude of changes in ER and PR status and their effect on survival outcomes was reviewed by Tacca et al[34]. The research indicated that it was the residual disease, rather than subtype evaluated on the initial biopsy, should be considered for patient prognosis. 23% of the HR status converted after NCT, of which 42% initially HR negative became HR positive. This HR positive convertion was significantly correlated with better OS, compared with patients with unchanged HR-negative tumors. A research conducted by Napa Parinyanitikul et al. [35] reported that the rate of 5-year OS and relapse-free survival(RFS) were 87% and 71% in patients with a > 20% change in ER and PR expression, significantly better than a < 20% change in ER and PR expression group, in which the rate of 5-year OS and RFS were 73% and 57%, respectively.

A retrospective study proved that the OS for patients whose tumors changed from HR positivity to negativity may be worse than that of patients whose tumors remained positive after chemotherapy, while tumors changed from HR negativity to positivity may be better than that remained positive [36]. It also found that the incidence of HR positive tumors changed to HR negative was more frequently observed in HER2 positive tumors than HER2 negative tumors, besides a relatively high Ki67 level was observed in tumors with HR alteration compared to the tumors remained negative. Xi Jin et.al [32] considered that high Ki67 expression was observed in the groups with loss of HR status, loss of HER2 status and the subtype converted into TNBC.

Ignoring the influence of the discordance of the breast cancer biomarkers on prognosis, it might also be associated with whether the patients who experienced the decrease of HR positivity received adjuvant endocrine therapy or whether they are sensitive to the adjuvant endocrine therapy. T Hirata et al. [37] found that the DFS and OS in patients with HR status converted who accepted adjuvant endocrine therapy were similar to those with HR-positive both before and after NCT who accepted adjuvant endocrine therapy. However, the DFS of adjuvant endocrine therapy naive patients whose lesions show HR status conversion was significantly shorter than that of endocrine therapy administered patients whose lesions were HR-positive both before and after NCT. Analysis results of OS was similar to DFS. Therefore, it indicated that it is the non-administration of adjuvant endocrine therapy seemed to be associated with a worse prognosis, rather than the change in the status alone to influence the long-term outcome. Endocrine therapy appears to be suitable for patients with tumors positive for HR status at least once, that is, either before or after NCT.

5. Discordance of HER2 before and after NCT

HER2 positive is an important indicator of prognosis. Based on the results of previous studies, it was found that when immunohistochemical methods were used to determine HER2 status, 5.1%–30.0% of breast cancer patients changed after NCT[[30]]], [33]]], [38]]] [39],].

The application of trastuzumab administered with NCT appeared to increase the chances in the alteration of HER2 status. A prospective study showed that 43% of patients had a change in HER2 status after NCT combined with trastuzumab-targeted therapy[40]. The discordance of HER2 before and after neoadjuvant therapy may be related to the tumor heterogeneity, treatment options, and tumor evolution. However, some investigators suggested that tumors with altered HER2 IHC scores after NCT might be in stable HER2 gene amplification or nonamplification by FISH analysis, that is, neoadjuvant treatment resulted in the HER2 status alteration by IHC, but it revealed stable gene amplification status by FISH[41]. As shown in the study, whether determined by IHC or FISH for HER2 status, the observed rates of biopsy-to-resection change was 25% for IHC,7% for FISH, with significantly statistical difference [42].

6. Alternation of molecular subtype after primary systemic treatment

A prospective observational study suggested that the switch to the TN phenotype after NCT was an independent prognostic factor for worse survival for both DFS and OS[32]. Another research identified 398 women, of whom 162(40.7%) patients had a change in at least 1 of the receptors from pretreatment to residual disease. Of the 193 HR positive tumors, 9 (4.7%) and 29 (15.1%) became HER2 positive and TNBC, respectively. Of the 72 HER2 positive tumors, 20 (27.8%) and 9 (12.5%) became HR-positive and TNBC, respectively. Of the 128 TNBC tumors, only 2 (1.6%) and 33 (25.8%) became HER2 positive and HR positive, respectively. It is indicated that any receptor change was associated with better RFS. These results might be explained by the fact that TNBC is currently the breast cancer subtype with the worst outcome and comprise the largest group of patients whose receptor status did not change.

7. The mechanism of the discordance

When we estimate whether the expression status of biomarkers is altered between pre- and post-treatment tumors, the following factors causing differences between CNB and surgical specimens need to be considered. The mechanism of the main cause for the switch of HR positive to HR negetive after NCT might be that chemotherapy can decrease the circulating levels of hormone by suppressing the ovarian function and adrenal glands, which may alter the HR status of residual tumors from positive to negetive after NCT [43].

Other explanations for the conversion of receptor status include: (1) sampling site and the heterogeneity of the tumor: false-negative identification of the HR status and the HER2 status in CNB due to intratumoral heterogeneity has been reported previously, the conversion of HR or HER2 from negetive to positive may be due to the availability of tumor material for CNB, because CNB may represent only a small

proportion of clones of different phenotypes; (2) the pathological scoring system; (3) genetic mutations; (4) statistical errors; (5) staining techniques; (6) the tumor itself responds to treatment: regression to a positive HR status under the influence of chemotherapy, since all cells are originally derived from well differentiated hormone receptor positive breast cancer cells. W Arnedos et al.[44] compared the IHC markers of CNB with surgical excision samples from breast cancer patients who had not received NCT. The consistency rates of ER, PR, and HER2 were 98.2%, 85%, and 98.8%, respectively, and the difference in PR expression was statistically significant. Reasons to explain the discrepancy for PR are the fact that PR tends to be distributed more heterogeneously within the tumor. The poor outcome of patients associated with the conversion of HR status and the switch to the TN phenotype after NCT might be the result of a high proportion of proliferating cancer cells and their biological behavior.

8. Conclusion

To figure out the characteristics of residual diseases after NCT could be important for evaluating the prognosis of patients with breast caner. HER2 positive and TNBC trend to be more easily to get pCR after NCT. A reduction in HR expression, increase in Ki67 expression and subtype changes to TNBC after NCT are associated with poor prognosis. Although pCR is related to better prognosis, treatment decisions should be made on an individual basis in our clinical practice, rather than going after pCR blindly. Until more comparable studies are done, re-testing of the hormone and HER2 receptors should be considered in certain situations to optimize adjuvant systemic therapy.

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