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TREATMENT OF VARIOUS CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER WITH A TRIPLE NEGATIVE PHENOTYPE

РАЗЛИЧНЫЕ РЕЖИМЫ ХИМИОТЕРАПИИ ПРИ ЛЕЧЕНИИ МЕТАСТАТИЧЕСКОГО РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ С ТРОЙНЫМ НЕГАТИВНЫМ ФЕНОТИПОМ

©Almuradova D.,
Tashkent Medical Academy, Tashkent, Uzbekistan
©Алмурадова Д. М.,
Ташкентская медицинская академия,
г. Ташкент, Узбекистан
©Atakhanova N.,
Tashkent Medical Academy, Tashkent, Uzbekistan
©Атаханова Н. Э.,
Ташкентская медицинская академия,
г. Ташкент, Узбекистан

Abstract. Breast cancer (BC) is the most common cancer in women worldwide. This paper presents results of treating patients with metastatic triple–negative breast cancer (BC). All the patients underwent surgical intervention, adjuvant, neoadjuvant chemotherapy and radiotherapy were evaluated the volume of which depended on the stage of the disease. The side effects of different treatment options were analyzed. Triple–negative breast cancers have a relapse pattern that is very different from hormone–positive breast cancers: the risk of relapse is much higher for the first 3–5 years but drops sharply and substantially below that of hormone–positive breast cancers after that. Five–year relapse–free and overall survival rates were traced in this patient group. It is concluded that the used procedures of combination treatment for metastatic triple–negative BC are highly effective.

Аннотация. Рак молочной железы является наиболее распространенным раком у женщин во всем мире. В этой статье представлены результаты лечения пациенток с метастатическим тройным негативным раком молочной железы. Все пациентки подверглись хирургическому вмешательству, адъюванту, неоадъювантной химиотерапии и лучевой терапии, оценка которых зависела от стадии заболевания. Проанализированы побочные эффекты различных вариантов лечения. Тройные негативные раковые опухоли молочной железы имеют характер рецидива, который сильно отличается от гормонально–позитивного рака молочной железы: риск рецидива значительно выше в течение первых 3–5 лет, но после этого резко падает и существенно ниже, чем при гормонально–позитивных раковых опухолях молочной железы. В этой группе пациентов прослеживалась пятилетняя безрецидивная и общая выживаемость. Сделан вывод о том, что применяемые процедуры комбинированного лечения метастатического тройного негативного рака молочной железы являются высокоэффективными.

Keywords: metastatic triple-negative breast cancer, palliative chemotherapy, prognoses.

Ключевые слова: метастатический тройной негативный рак молочной железы, паллиативная химиотерапия, прогнозы.

Introduction

BC is a heterogeneous disease, and therefore, a “golden standard” treatment, suitable for all the molecular types of cancer, is not available [2–3]. The most important biological markers, not only for classification of BC but also for, the therapeutic strategy are the hormonal receptors (estrogen [ER] and progesterone [PgR] receptor) and the HER2 receptor status [5]. Triple negative (TH) — RE (−), RP (−), HER2 (−), is detected in 8–20% of cases, the most aggressive with unfavorable prognosis. Fundamentally, under the conditions of an early stage, triple negative breast cancer is not associated with later stages and pains a short period from relapse to death [1, 3]. Women with TNBC have a higher level of distant metastasis and a worse prognosis than women with other breast cancer subtypes. There is no single standard of treatment for “triple–negative” breast cancer [2, 6].

Triple–negative breast cancer is very often detected in the last stages of the disease when there is distant metastasis and there is a serious inflammatory process. Triple–negative breast cancer is very often detected in the last stages of the disease when there is distant metastasis and there is a serious inflammatory process. In many cases, this pathology is hereditary, and its age–old border has no boundaries, that is, it can occur at any age, but most often it occurs in carriers of the genetic mutation BRCA-1 and BRCA-2. Based on the current molecular and biological characteristics, the following phenotypes of TN BC are distinguished: luminal A–receptors of estrogen — RE (+) and / or progesterone receptors — RP (+), HER2 (−), low Ki-67 (<20%), which is diagnosed in 56–61% of cases–estrogen–dependent, occurs at the age of menopause, is well amenable to hormonal therapy; luminal B (HER2–negative) — RE (+) and / or RP (+), HER2 (−), high level of Ki-67 (> 20%) — estrogen–dependent, poorly amenable to hormonal therapy, has unfavorable prognosis; luminal B (HER2–positive) — RE (+) and / or RP (+), HER2 (+), any level of Ki-67, occurs in 9–16%; HER2–positive non–luminal — RE (−), RP (−), HER2 (+), is 8–16% — HER2–positive–estrogen–independent, more aggressive, chemotherapy; Triple negative (TH) — RE (−), RP (−), HER2 (−), it is detected in 8–20% — basal–like — estrogen–independent, the most aggressive with an unfavorable prognosis. [3–4]. This classification is widely used in recent years to select adequate treatment tactics and determine the prognosis of the disease. Its popularity is due to the fact that molecular subtypes reflect not only important differences in the etiology and pathogenesis of breast cancer but also the features of the clinical course and outcome of the disease [5, 7]. Three times negative breast cancer is a subtype of tumors with a high risk of progression of the disease, as well as a special character of metastasis, which leads to early damage to internal organs and the central nervous system. Three times negative breast cancer, the most frequent localization of hematogenous metastases is the brain and lungs (the ratio of probabilities was 5.32 and 2.27, respectively), and the metastatic lesion of the bones of the skeleton.

Triple–negative breast cancer is characterized by early dissemination, a tendency to extensive distant metastases. About 20% of patients die in the first 3 years of follow–up. Traditionally applied therapies give a short–term, unstable effect, which makes it necessary to use optimal treatment algorithms to treat this contingent of patients.

Within this phenotype, there is significant molecular heterogeneity. Cluster analysis of the expression of the genes of three times negative breast cancer made it possible to identify 6 of its subtypes: basal–like-1 (BL1), basal–like-2 (BL2), immunomodulating (IM), mesenchymal (M), mesenchymal stem–like (MSL), the subtype of luminal androgen receptors (LAR). This classification reflects the genomic, molecular and biological characteristics of the triple negative breast cancer that are required to determine the molecular targets of therapy, as well as to select the most effective treatment regimens. Antineoplastic drug therapy of breast cancer is one of the stages of complex treatment [3, 6]. Therapy of breast cancer with triple–negative phenotype is a difficult clinical task. Until now, chemotherapy remains the main method of treatment for breast cancer

patients with triple–negative phenotype. However, the results of its use are unsatisfactory, and there is an acute need to find new therapeutic targets, the impact on which could increase the effectiveness of this prognostic treatment for an extremely unfavorable subgroup of patients.

TN breast cancer differs from other subtypes of breast cancer by a much more aggressive course (early and predominantly visceral metastasis) and an unfavorable prognosis. Prior to the introduction of anti–HER-2 therapy in clinical practice, HER-2 + breast cancer had similar characteristics, but at the moment the appearance of trastuzumab and other drugs from this group significantly changed the prognosis and the course of HER-2 + breast cancer. Most likely, the worst (currently) results of treatment for breast cancer are associated with two main causes — the biological characteristics of TN tumors and the absence of additional (except chemotherapy) methods of its treatment. For TN breast cancer characterized by active visceral metastasis, which threatens rapid deterioration and death of the patient in a short time, whilethat characteristic of other subtypes (e. g., luminal breast cancer), bone metastases even without treatment may not lead to death for a long time. The most frequent localization of metastasis in breast cancer is lung (40% of patients, compared with 20% for other BC subtypes) and the brain (30% for TN versus 10% for other subtypes). The incidence of metastasis in the liver is comparable for TN subgroups and is 20% and 30%, respectively. Another characteristic clinical feature of metastasis of TN breast cancer is a more rare metastasis in the bone (20% compared to 40% in other subtypes), but with TN breast cancer, metastases in the bone are more often combined with bone marrow damage [8–9]. However, unlike other subtypes of breast cancer at early stages, it can be a truly curable disease, in which adjuvant therapy not only removes relapse but actually destroys all tumor cells in the body of some patients. Thus, with the luminal subtype, although characterized by a more favorable course even at the stage of a common disease, after radical treatment and adjuvant therapy relapses occur 2–10 (sometimes, 20 years or more) after the treatment is completed. With early breast cancer, the situation is significantly different: in the first 3–5 years after treatment, the risk of progression is incomparably higher than in other subgroups [10–11]. Unfortunately, there is practically no evidence of optimal regimens for chemotherapy in breast cancer. At a time when most of the basic regimens for the treatment of metastatic breast cancer underwent clinical testing, a subgroup such as breast cancer was not separately identified. Nevertheless, based on the results of retrospective analyses of already conducted studies and a number of prospective studies, it can be said that the best results were obtained with the use of platinum preparations, as well as intensified regimens [14], including 2 chemotherapy lines. There is no single–valued data on the benefits of any drug or regimen for metastatic breast cancer. The main attention of researchers in recent years has been attracted to the search for new targets for targeted therapy for breast cancer. Despite the variety of medications used in the standard treatment regimen for patients with three times negative breast cancer today does not exist [12–13].

However, patients with this form of the disease often demonstrate resistance to chemotherapeutic drugs, they often record relapses. Tumors of this kind are also immune to targeted hormone therapy because they lack estrogen, progesterone and epidermal growth factor (HER2) receptors, so Australian scientists have focused on finding other receptors [14, 16]. So, they found out that in 35% of cases three times negative breast cancer in tumors there is an expression of androgen receptors (AR). And then experimentally confirmed that targeted therapy, which uses hormone agonists (a substance that initiates a physiological reaction in combination with a receptor), AR — is effective and contributes to a decrease in the resistance of cancer cells. Interestingly, 10–35% of TNBC express androgen receptors. In addition, it has been suggested that a subset of cases of TNBC may benefit from the addition of an androgen blockade to their therapy [15, 17].

Purpose of the study

The purpose of this study is to evaluate the effectiveness of various chemotherapy regimens for metastatic triple negative breast cancer with improved long–term treatment outcomes.

Materials and methods of research

The object of our study was patients with breast cancer with a triple negative phenotype. In total, retrospective and prospective groups of patients n = 94 who received treatment in 2012–2016 in Tashkent City oncology in the department of oncology and chemotherapy were studied. Criteria for selecting patients:

1. Progression of breast cancer was detected in the period from 12 to 60 months after the operative removal of the primary tumor (metachronous metastases);
2. ECOG 0–1.
3. The age of patients older than 18 years.
4. The presence of the result of immunohistochemical analysis of the primary tumor, and in the experimental group a comparative analysis of the primary tumor and distant metastases.
5. Functional status according to ECOG (FS) was from 0 to 2.

All patients had measurable normal kidney and liver function, satisfactory parameters of general and biochemical blood tests (leukocytes> 4.5 × 109 / L, neutrophily> 2.0 × 109 / L, hemoglobin> 9 g / dL, blood transfusions were not tolerated for the last two weeks, platelets> 100 × 109 / L, creatinine <130 μmol / L, total bilirubin <1.5 of the upper limit of normal (CGI), ALT and ACT <1.5 VGN. After randomization, patients in a 2:1 ratio were included in two treatment groups: 1) chemotherapy with doxorbicin, and/or 2) chemotherapy with platinum drugs. As chemotherapy, the following options were used: taxanes (docetaxel or paclitaxel), gemcitabine, vinorelbine, doxorubicin, endoxane, capecitabine. All patients underwent palliative polychemotherapy according to the scheme:1) Xeloda 1500 mg/m^2 + doxorubicin 50 mg/m^2 was prescribed to 14 (21.8%) patients, of whom 5 (4.8%) received 4 courses and 9 (15.7%) — 6 courses each 21 day; 2) CAP (cyclophosphamide 500 mg/m^2 + doxorubicin 50 mg/m^2 + cisplatinum 50 mg/m^2) was performed in 16 (26.8%) patients, of whom 6 (54.3%) patients received 4 courses and 28 11.5%) — 6 courses every 21 days; 3) paclitaxel 175 mg/m^2 + carboplatin 375 mg/m^2, 16 (17.1%) patients were administered 6 cycles every 21 days; 4) paclitaxel 175 mg/m^2 + doxorubicin 50 mg/m^2, 11 (6.3%) patients were given 6 cycles every 21 days; 5) gemcitabine 1275 mg/m^2 + carboplatin 375 mg/m^2 1.8 days, 16 (17.1%) patients were administered 6 cycles every 21 days; 6) gemcitabine 1275 mg/m^2 + doxorubicin 50 mg/m^2 1.8 days, 12 (17.1%) patients were administered 6 cycles every 21 days; 7) navelbine 35 mg/m^2 + carboplatin 375 mg/m^2 1.8 days, 12 (17.1%) patients were administered 6 cycles every 21 days; 8) navelbine 35 mg/m^2 + doxorubicin 50 mg/m^2 1.8 day, 12 (17.1%) patients were administered 6 cycles every 21 days; In these groups, the effectiveness of various chemotherapy regimens of thrice negative breast cancer was studied depending on the histological type of the tumor, the clinical stage of the process, followed by an assessment of the quality of life according to the scale and the international CCC toxicity scale. Also, a study was conducted of standard clinical and biochemical indicators, with the determination of the oncomarkers level before treatment, during the treatment period and during the dynamic control. To assess the immediate therapeutic effect, we used the determination of tumor size, using mammary glands and regional lymph nodes, mammography, ultrasound, radiologic and metastatic forms of control of CT and MSCT of abdominal and thoracic organs.

Results

The study demonstrated an increase in the frequency of the overall response to treatment of patients with TN breast cancer when using a more effective chemotherapy regimen for paclitaxel with cisplatin compared with gemcitabine with carboplatin (47.8% and 29.6%, respectively). However, there is a significant difference in the degree of pathomorphological effect: in group 1 partial regression of the tumor was detected in 9 pathomorphological tumor regression — in 7, partial — 3, stabilization — 4, in the third group partial regression of the tumor was detected in 11 patients, 5 patients; in the 4th group, complete pathomorphological regression of the tumor — in 9,

partial — 3, stabilization — 2, in the 5th group, complete pathomorphic regression of the tumor — in 12, partial — 3, stabilization — 1, in the 6th group full pathomorphological regression tumors — 8, partial — 2, stabilization — 2, in the 7th group complete pathomorphological regression of the tumor — in 9, partial — 2, stabilization — 1, in the 8th group complete pathomorphological regression of the tumor — in 7, partial — 2, stabilization — 3. This work also demonstrated a low level of toxicity in this combination of drugs. Nevertheless, it was patients who included platinum preparations in HT (regimens of gemcitabine with carboplatin) that allowed complete pathomorphological regression of the tumor in 69% of cases, and the rest of the control group was achieved in 37% of patients. In addition to evaluating the effectiveness of palliative PCT, its side effects were analyzed, which were noted in all patients. The main manifestations of toxicity were hematologic toxicity (leukopenia and thrombocytopenia), nausea, vomiting, stomatitis, palmar–plantar syndrome, etc. The above side effects required corrective symptomatic therapy but did not lead to a delay or withdrawal of treatment. The median time to progression in the groups of patients receiving taxane / gemcitabine–based chemotherapy + cisplatin was 9.2 and 8.0 months, respectively ($p < 0.001$), and in patients receiving capecitabine + doxorubicin — 8.6 and 5, 7 months, respectively ($p < 0.001$). There were no statistically significant differences in overall survival, while 1-year survival in patients treated with doxorubicin in combination with capecitabine was significantly higher with TN breast cancer compared with the group of monotherapycapecitabine: 81% and 74%, respectively ($p=0.076$). The results of this one more indication for the use of doxorubicin — in combination with capecitabine in I–line treatment for patients with HER-2 negative metastatic liver damage with triple negative breast cancer. The safety and efficacy of platinum in combination with taxane–containing regimens of chemotherapy in the first line of treatment of HER-2 negative metastatic cancer are three times negative for breast cancer. However, the increase in time to progression was demonstrated only when it was used in the first line of treatment. In order to determine the effectiveness of platinum in combination with the second line of therapy for metastatic breast cancer, a study of this study was initiated. The median of overall survival in patients with TN breast cancer who received gemcitabine/taxanes + cisplatin was very promising and was significantly higher than inchemotherapy with anthracyclines, the differences between the groups were very close to statistically significant ($p=0.0534$). Comparative sub–analysis of the results of the study showed that the best results were obtained from the cohort of patients who had platinum formulations. It should be noted that these patients were characterized by an extremely unfavorable clinical picture: more than 3 metastatic zones were present in 32–48% of patients, 62–74% of patients had visceral metastases, progression less than 6 months after the first chemotherapy line was recorded in more than a third of patients (33.8%). Nevertheless, it was in patients with breast cancer that the differences in time to progression and immediate efficacy proved to be the most significant. The data on the median overall survival in patients with TN breast cancer and metastatic lung lesions that received gemcitabine + cisplatin in the II line of therapy is also very promising, with the differences between the groups very similar to those of statistically significant ($p = 0.0534$) [14]. Thus, the use of platinum drugs in the treatment of HER-2 negative metastatic breast cancer (including TN Thyroid cancer) can increase the direct efficacy and slow the progression of the tumor in a number of patients. At the same time, in this study, the differences in the frequency of achieving complete morphological remission in patients who received platinum in the palliative regime and who did not receive it was minimal: 47% and 51%, respectively [17–18].

Thus, the use of platinum drugs in the treatment of HER-2 negative metastatic breast cancer can increase the direct efficacy and slow the progression of the tumor in a number of patients.

Conclusions

The primary goal of this study was progression–free survival, and overall survival, immediate efficacy, and tolerability were secondary. Based on the results of this study, the course II chemotherapy line allowed to significantly increase the median time to progression, regardless of the regimen of therapy. Immediate efficacy, as might be expected, was also statistically significantly

higher in patients who received platinum drugs. However, differences in median overall survival and 1-year survival in the analysis of all included patients were statistically unreliable. In combination with gemcitabine/taxanes with platinum preparations in patients with metastatic TH breast cancer, a whiter high percentage of complete regression of primary tumor localization and metastatic organs effect anthracyclines was noted. The median before the disease progression was 11 months and the 1-year survival rate was 49%. Summing up, it can be stated that the antitumor effect due to the lack of expression of ER, RP and HER2-neu and, as a rule, has a more aggressive course and an unfavorable prognosis. The variety of molecular–biological features causes many possible approaches to drug treatment, none of which, unfortunately, provides a stable positive response. However, in the last decade, new medicines have been actively developed, based on the identification of potential molecular targets for cytotoxic targeting, which allow individualizing therapeutic algorithms and looking forward to the future.

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