Volume 1, Issue 8, November 2023 ISSN (E): 2938-3765

CLINICAL AND MORPHOLOGICAL CHARACTERISTICS OF BREAST CANCER WITH TRIPLE NEGATIVE PHENOTYPE

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Abstract
Triple negative breast cancer (TNBC) is a type of cancer with unmet clinical need. This type of breast cancer has the worst clinical outcome due to its aggressiveness, high heterogeneity, and lack of therapeutic targets. Chemotherapy is still the standard of care for this type of cancer, but many patients develop treatment resistance and metastases. In this review, we highlight current challenges for effective treatment of triple negative breast cancer. We discuss the importance of stratification into different molecular subtypes and identification of resistant cells in tumors, which is necessary to identify future strategies for effective and precise therapy. Targeted therapy for this type of breast cancer is limited, and patients are primarily treated with conventional chemotherapy and radiotherapies, which are not specific and do not target resistant cells. Thus, one of the major clinical challenges is to find compounds that target drug-resistant cell populations responsible for the transformation of secondary tumors. Molecular profiling of different TNBC subtypes offers hope for better identifying these tumor-specific resistant cells.

Keywords: triple negative breast cancer , genomic disorders and immunophenotypes .

Introduction

Relevance

Breast cancer is one of the most common malignant tumors in women worldwide. Breast cancer ranks first in the structure of cancer incidence and its frequency is steadily increasing.

“Triple negative” breast cancer is a tumor whose cells do not contain estrogen receptors, progesterone receptors and do not have amplification Her 2/ neu . According to various authors, tumors of this type account for approximately 15% of all invasive breast cancer, reach large sizes and generally have a poor prognosis [1]. An interesting pattern has been revealed that triple negative breast cancer is clearly associated with a mutation in the BRCA 1 gene region [2]. There is evidence that patients with triple negative cancer are less sensitive to chemotherapy, with the exception of platinum drugs [4].

In further studies published in the press in recent years, reports have appeared that the identification of a triple negative immunophenotype can serve as a reliable prognostic marker in the early stages of the process, when there are no signs of damage to the lymph nodes.

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No less important for correctly establishing the prognosis in patients with “triple negative” cancer is taking into account the state of the receptors not only of estrogen and progesterone, but also of androgens [3].

In practice, the introduction of the concept of “triple negative” cancer into daily clinical life was complicated by the fact that this group of breast cancer included cancers of different traditionally accepted morphology and immunophenotype . A significant proportion of these neoplasms are occupied by so- called basaloid cancers. The relationship between the three negative parameters and the morphology of breast cancer is unclear and a factor that requires urgent clarification.

Some specificity emerges when analyzing the nature of distant metastasis in patients with TNBC. If the risk of developing metastases in the lungs and liver in patients with TNBC is higher compared to other types of breast cancer, 4.41 and 2.13, respectively [10], especially in the first five-year period, then the frequency of bone metastases in these two groups is no different - risk index 0.8 [13]. Of particular interest is the dynamics of the development of metastases over certain observation intervals. For example, according to some data, patients with TNBC are four times more likely to develop distant metastases and die in the first 5 years after diagnosis [11]. At the same time, patients with TNBC do not differ from other patients in the frequency of locoregional relapses.

Clinical and morphological features of breast cancer The most common variant of the morphological structure of the tumor in TN breast cancer is infiltrative ductal carcinoma, a high degree of malignancy, which, before the advent of molecular and IHC classification, was regarded as a morphological variant of the tumor with an unfavorable prognosis.

The histological characteristics of TN breast cancer are mainly determined by secretory cell carcinoma or adenoid cystic carcinoma (these two types are considered less aggressive); medullary carcinoma and invasive ductal carcinoma of a nonspecific type without subtypes also occur; highly aggressive metaplastic cancer [4,7].

Medullary TN breast cancer in young women is often associated with BRCA1 overexpression . Rare forms of the histological variant of TN BC include apocrine carcinoma.

Metaplastic carcinoma is also rare and comprises less than 1% of all breast carcinomas. This type of tumor is histologically heterogeneous and by its nature can be epithelial or mixed - epithelial-mesenchymal . When immunophenotyping is performed , it is most often triple negative, gene profiling of which allows them to be classified as basal-like breast carcinomas. These tumors may be metaplastic or mixed with other types of invasive cancer. Components visualized in these tumors, which are typically uncommon in other breast carcinomas, have squamous differentiation, spindle cellular components, chondroid , osseous, and rhabdomyoid elements. These carcinomas have a poor prognosis.

Medullary carcinomas are characterized by the presence of ductal syncytial growth, accounting for 3% to 5% of invasive breast carcinomas. Medullary carcinomas are characterized by the presence of ductal growth, with clearly visible delineated fields, nuclear pleomorphism , a high frequency of the mitotic index, the presence of a diffuse lymphoid infiltrate and the absence of glandular elements.

The described characteristics represent the immunophenotyping of TN BC, which, when assessed from a molecular point of view, belongs to the basal-like subtype of BC. It should be noted that medullary carcinomas have a better prognosis compared to invasive ones. The adenoid cystic variant of breast cancer is quite rare and is currently not well studied.

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However, as mentioned above, even at the morphological level, TN BC is extremely heterogeneous - according to IHC criteria, the TN BC category includes such rare subtypes of BC as apocrine, metaplastic and medullary , which have a very favorable prognosis [9].

In general, the TN BC subgroup is characterized by larger average sizes of the primary tumor compared to other BC subtypes; however, on the other hand, in TN BC, metastatic lesions of lymph nodes are less common, even with a significant size of the primary tumor. In addition, according to a number of studies, in comparison with other subtypes of TN breast cancer, the correlation between the size of the primary tumor and survival is weakest [10]. A possible explanation for this is the aggressive nature of the tumor, which causes early hematogenous metastasis [10]. At the same time, according to other studies, really early stages of TN BC (TI $_a$, T 1 $_b$ without lymph node involvement) have a good prognosis - 5-year OS exceeds 95% [11]. In addition, data on the absence of a relationship between the size of the primary tumor, lymph node involvement and survival are contradictory, because According to other studies, such a relationship still exists. Moreover, in a number of studies, tumor size and the presence of involved lymph nodes were found to be independent prognostic factors [12].

Other (except for tumor size, lymph node and special morphological subtypes) clinical, morphological and laboratory factors of prediction and prognosis in TN breast cancer have either not been studied or, according to available studies, have not shown their significance [5 , 7].

Unsatisfactory results of treatment for TN breast cancer are associated with two main reasons: 1) biological features of this tumor subtype; 2) the absence of additional (except chemotherapy) methods of its treatment.

One characteristic clinical feature of metastasis of TN breast cancer is the rarer metastasis to the bones (20% compared to 40% in other subtypes), in addition , in TN breast cancer they are more often combined with bone marrow lesions [12,2 1].

However, unlike other subtypes, TN breast cancer in the early stages may turn out to be a truly curable disease, in which ACT not only delays relapse, but actually completely destroys micrometastases . Thus, with luminal subtypes, although characterized by a more favorable course even at the stage of widespread disease, after radical treatment and chemotherapy, relapses occur 5-10, sometimes 20 or more years after completion of treatment [4,9].

In early TN breast cancer, the situation is significantly different: in the first 3-5 years after completion of treatment, the risk of progression is incomparably higher than in other subgroups. However, subsequently (5-7 years after completion of therapy), the risk of disease recurrence in TN breast cancer sharply decreases, and after 7-8 years the survival curve reaches a plateau - relapses of the disease are no longer observed [7].

This once again confirms the need for a differentiated approach to analyzing the results of treatment of early stages of breast cancer depending on tumor subtypes. The best treatment results for subtypes other than TN breast cancer may be due to the late development of micrometastases due to the low proliferative activity of the tumor and/or long-term survival after their appearance, but not cure of the disease [2, 7]. In the case of TN breast cancer, despite the worse overall treatment results, a certain cohort of patients can achieve cure [11,20] .

Predictive value of clinical and morphological parameters in patients triple negative breast cancer

Unfortunately, such traditionally analyzed clinical and morphological parameters as the patient's age, the state of menstrual function, the prevalence of the tumor process, the histological type of the tumor, the degree of its malignancy, are more often considered as prognostic criteria characterizing the possible outcome of the disease, and do not always allow answering questions regarding the effectiveness of preoperative chemotherapy [13,14].

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In his analysis Masuda N. et al . studied the predictive value of such clinical parameters as the patient's age, the size of the primary tumor node and the condition of the lymphatic system in 33 patients with triple-negative breast cancer who received preoperative 4 courses of chemotherapy including anthracyclines (FEC : 5-fluorouracil 500 mg/ m2, epirubicin 100 mg/m, cyclophosphamide 500 mg/m) or taxanes (paclitaxel 80 mg/m). According to the results of the study, the authors did not find a correlation between these parameters and the achievement of VUR (p=0.69; p=0.09; p=0.78) [19].

The results obtained regarding morphological criteria also remain contradictory. So, Masuda N. et al . There was no correlation between the achievement of PMR and the histological type of tumor and the degree of its malignancy (p=0.06 and p=0.26) [20]. At the same time, a study by Montagna E. et al . showed that metaplastic breast carcinoma with a triple negative phenotype is characterized by less sensitivity to systemic treatment compared with invasive ductal triple-negative cancer [130].

Taking into account the heterogeneity of TN of breast cancer itself, it is necessary to conduct further studies aimed at identifying signs of tumor chemo -sensitivity in order to identify a cohort of patients with the greatest benefit from existing chemotherapy regimens. Thus, according to a study by Masuda N et al , which included 143 patients with TN breast cancer, the molecular genetic subtype turned out to be an independent predictive factor regarding the achievement of complete pathomorphological remission after NACT [16].

It is the heterogeneity of TN BC that most likely determines one of the characteristic features of this subtype - the high immediate effectiveness of chemotherapy (high frequency of achieving complete clinical and pathomorphological remissions) and, at the same time, unsatisfactory long-term treatment results. As shown in one of the previous studies, patients with chemotherapy-sensitive early stages of TN breast cancer have a favorable prognosis, at least comparable to the results of treatment of other breast cancer subtypes [3, 6].

Thus, according to neoadjuvant studies, the frequency of objective effects in TN breast cancer can reach 50-80%, which is significantly higher than in other subtypes of breast cancer, however, the survival rate of patients with early and locally advanced stages of TN breast cancer who received treatment with such high immediate effectiveness is still equally turns out to be lower than with others tumor subtypes [4,5].

The median survival after detection of TN breast cancer metastases does not exceed 13–20 months , while in patients with other subtypes of breast cancer it is 22–40 months [16]. Perhaps this behavior of TN breast cancer is due to its general molecular genetic characteristics (high proliferative activity, ensures sensitivity to cytotoxic therapy, and, at the same time, high aggressiveness of the disease) [1,3,18].

However, as mentioned above, the most likely explanation is the significant heterogeneity of triple negative breast cancer: within the same subgroup, united only by the negative status of three receptors, there are tumors with high sensitivity to chemotherapy and a favorable prognosis and an unfavorable prognosis, tumors that are not sensitive to chemotherapy, but at the same time having a different prognosis [1,4]. For example, according to a recently published study [1-3], among patients with TN BC whose tumors did not respond with complete pathomorphological remission to NPCT, there is a cohort of patients with a good prognosis due to a favorable genetic subtype of TN BC . The survival rate of such patients, despite the lack of complete morphological remission of the tumor, was 79.8% versus 48.5% among patients belonging to other subtypes of TN BC [15,21].

The second factor responsible for the unsatisfactory results of treatment for TN breast cancer is the shortage of available treatment methods for this tumor subtype. Before the advent of targeted therapy, all patients with breast cancer received only chemotherapy, which acted only on rapidly dividing tumor cells of highly aggressive subtypes of breast cancer, while the survival of other

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patients was determined not so much by therapy as by the biological characteristics of the tumor [9,17].

Against the background of the successes achieved in the treatment of tumors that received additional methods of drug therapy (targeted), a subgroup of patients with TN BC began to clearly stand out, for which the situation has not changed, the only method of treatment remained chemotherapy [18,22]. Moreover, empirically selected chemotherapy, because With all the abundance of cytostatics used in breast cancer, there are no factors that predict the sensitivity of a particular tumor to a particular drug or treatment regimen [14,16].

The preferred chemotherapy regimens for TN breast cancer have not yet been determined [21], which makes it an extremely difficult clinical task to determine the priority areas of scientific research that are currently being carried out, which also determines the conduct of this study.

summarize the main literature data on TNBC at this stage of our knowledge as follows. TNBC is certainly a problem that deserves special and close attention of clinical oncologists and representatives of related theoretical disciplines [20,23]. There is no doubt that, from the standpoint of traditional nosological concepts, TNBC is a heterogeneous group, most of which are represented by basaloid cancers, with certain genomic abnormalities and immunophenotype . When planning the treatment of these patients, it is necessary to use schemes and regimens that are non-standard for breast cancer.

Conclusions

Thus, TN breast cancer currently represents an unresolved scientific and practical problem in the field of oncology, requiring additional research both in relation to the search for optimal approaches to the use of already available treatment and diagnostic options, and for the search for new treatment options, as well as fundamental research in the field of studying the biological characteristics of the disease. Currently, there is no uniform standard for the treatment and monitoring of TNBC. The implementation of these tasks, including optimization of tactics for assessing overall (OS) and disease-free survival (RFS) of patients and, accordingly, by improving subsequent treatment, developing a set of measures for disease prevention and rehabilitation, remains one of the current areas of oncology.

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