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Impact of Capecitabine Combination Regimens in the Treatment of Triple-Negative Breast Cancer

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Annotation

Triple-negative breast cancer (TNBC) represents a biologically diverse group of tumors with variable prognoses and treatment responses, largely influenced by the underlying spectrum of genetic alterations driving tumorigenesis and disease progression. This retrospective study encompassed 126 patients with histologically confirmed TNBC, treated in both inpatient and outpatient settings between 2011 and 2017. Participants were stratified into three cohorts: Group 1 (n=47) received neoadjuvant polychemotherapy (NPCT), followed by radical surgery and radiotherapy (RT) according to standard protocols; Group 2 (n=43) underwent initial radical surgery followed by adjuvant polychemotherapy (APCT) and RT; and Group 3 (n=34) received NPCT, radical surgery, RT, and subsequent monochemotherapy with capecitabine. Survival analysis revealed substantial differences in 5-year disease-free survival (DFS) depending on histological subtype. Patients with invasive lobular carcinoma demonstrated a 5-year DFS rate of 49.5 ± 6.4%, notably lower than those with invasive ductal carcinoma of no special type (NST) at 79.8 ± 3.7%, and medullary carcinoma at 88.2 ± 2.7%. Comparable trends were observed for 5-year overall survival (OS): 73.2 ± 3.9% for NST and 62.5 ± 17.6% for lobular carcinoma. Among histological variants, metaplastic carcinoma exhibited the poorest outcomes, with 3-year DFS and OS rates of 43.4 ± 3.2% and 38.2 ± 3.9%, respectively; none of the patients with this subtype survived beyond five years. Conversely, medullary and apocrine subtypes displayed favorable behavior, with no recorded disease progression and a 5-year OS reaching 97%. The most favorable long-term outcomes were associated with neoadjuvant regimens incorporating platinum agents and taxanes, whereas anthracycline-based regimens yielded inferior results, falling short of standard chemotherapy combinations in terms of durability of response.

Key words: Triple negative breast cancer, neoadjuvant polychemotherapy, immunohistochemistry.

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Introduction. Breast cancer remains one of the five most frequently diagnosed malignancies worldwide and is the leading cause of cancer-related mortality among women under 50 years of age. Despite the growing availability of medical services, the detection rate of breast cancer during routine preventive screenings remains suboptimal, while the proportion of patients diagnosed at advanced stages (IIIB–IV) — a key indicator of diagnostic effectiveness — remains unacceptably high. Improving therapeutic outcomes in breast cancer is largely dependent on early, and ideally preclinical, detection of the disease. Notably, up to 25% of all breast cancer cases are diagnosed in women of reproductive age [1,3].

These data highlight the importance of stratifying therapeutic outcomes by molecular subtype, particularly in early-stage disease. Superior survival outcomes observed in non-triple-negative breast cancer subtypes may be attributed not to curative treatment, but rather to the indolent nature of micrometastases and prolonged survival following their emergence — reflecting low tumor proliferative activity [4]. Conversely, although triple-negative breast cancer (TNBC) is typically associated with worse overall prognosis, a distinct subset of patients may achieve long-term remission or even potential cure [2]. To date, there is no established standard for chemotherapy regimens in TNBC, making the identification of optimal therapeutic strategies a critical and complex challenge. This uncertainty underscores the urgent need for focused clinical investigations aimed at determining effective treatment protocols and informing personalized care. Thus, triple-negative breast cancer remains a significant unresolved issue in both clinical and translational oncology [5]. It requires continued efforts not only to optimize the use of existing diagnostic and therapeutic tools, but also to explore novel therapeutic avenues and to deepen our understanding of the disease's unique biological behavior through fundamental research.

Aim of the Study: To enhance the diagnostic and therapeutic strategies for patients with triple-negative breast cancer.

Material and research methods. The work used data from 126 patients with a verified diagnosis of TN in breast cancer, who received inpatient and outpatient treatment in the period from 2011 to 2017. in the conditions of the Tashkent city branch of Oncological center in the departments of oncomammology and chemotherapy. The distribution by stages was as follows: $T_1N_0M_0$ (I st.) - 12 patients (9.5 %) , $T_2N_0M_0$, $T_1N_1M_0$ (II a Art.) - 19 patients (15.1%), $T_2N_1M_0$ (IIb st.) - 29 patients (23%), $T_4N_0M_0$ (III a st.) - 26 patients (20.6%), $T_4N_{1-2}M_0$ (IIIb Art.) - 22 patients (17.5%), $T_4N_3M_0$ (III from Art.) -18 patients (14.3%); and by age: under 35 years old - 22 (17.5%), 35-44 years old - 38 (30.1%), 45-54 years old - 41 (32.5%), over 55 years old - 25 (19.5%). eight%).

A retrospective analysis of case histories and outpatient cards was carried out with an assessment of the results of instrumental and laboratory methods of examination.

When collecting material from primary documentation , anamnestic, clinical, pathomorphological and IHC data were taken into account, with the following included : adjuvant and neoadjuvant chemotherapy, volume of surgical treatment , results of treatment with the study of objective data of clinical and pathomorphological regression , histological and IHC tumor characteristics , date of occurrence of local recurrence , date of death.

The age had a uniform distribution, the patients were predominantly young up to 46 years old and over 45-50 years old, which accounted for 40%, the distribution by stages was as follows: IIa - 8.8 %, IIb - 38.2%, IIIa - 38.2%, IIIb - 8.8%, IIIc - 5.8%. All groups taken for the study were comparable in terms of the main prognostic factors: age, general condition, the extent of the tumor process. As can be seen from table 3.1. depending on age, the majority of patients were aged 35-54 years, i.e. relatively young, with the

largest number of them being at the age of 45-54 years, which amounted to 32.5%, slightly less - at the age of 35-44 years - 30.1%, respectively.

The analysis of the histology ductal cancer was the most common - 66.7%, the least - apocrine and metaplastic types, 5.6 and 1.6%, respectively, while invasive lobular and medullary occurred, respectively, in 11.1 and 15.1 % of patients. As noted earlier, according to the degree of malignancy, the patients had mainly 2nd and 3rd degrees - 66.7 and 33.3%, respectively. According to the definitions of the expression of estrogen receptors, progesterone and the HER-2/ neu gene in all patients, it was negative, which confirmed the diagnosis of TN in all patients included in the study. The study of the expression of Ki -67 showed its high activity up to 80-95%, which indicates a high proliferative activity of this type of tumor and an aggressive course of the process, contributing to an unfavorable outcome of the disease.

The analysis of the history data showed that in the vast majority of cases (89.8%), the patients themselves detected the presence of a node in the breast, and in some cases noted its rapid growth. Sometimes the tumor was an accidental finding detected during a medical examination.

On the border of the outer quadrants, the tumor was localized in 53 patients, in the inner quadrants in 11, in the central sections - in 18 patients. At the same time, 12 patients had a multicentric form of tumor growth, 23 had the disease manifested by clinical symptoms of an edematous-infiltrative form, necrosis with ulceration of the tumor - in 5. The majority of patients in this group were young and middle- aged patients (30-50 years old - 59 ,1% and 50 -60 years old 23.8%), having a somatic status according to ECOG 1-2 points.

All patients underwent surgery, depending on the subsequent chemotherapy regimens, they were divided into 3 groups (Fig. 2.3):

group 1 - 47 patients who received NPCT with a radical operation and RT according to the standard method;

group 2 - 43 patients who underwent radical surgery with APCT and RT according to the standard method;

group 3 - 34 patients who received NPCT with a radical operation and RT according to the standard method, followed by the appointment of monochemotherapy capecitabine.

Patients (n = 124) underwent surgical interventions in various volumes: radical resection (RR) - 28 (22.5%); radical mastectomy (RME) - 78 (62.3%), skin- sparing or subcutaneous mastectomy with reconstruction with an expander and subsequent replacement of the expander with an implant - 4 (3.2%), simple mastectomy - 3 (2.4%), except for 2 (1.6%) patients who did not undergo intervention due to the presence of a severe concomitant disease. In 4 patients, skin- sparing or subcutaneous mastectomy with expander reconstruction was performed; after RT, the second stage of breast reconstruction was performed - replacement of the expander with an implant. 2 patients underwent prophylactic subcutaneous mastectomy with simultaneous reconstruction with an implant. In the postoperative period, patients received treatment according to the standards. During the surgical stage of treatment among 124 patients with TN in the postoperative period, complications were noted, primarily due to the volume of surgical interventions performed, so in 18 (14.5%) cases, the development of lymphostasis of the upper limb was recorded; in 13 (10.5%) - prolonged lymphorrhea ; in 1 (0.8%) case – marginal necrosis of the flap (after RME), as a result of which the healing of the postoperative wound was partially due to secondary intention.

The result of the study. Currently, CT is actively used in the neoadjuvant regimen in the treatment of patients with TN in breast cancer, as it allows to reduce the size of the primary tumor, which helps to achieve an increase in the number of organ- preserving operations performed while maintaining a cosmetic result. It also allows assessing the sensitivity of the tumor to the treatment in a short period of time. In this study, the evaluation of the effectiveness of NAC in patients with TN breast cancer was

carried out using the analysis of the frequency of complete morphological regressions. 5 year old OV amounted to : at I st. - 89.7 % , IIa - 84.5 %, II b - 77.8 %, IIIa - 53.3 %, III b - 45.4%, Sh c - 24.0%. 5 year old BRV at patients who received complex treatment for about TNBC, amounted to: at I Art. – 90.9%, II a - 85.9% IIb _ - 80.3%, III a - 48.9%, III b - 53.9%, III c - 45.1% (p <0.001) patients. Death in the first year of observation was recorded in 1 (0.8%) case. The efficacy and safety of combinations of various chemotherapy regimens followed by continued treatment in monotherapy with capecitabine as a treatment for TN in breast cancer is undeniable. The data obtained show that the addition of capecitabine after the use of systemic chemotherapy leads to an increase in median progression-free survival (compared with chemotherapy alone) from 36.7 to 27.9 months (p <0.001) (Table 3.9).

Table 3.9. The effectiveness of the combination of capecitabine with chemotherapy

Goals	complex treatment with capecitabine up to 6 courses (n = 36)	complex treatment without capecitabine (n =83)	R
Immediate efficiency, %	39.5	29.6	<0.001
Median time to progression, months	36.7±3.9	27.2±4.3	<0.05
5-year survival, %	84.6	81.5	<0.01
Median overall survival, months	49.7±3.4	36.4±1.7	<0.001

5-year OS was statistically significantly higher in the group of patients treated with capecitabine - 84.6% compared with the control group of 81.5% (p <0.001). When analyzing the safety of new, not typical for the used drugs, no adverse events were noted. The addition of capecitabine after chemotherapy regimens in patients with TN breast cancer led to a significant increase in the frequency of DFS and OS. The results confirmed that the effectiveness of the combination of capecitabine after systemic polychemotherapy in patients with TN in breast cancer was significantly higher compared to systemic chemotherapy alone.

Conclusions: In our study, we conducted a retrospective study of the case histories of patients with TN breast cancer with the following characteristics: mean age 49±8.5 years; histopathological differentiation of the tumor - G-3; with the definition of tumor subtypes, which is the main criterion for an unfavorable prognosis of TN in breast cancer. Administration of capecitabine monotherapy after SCT increased median progression-free survival (compared to chemotherapy alone) from 46.7 to 49.2 months, improving 5-year OS to -84.6% versus 81.5%.

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