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Modern Algorithm for Diagnosis and Treatment of Patients with Triple Negative Breast Cancer

Atakhanova N.E 1
Almuradova D.M. 1
Ziyaev Sh.V. 2
Gaziev L.T. 3
Tashkent Medical Academy. Uzbekistan 1
Tashkent City Branch of Republican Specialized Scientific and Practical Medical Center for Oncology and Radiology. Uzbekistan 2
Jizzakh Branch of Republican Specialized Scientific and Practical Medical Center for Oncology and Radiology. Uzbekistan 3

Abstract:
Triple negative breast cancer is a type of cancer with unmet clinical need. “Triple negative” breast cancer is a tumor whose cells do not contain estrogen receptors, progesterone receptors and do not have amplification Her 2/ neu . 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 article, we highlight existing 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, diagnostic algorithm, treatment algorithm.

Introduction

Triple-negative cancer is a subtype of breast cancer, the main characteristic of which is the lack of expression of both steroid hormone receptors and Her -2/ neu [2,4]. This type of tumor has an aggressive clinical course and a poor prognosis in terms of relapse-free and overall survival [1,3]. The presence of a triple negative receptor status causes the ineffectiveness of such types of targeted treatment as hormonal therapy and targeted therapy with Herceptin , in contrast to luminal and Her-2/ neu -positive tumors [6,7]. In this regard, chemotherapy today remains the only accepted method of systemic treatment in this category of patients [5,8].

Over the past few years, great advances have been made in the comprehensive treatment of TNBC. But, despite this, TN breast cancer remains one of the aggressive forms of malignant breast tumors with a high level of metastasis and low survival compared to other subtypes of breast cancer [4] .

One of the most serious problems that clinicians face when planning treatment for breast cancer is the extreme variability in the sensitivity of breast cancer to therapeutic interventions. The number of parameters for rational choice of therapy method is very limited.

Research in recent years using the achievements of molecular biology in general and molecular pathology in particular has significantly expanded the range of methodological capabilities of oncologists and has made it possible to establish a close connection between the expression of a large group of genes and the features of the clinical course of breast cancer.

This division turned out to be easily reproducible and, moreover, correlated with a number of characteristics of tumors of these two groups. What is especially important is that the characteristics could be established using simpler immunohistochemical staining methods, namely using antibodies to different groups of keratins [11,12].

Further study of the issue led to even more interesting results. It turned out that this so-called The molecular profile of breast cancer correlates with a number of clinical and laboratory parameters, as well as with sensitivity to different drug therapy regimens [10]. Subgroups of breast cancer were identified, and among these subgroups, the most attention was drawn to the group of tumors in which estrogen and progesterone receptors are not detected and amplification of the Her 2/ neu gene is not observed - the so-called “triple negative” breast cancer [11]

“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 [3,7]. An interesting pattern has been revealed that triple negative breast cancer is clearly associated with a mutation in the BRCA 1 gene region [9,10]. There is evidence that patients with triple negative cancer are less sensitive to chemotherapy, with the exception of platinum drugs.

A diagnostic algorithm is a system of rules for performing a certain sequence of operations that ensure the correct diagnosis. The specificity of the diagnostic algorithm determines its features and determines the advisability of identifying it as a separate class of algorithms [9,10] .

To create a diagnostic algorithm for the purpose of making a diagnosis, it is necessary to ensure: collection of information about the patient’s condition, which subsequently must be subjected to logical processing in order to make a decision.

The treatment and diagnostic algorithm can be divided into three algorithms:

1) examination algorithm;
2) information processing algorithm;

3) algorithm for decision making. Each of them can be developed and applied as a separate algorithm. The value of using an algorithm increases when they are used in the form of a single diagnostic algorithm, followed by a treatment profile.

The main practical goal and significance of the algorithm is the precise direction and orientation of the doctor's actions at all stages of diagnosis, which boil down to the implementation of clearly formulated, scientifically based recommendations and rules. In this case, the main task of the created algorithm is to diagnose TN BC, with the help of . in which the doctor, having a certain set of actions, can make the correct diagnosis in the shortest possible time, through minimal technical and methodological efforts.

The effectiveness of the algorithm is directly dependent on how logical and effective its discreteness and certainty are. This is achieved using the scientific approaches carried out in this work to identify certain signs and significant factors that determine and allow the diagnosis of TN BC.

The data obtained helped to carry out the simplest elementary mental and sequential steps on the path to diagnosis, based on certain selected signs, to combine and arrange them in such an optimal sequence so that diagnosis through the created algorithm would be available to any doctor.

In this case, the analysis made it possible to highlight the following:

At the initial stage of diagnosis, it is necessary to conduct ***a clinical examination of the patient*** with ultrasound of the mammary glands, breast, abdominal cavity, pelvis, CT scan and scintigraphy of skeletal bones for metastases;

The next stage includes ***performing a puncture trephine biopsy, if necessary, MSCT gr. cells, PET – according to indications;***

In order to confirm TN of breast cancer, it is necessary to conduct an IHC study to determine the expression of RE, RP, RA, Ki 67, Her 2/ neu . The absence of estrogen , progesterone and Her 2/ neu receptors confirms the diagnosis of TN BC.

The use of the algorithm should be simple and not require very high professional qualifications from the user, otherwise this is a convincing sign that the algorithm is unsuitable for the practical work of a doctor. In this case, discreteness and certainty are not brought to the level of elementary operations, and the sequence is not optimal. Such a diagnostic algorithm will not give high results.

The created algorithm in this case made it possible to determine the type of breast cancer - TN BC; the further stage should ensure the conduct of genetic studies for the presence of BR C A 1.2 expression.

Confirmed TN breast cancer subsequently requires the determination of molecular biological subtypes, since a study of TN breast cancer showed that the response to therapy depends on the molecular biological subtypes of the tumor: basal-like - 1; Basal-like – 2, Immunomodulatory (M), mesenchymal , mesenchymal-luminal ; androgen receptor.

Also, in case of TN BC, it is necessary to divide into histosubtypes - medullary , metaplastic , invasive nonspecific, apocrine. This division is necessary, since depending

on the histosubtypes of TN breast cancer, treatment tactics change, which also requires individual selection of chemotherapy and complex therapy

At this point, the diagnostic stage ends and is histologically and morphologically confirmed with full confidence. TN of breast cancer, which, as an analysis of the conducted studies shows, requires an individual approach depending on the subtypes.

A study on AR content is mandatory, since this requires adjustment and selection of cytostatics .

In order for the diagnostic algorithm to be widespread, it is necessary to find a large-scale criterion that would serve as the key to recognizing a large group of breast cancer subtypes. Therefore, it is necessary and mandatory to conduct a trephine biopsy and IHC study.

Apparently, the most rational, and, moreover, largest-scale criterion for creating this diagnostic algorithm is IHC diagnostics.

Creating a diagnostic algorithm in any area of clinical medicine is a complex task - it must be extremely simple and at the same time be based on a minimum of the most necessary, preferably publicly available, research methods.

To create a real diagnostic algorithm, the following principles must be observed:

1. Divide the entire path of thinking - from determining the leading syndrome to a comprehensive diagnosis - into an extremely short series of successive stages (steps).

2. At each stage, identify and diagnostically evaluate only one symptom or significant factor.

3. At each stage, divide the assessment of each symptom into such elementary criteria, for an unambiguous correct solution of which a minimum level of qualification is required.

4. The sequence of stage-by-stage arrangement of symptoms in the chain of the diagnostic algorithm must meet the following requirements:

a) the first symptom should be the most important;

b) subsequent steps should constantly narrow the range of differentiated subtypes of breast cancer.

The diagnostic algorithm should be completed with prescriptions that make it possible to determine the next stages of the disease, predict its complications and outcome, with the selection of tactical treatment.

5. The basis for creating a diagnostic algorithm should always be clinical expediency. And using this algorithm, the doctor comes to the correct diagnosis.

6. The diagnostic algorithm, at least in its first stages, should include: only those research methods that allow obtaining reliable and most significant diagnostic information with the least amount of time and effort. The diagnostic algorithm can be expressed using graphical diagrams, which is what we did, followed by a description. The inclusion of visual information in the description of the diagnostic algorithm increases the cognitive value, certainty and effectiveness of the diagnostic algorithm .

The created ***treatment algorithm*** fully reflects the results of the study of NPCT and APCT regimens, which show significant results and high efficiency when prescribed in accordance with the studied and defined morphological subtypes of breast cancer.

As the results showed, the most effective was the TC(DC) regimen, in which pathomorphosis was achieved in the tumor in 63%, and in the tumor and lymph nodes - 55.6%, respectively. When using the FAC/AC and AC→T NPCT regimens, it was observed least of all in equal proportions - 14.7% with the FAC/AC regimen, which is comparatively more - 44.7% in the tumor, 40.8% in the tumor and lymph nodes with circuit AC→T.

Based on the studies and results, an algorithm for the diagnosis and treatment of TN breast cancer was developed, compliance with which significantly increases the effectiveness of cytotoxic therapy, including DFS and OS of patients, which is consistent with the treatment regimens used (Fig. 1, 2) .

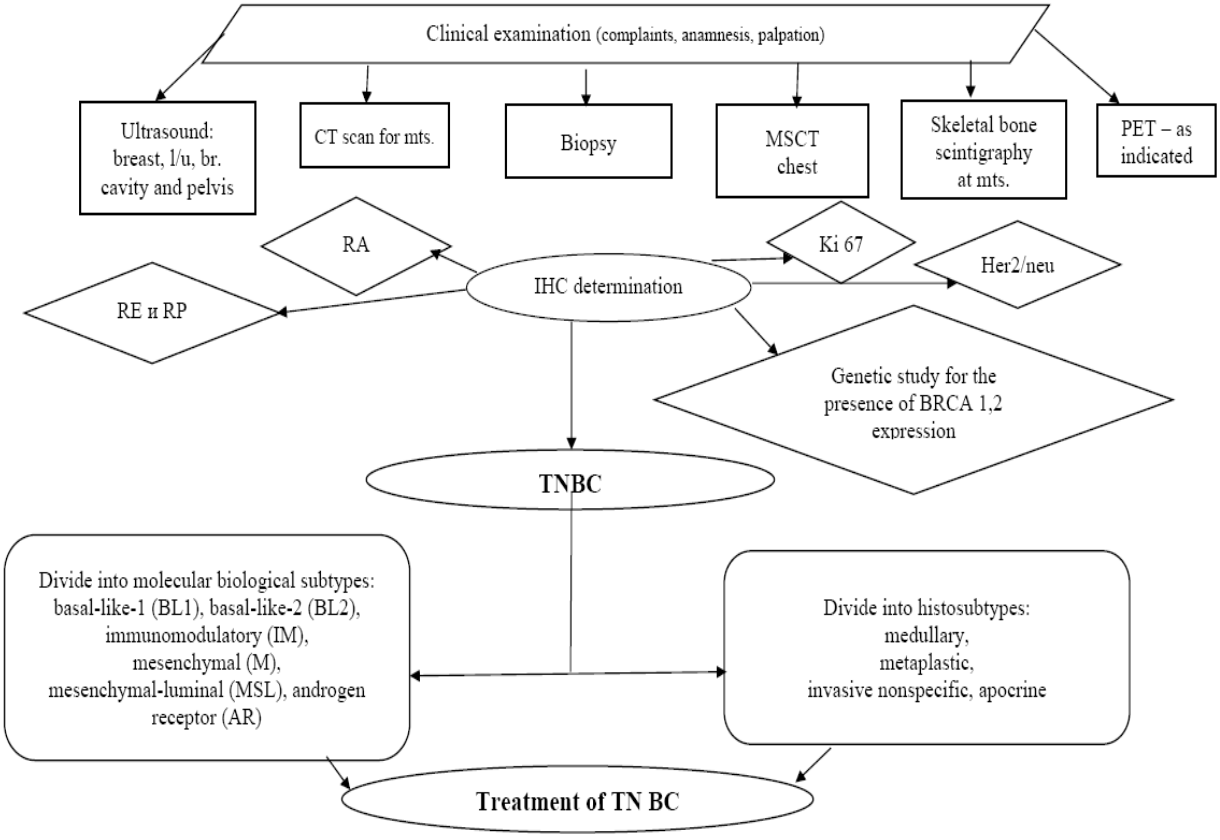

Fig 1. Algorithm for diagnosing TN BC

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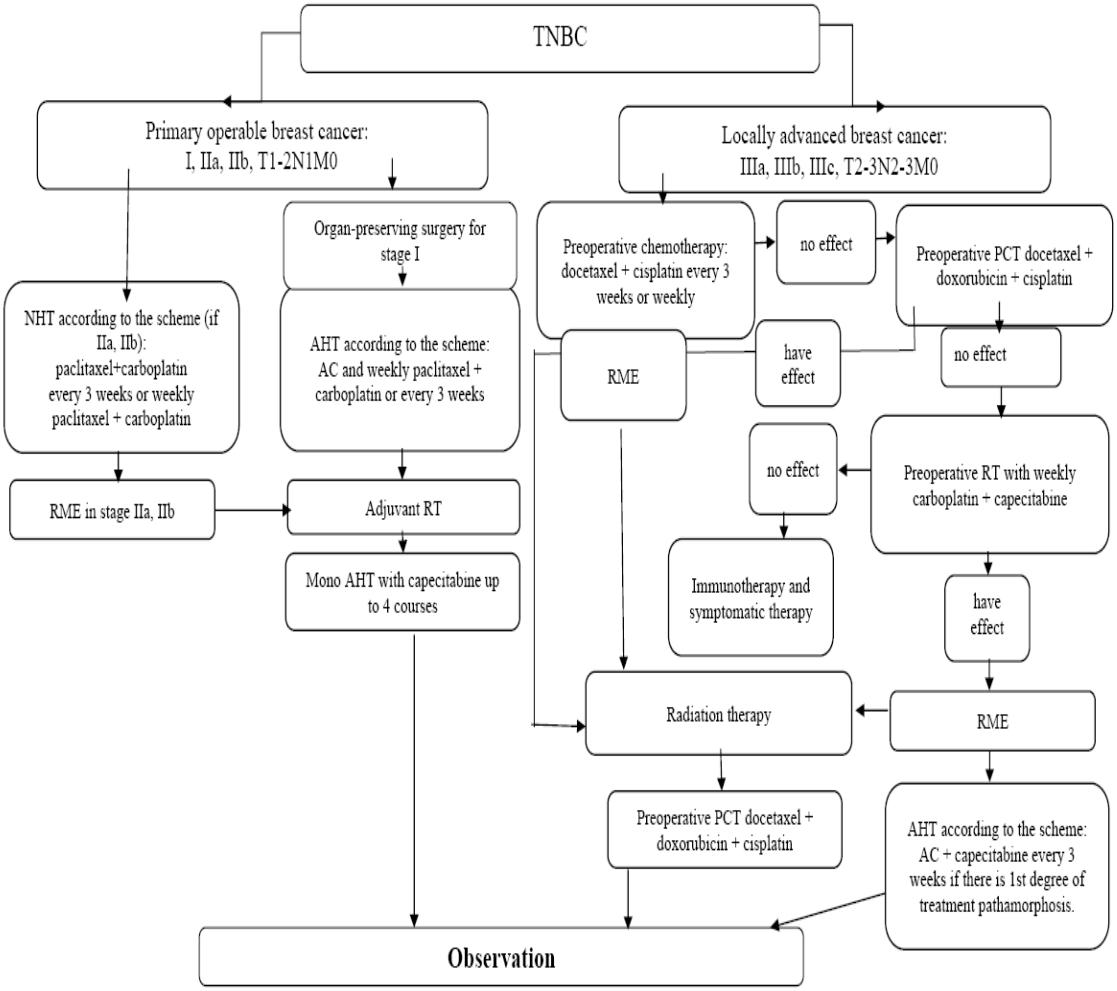

Fig 2. Treatment algorithm for TN breast cancer

pathomorphosis) against the background of chemotherapy; 12 (25.5%) had partial regression (grade III pathomorphosis); in 9 (19.1%) – stabilization (grade II pathomorphosis); 4 (8.5%) had disease progression. In patients receiving NPCT according to the TC regimen, the rate of achieving complete pathomorphological regression was significantly higher (93.7%) than in patients receiving the FAC (18.7%) or AC→T (26.6%) regimen.

A study of the used NPCT regimens for the edematous-infiltrative form showed low efficiency, but the use of docetaxel with cisplatin contributed to an increase in the response rate to chemotherapy, while complete pathomorphological regression was significantly higher (78.6%) than in patients treated with paclitaxel and carboplatin .

In addition to assessing the effectiveness of NCT, an analysis of its side effects, which occurs in all patients, was carried out. The main negative effects were hematological toxicity - leukopenia and thrombocytopenia, nausea, vomiting, stomatitis, hand-foot

syndrome, etc. The above side effects require corrective symptomatic and accompanying therapy.

Thus, the results of the study made it possible to create an algorithm for the treatment of patients with TN breast cancer, taking into account all the clinical and morphological signs of the disease and the effectiveness of the treatment regimens used.

Conclusions

In conclusion, we can conclude that the lack of AR expression in breast cancer patients determines a worse prognosis, despite a more favorable molecular subtype of the tumor. In the course of the study, informative and significant clinical, morphological and molecular parameters were studied and determined based on the prognosis model, which make it possible with a sufficient degree of probability to predict the possibility of achieving complete morphological regressions, as well as to determine the possible outcome of the disease in patients with TN BC with mandatory recording and IHC - determination of AR status of the tumor.

Based on the studies and results, an algorithm for the treatment of TN breast cancer was developed, compliance with which significantly increases the effectiveness of cytotoxic therapy, including DFS and OS of patients, which is consistent with the treatment regimens used.

Complex drug therapy for TN breast cancer should begin with NPCT followed by surgical and radiation components, regardless of the stage of the process. NPCT for the edematous-infiltrative form should include a docetaxel regimen with cisplatin or carboplatin.

After the recommended complex therapy, treatment should be continued with monochemotherapy capecitabine regardless of the therapeutic pathomorphosis of the tumor.

Carrying out only one surgical treatment is also unacceptable in the treatment of TN BC, since according to our data, in all patients who underwent surgery as treatment, progression of the disease was detected already in the first year of observation. This algorithm has an important positive prognostic value in the treatment of TN breast cancer and provides better DFS and OS rates.

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