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Predictive molecular markers of resistance to chemotherapy in breast cancer

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Abstract

Backgraund: Breast cancer is one of the three most common cancers along with lung and colon cancer. It is a leading cause of cancer deaths in both developing and developed countries. Within 2 decades, neoadjuvant chemotherapy (NAC) has become a standard treatment option in breast cancer. Relevant articles were identified by means of PubMed, Embase, Web of Science, Cochrane Library and Springer Link databases published during the years 2010-2019, describing the role of molecular biomarkers in the assessment of NAC for breast cancer.

Conclusions: The size of the breast primary tumor, the affection of the regional lymph nodes, the degree of tumor differentiation, the expression of hormone receptors, HER2neu, ki67 serve as main criteria for predicting the response to NAC. Preoperative core needle biopsy is the gold standard procedure in cancer diagnostics, in the analysis of predictive biomarkers, particularly utilizing histomorphological characteristics. Carrying out a larger number of cycles of NAC as well as correlating the schemes in relation to the immunohistochemical types have a direct influence on obtaining a good response to treatment. Patients with a pathologic complete response had superior survival outcomes compared with patients who had residual disease.

Key words: breast cancer, neoadjuvant chemotherapy, biomarker, predictor.

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Introduction

Breast cancer (BC) is the most common malignancy among women, with a growing incidence. Every tenth primary cancer patient is diagnosed with breast cancer. It is also the leading cause of cancer death in women [1].

Breast cancer is a group of heterogeneous diseases with numerous genetic alterations and relatively uniform histological phenotypes. Therefore, identification of the histological characteristics that can help to predict the therapeutic response or the clinical prognosis in breast core needle biopsy (CNB) specimens can prove valuable [2].

Neoadjuvant chemotherapy (NAC) of BC improves outcomes, especially in patients with locally advanced and inflammatory cancer. Further insight into clinic-pathological factors influencing outcomes is essential to define the optimal therapeutic strategy for each category of patients and to predict the response to the treatment [3].

Presently, preoperative core needle biopsy (CNB) is the gold standard procedure in cancer diagnostics. In addition to its diagnostic role, recent data have suggested another role for CNB in the analysis of predictive biomarkers, particularly utilizing histomorphological characteristics [4].

In addition, significant volume reduction in tumors after neoadjuvant chemotherapy may permit subsequent, successful breast-conserving surgical treatment [5].

There is significant variability in the histopathologic response of tumors to neoadjuvant chemotherapy, with approximately 15% of patients achieving a complete response, whereas, at the other end of the spectrum, 15% of patients display minimal change or progressive disease. Currently, the underlying mechanism for this variability is unknown. Contributing factors may include the diverse genetic background and hormonal environment of the tumor. Previous studies have focused on the correlation between the response of tumors to chemotherapy and various factors, such as histologic grade, DNA ploidy, cell kinetics, and hormonal receptor status of the primary tumor. However, those studies yielded inconsistent results [6, 7, 8].

Therefore, despite the cumulation of more information about biomarker impact in breast cancer chemotherapy, mostly treatment regimens are standard, so the 5-year survival rate did not serve to make significant changes.

It was searched what the PubMed, Embase, Web of Science, Cochrane Library and Springer Link databases published during the years 2010-2019. The author identified relevant articles describing the role of molecular biomarkers in the assessment of neoadjuvant chemotherapy for breast cancer.

Discussion

The purpose of this review is to present the role of assessing predictive molecular markers in selecting the chemotherapeutic treatment needed for breast cancer patients.

NAC that is designed to be used before surgical removal of a tumor has attracted special attention in oncology [9].

The application of neoadjuvant chemotherapy in locally advanced breast cancers has demonstrated high efficacy by transforming inoperable tumors into operable, avoiding radical mastectomies in ~ 25% [9].

The indications for NAC at present are quite broad: BC in

the early stages in preparation for organ-threatening operations, locally advanced BC, edema-inflammatory form of the disease, regional lymph nodes affection, and big size of the primary tumor [10].

There are several benefits of using neoadjuvant chemotherapy. It provides a unique opportunity to evaluate the response to treatment with a complete pathological response that acts as a surrogate marker of survival and for a faster assessment of the efficacy of new therapeutic agents and early cessation of ineffective treatment. In addition, in case of resistance to treatment, dose adjustment and / or switching to another drug relieves patients of the burden of toxicity and side effects. NAC provides an opportunity for individualized therapy and allows the collection of tumor samples before, during, and after treatment for translational research [11].

A number of data have been published in the literature on the importance of applying long-term neoadjuvant chemotherapy in cases of chemoresistant breast cancer [12, 13, 14].

The appearance of chemoresistance of primary breast tumors is of primordial importance in the modern treatment of BC. The theoretical-practical aspects that clarify the acquisition of cancer cell resistance to chemotherapeutic drugs are insufficiently studied in the literature. Various theories are assumed by which the gene encoding the transport protein of chemotherapeutic drugs is disrupted, the genetic modification of the receptors of the cancer cell membrane, the changes of intracellular transport, etc. Thus, the study of the predictive factors of the appearance of chemotherapeutic resistance is of great importance in the evaluation of individualized drug treatment schemes [15].

The response rate of the tumor to NAC can be evaluated by several methods: clinical examination (assessment of tumor size, skin changes and peritumoral regions), breast imaging (ultrasound, mammography, MRI), postoperative morphopathological examination. Particular attention is paid to the assessment of the degree of pathomorphosis in the postoperative histopathological examination, the assessment of morphological changes of the tumor and peritumoral region, the assessment of tumor cellularity [16].

The response to NAC is assessed by changing the size of the primary tumor and the affected lymph nodes in the pre- and post-treatment phase. There are 3 types of response to NAC in the literature: pathologic complete response (PCR), near complete response (NCR) defined by the presence of residual primary tumor < 1 cm^3, partial pathologic response (PPR) defined by the presence of residual primary tumor measuring > 1 cm^3 [8].

In cases with PCR, the authors mention a better prognosis [17].

Studies have shown a response rate to NAC with a variation between 20-30% depending on the immunogenetic profile and the chemotherapeutic scheme used [18].

Achieving complete and partial remission of NAC has better long-term results, with better overall survival compared to cases where tumors do not respond to therapy [19].

Several studies have shown that the immuno-genetic profile of the tumor can serve as a primary criterion in assessing the rate of subsequent response to treatment. Triple-negative and HER2neu-positive tumors (with hormone-negative receptors) are more aggressive and serve as a criterion for performing NAC. The best response to NAC is found in tumors with small size, high degree of differentiation, the presence of tumor necrosis, hormone-negative receptors, the presence of HER2neu receptor positivity [20, 21].

Luminal type A, compared to other immunohistochemical types, has a better prognosis and in most cases does not require neoadjuvant treatment. The rate of PCR after NAC in the case of Luminal A type is 6%, compared to Luminal B – 10%, Her2neu – 47%, Basal-type – 37% [18, 22, 23].

Total and breast PCR rates were higher in HR negative (HR–) patients (26% and 32%, respectively) than in HR positive (HR+) patients (4% and 7%, respectively). Compared to HR+ patients, HR– patients had higher recurrence rates (38% versus 22%). Human epidermal growth factor receptor 2 positive patients treated with neoadjuvant trastuzumab (NAT) demonstrated higher total PCR (34% versus 13%), breast PCR (37% versus 17%), and nodal PCR rates (47% versus 23%) compared to HER2+ patients not treated with NAT. Furthermore, HER2+ patients who received NAT had lower recurrence rates (5% versus 42%) and increased overall survival (97% versus 68%) [18].

Zhang and co-authors noticed that HER2+ patients have poor response to neoadjuvant chemotherapy with 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) [17].

So, Transtuzumab, humanized anti-HER2 monoclonal antibody, is considered to be first-line treatment for the patients with HER positive Breast Cancer [2, 17].

The Ki67 index also plays an important role in assessing the need for NAC performance. Some authors have evaluated the higher efficacy of NAC in cases with high Ki67 [15].

NAC cannot modify the molecular subtype of the tumor. Changing the status of receptors after neoadjuvant chemotherapy does not show any change in the cellular origin of the tumor [24].

The histological grade of the CNB specimen represents the significant predictors of chemotherapeutic response using the percentage of the area occupied by the tumor infiltrating lymphocytes (TILs), retraction artifact status, small cell-like feature status, level of tumor necrosis, and clear cytoplasm status [4].

The authors mention a directly proportional correlation. The higher grade of differentiation has the better response rate to NAC. Histologically low differentiated tumors have a lower response rate to NAC. The degree of pathomorphosis is the main indicator of the response to NAC. Usually the absence of response correlates directly with the first grade of pathomorphosis, while the fourth grade of pathomorphosis correlates directly with PCR [4, 15, 23].

The assessment of the prognosis depending on the changes of the tumor biomarkers serves an important criterion in establishing the subsequent medical conduct of this patient. The change in the status of hormone receptors after performing NAC, from negative to positive, is interpreted as a favorable indicator of disease prognosis. The change in Her2 status from positive to negative confirms the efficacy of NAC and good prognosis of the disease. The absence of response to NAC in cases of Her2-positive and triple-negative tumors serves as an unfavorable prognostic factor [20, 25].

Randomized prospective studies are needed to select a more balanced choice of patient characteristics and treatment schemes at the beginning and to evaluate the treatment response more appropriately.

Conclusions

1. The size of the breast primary tumor, the affection of the regional lymph nodes, the degree of tumor differentiation, the expression of hormone receptors, HER2neu, ki67 serve as main criteria for predicting the response to neoadjuvant chemotherapy.

2. Preoperative core needle biopsy (CNB) is the gold standard procedure in cancer diagnostics, in the analysis of predictive biomarkers, particularly utilizing histomorphological characteristics.

3. Carrying out a larger number of cycles of neoadjuvant chemotherapy as well as correlating the schemes in relation to the immunohistochemical types have a direct influence on obtaining a good response to treatment.

4. Patients with a PCR had superior survival outcomes compared with patients who had residual disease.

5. The standardization and improvement of methods to assess the response to induction chemotherapy are sorely needed.

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