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EVALUATION OF THE EFFECTIVENESS OF NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER

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ABSTRACT

Relevance: *Breast cancer is the most common cancer among women. Modern treatment of locally advanced breast cancer requires a multidisciplinary approach, including local treatment: surgical and radiotherapy, systemic treatment, and a wide range of medications. The importance of systemic therapy is to improve relapse-free survival based on the control of micrometastases with the potential to spread throughout the body.*

Systemic therapy for operable breast cancer includes adjuvant therapy and neoadjuvant therapy. Hormone therapy, chemotherapy, and targeted therapy represent systemic therapy, which can be prescribed individually or in combination.

For the most effective breast cancer treatment, tumors are classified into subtypes depending on the expression of biological markers. The presence of expression of the estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and the rate at which tumor cells divide are determined by determining the Ki67.

It is known that neoadjuvant chemotherapy (NCT) has clinical significance in locally advanced and inoperable breast cancer. NCT increases the frequency of organ-preserving operations and the overall survival rate when a complete pathomorphological regression of the tumor (pCR) is achieved.

The study aimed to *conduct a literature review of previously published publications on the effectiveness and expediency of neoadju-vant chemotherapy for breast cancer.*

Methods: *The search and analysis of scientific publications were carried out in the databases Web of Science, Pubmed, and Scopus for ten years, from 2013 to 2023. According to the search, about 3000 articles were found, and 39 sources were left during the selection according to the inclusion and exclusion criteria*

Results: *Efficiency of NCT depending on different immunophenotypes in breast cancer patients was established. Tumor response was assessed according to RECIST criteria. A complete pathological response was observed more often in more aggressive subtypes of breast cancer – Her2-positive and triple-negative cancer. The relationship between pCR and long-term outcomes – OS and DFS have also been estab-lished.*

Conclusion: *Neoadjuvant chemotherapy is a systemic treatment of breast cancer, the main purpose of which is to reduce the size of the tumor for the possibility of performing organ-preserving surgery, as well as to increase the overall and relapse-free survival rates. NCT allows for evaluating the effectiveness of therapy in vivo and using alternative treatment regimens without tu-mor response to the therapy.*

Keywords: *breast cancer, neoadjuvant chemotherapy.*

Introduction: Modern treatment for locally advanced breast cancer (BC) requires a multidisciplinary approach which includes local (surgery and radiotherapy) and systemic therapy with a wide range of medications. Systemic therapy is important for improving relapse-free survival (RFS) by controlling micro metastases prone to spread throughout the body.

Systemic therapy for operable BC includes adjuvant therapy after surgery and neoadjuvant therapy before surgery. These treatment methods are equally effective in improving RFS when similar drugs and evidence-based regimens are based [1]. Systemic therapy might include hormone therapy, chemotherapy, and targeted therapy, which can be prescribed individually or in combination.

For the most effective BC treatment, tumors are classified into subtypes by the expression of biological markers, such as the estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67, which is a tumor's proliferation index. The presence or absence of these receptors identifies five immunophenotypes of tumors, presented in Table 1.

Table 1 – Breast cancer (BC) classification by phenotype based on tumor biological features [2, 3]

BC classification by immunophenotype	Presence of receptor expression
Luminal A	ER (+) and/or PR (+), HER2 (-), Ki 67 <20%
Luminal B, HER2 negative	ER (+) and/or PR (+), HER2 (-), Ki 67 >20%,
Luminal B, HER2 positive	ER (+) and/or PR (+), HER2 (+), Ki 67 any
Triple-negative	ER (-), PR (-), HER2 (-)
HER2 positive (non-luminal)	ER (-), PR (-), HER2 (+)

Neoadjuvant chemotherapy (NCT) has a known clinical significance in locally advanced and inoperable BC [4]. NCT can transform an inoperable breast tumor without distant metastases into an operable one, leading to a slight increase (7% to 12%) in the share of organ-preserving operations [5-6]. Studies have shown that patients who present complete pathomorphological regression of the tumor (pCR) after NCT have more prolonged overall survival (OS) and RFS, especially with triple-negative and HER2-positive BC [7-9]. NCT aims to increase the share of organ-preserving operations and support choosing adequate adjuvant therapy in the future. The regimen choice aims to achieve the maximum antitumor effect in accordance with cancer etiopathogenesis.

The study aimed to conduct a literature review of previously published publications on the effectiveness and practicality of neoadjuvant chemotherapy for breast cancer.

Materials and methods: The search and analysis of scientific publications were carried out in the databases Web of Science, Pubmed, and Scopus for ten years, from 2013 to 2023. The keywords searched included "breast cancer" and "neoadjuvant chemotherapy." The criteria for including the source in the literature review were: reports on randomized and cohort studies conducted on large populations, meta-analyses, systematic reviews, and full versions of articles. The analysis should have included articles describing isolated cases, reports from conferences, abstracts, and papers without citations published in journals with dubious reputations. According to the search, about 3000 articles were found, and 39 sources were left during the selection according to the inclusion and exclusion criteria. The agreement of the author's opinions on the selected articles was 98%.

Results:

Criteria of tumor response to therapy.

The modern criteria for the tumor response to therapy are the RECIST criteria. These criteria are based on a one-dimensional measurement of tumors, as described in Schwartz L.H. et al. [10]. RECIST adopted a simplified measurement method using the sum of the longest diameters of the target lesions. In contrast, previous WHO criteria used the sum of the two longest diameters measured perpendicular to each other. RECIST designers believe these criteria should be updated and adapted to remain relevant [11]. In 2009, RECIST 1.1 was published, according to which the complete response (CR) is the disappearance of all target lesions and regression of any pathological lymph nodes (both target and non-target) to <10 mm. The partial answer (PR) is a reduction in the sum of the diameters of the foci by at least 30%. Disease progression (PD) is an increase of 20% or more in the sum of the diameters of the main foci (>5 mm), as well as the appearance of one or more new foci; unconditional progression of non–target foci. Disease stabilization (SD) means all other cases [12-13].

Modern clinical assessment methods include breast physical examination and imaging using mammography and ultrasound. Physical examination is often insufficient to assess the localized BC response to NCT. Therefore, such methods as two-dimensional and three-dimensional mammography, ultrasound, magnetic resonance imaging (MRI), and positron emission tomography (PET), as well as their combinations (PET-CT, PET-MRI), are essential to assess the treatment efficacy [14-18].

Tumor microscopy is a key diagnostic tool for accurately measuring tumor size. This method provides the most objective assessment of the true sizes of a neoplasm. The tumor size is determined by carefully comparing clinical examination and microscopy results. If a breast tumor is a distinct mass outside the point of origin, its size can be easily estimated using visualization and macroscopy. However, an accurate measurement may be challenging at a tumor location in an ill-defined area of genetic instability and with intra-tumor diffuse fibrosis. In addition, the detection and precise measurement of small malignancies detected by advanced imaging may pose a problem if they are not visible during a general examination of the sample. This is because a surgical sample submitted to a pathology laboratory may differ greatly from the in vivo form observed by the surgeon and radiologist due to the mammary gland tissue elasticity [19, 20].

Several authors have earlier classified tumor response to therapy by the generosity of changes in the tumor. E.g., I.D. Miller and S. Payne (Miller-Payne classification) identified five grades of pathomorphism in response to treatment; the grades are characterized in Table 2. This classification assesses the cell structure of postoperative material and compares the results with the tumor structure before treatment. The assessment of pathological response after NCT has recently become an important independent prognostic factor. A complete pathomorphological response (pCR) is the endpoint of efficiency determination, characterized by a complete absence of tumor cells in postoperative material [4].

Table 2 – Miller-Payne therapeutic pathomorphosis grading system [3]

Degree of pathomorphosis	Characteristic changes in a tumor
I	Subtle changes in individual tumor cells without reducing their number.
II	A slight reduction in cells (≤ 30% of the tumor)
III	Tumor cells lose 30 to 90% in number.
IV	Marked disappearance of invasive cells. Only widely dispersed small nests of cells are detected (>90% of cell losses)
V(pCR)	No tumor cells in sectional cuts from the primary tumor location.

The US Food and Drug Administration (FDA) established a CTNeoBC working group tasked to analyze the results of 12 combined randomized controlled trials of NCT in BC [21-22]. The group concluded that the most significant association between pCR and the long-term outcome was observed in more aggressive BC subtypes. pCR was defined as the absence of malignant cells in the residual primary tumor or regional lymph nodes. The best pCR of 50.3% was achieved in patients with non-luminal HER2-positive BC against the background of treatment with a monoclonal antibody to the HER2 receptor – trastuzumab. Without trastuzumab, pCR with this type of tumor amounted to 30.2%. In triple-negative BC, pCR after NCT was also frequent, reaching 33.6%. In stage III luminal HER2-negative BC, pCR was 16.2% [16]. With hormone-sensitive tumors, pCR values were lower in luminal type A tumors (6.4%) and higher in luminal type B tumors (11-22%) [23-28].

The results were similar in the I-SPY 2 study, where stage II or III BC cases were randomized for different variants of standard neoadjuvant therapy. The pCR was lowest in luminal HER2-negative BC (17.4%) and achieved 68% in a non-luminal HER2-positive tumor [29-31].

Three-year event-free survival achieved 95% in patients with pCR and 78% without pCR (95% confidence interval (CI): 0.12, 0.31). Similarly, 3-year RFS amounted to 95% in patients with pCR versus 81% without pCR (CI 95%: 0,13, 0,34) [32-34].

A meta-analysis confirmed no differences in outcomes between adjuvant and neoadjuvant therapy when the same drugs are used [35]. Breast preservation frequency after NCT is higher than after adjuvant therapy. However, patients receiving NCT had a higher incidence of local relapses [36]. NCT standard regimen includes anthracyclines followed by taxane [37]. Adding carboplatin to the standard regimen may be effective for patients with triple-negative RBC , especially with the BRCA1/2 mutation [30, 38, 39].

Discussion: NCT is systemic therapy for BC performed before the main surgical treatment. NCT targets to:

1. Reduce tumor volume: NCT can reduce the size of the tumor focus and make surgical removal of the formation possible.

2. Reduce the risk of relapse: NCT can reduce the likelihood of BC recurrence after complex treatment.

3. Evaluate the treatment efficacy: NCT results can indicate the efficacy of the selected chemotherapy by assessing the tumor pathomorphosis.

NCT regimens for BC may vary depending on many factors, including the tumor size, immunophenotype, disease stage, hormonal status, the patient's age, and general health.

NCT can include a single drug or a combination of chemotherapy drugs. Usually, drug combinations such as anthracyclines (doxorubicin) and taxanes (paclitaxel or docetaxel) are used for NCT. Other drugs, such as cyclophosphamide and fluorouracil, can also be included in combination. NCT is performed for several months before surgery. Usually, 3 to 8 courses are carried out, depending on the patient's response to treatment.

NCT has been proven effective depending on different BC immunophenotypes. The tumor response evaluated according to RECIST criteria showed that pCR was more frequent in more aggressive BC subtypes such as Her-2+ and triple-negative. The relationship between pCR and long-term outcomes such as OS and RFS has also been established.

Conclusion: NCT is currently the routine treatment for BC. The former main target of NCT was to reduce the tumor size (also known as stage reduction) to allow for breast-preserving surgery and possibly exclude axillary dissection in patients who opposed extended surgery. However, the current role of NCT has expanded to include patients with early stages of operable BC, such as stages II and III (T1-4N0-3M0). NCT improves cosmetic results and reduces postoperative complications, such as secondary lymphocytosis of the upper extremities. Clinical trials evaluating neoadjuvant and adjuvant chemotherapy showed no difference in BC treatment long-term effects with either approach.

NCT allows for assessing the therapeutic efficacy in vivo and applying alternative treatment regimens for tumor resistance to therapy. The endpoint, the response to chemotherapy, is a significant prognostic risk factor for relapse, especially in triple-negative and HER2-positive BC. The above advantages are the reason for the widespread introduction of NCT.

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АҢДАТПА

СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІНДЕ НЕОАДЪЮВАНТТЫ ХИМИОТЕРАПИЯНЫҢ ТИІМДІЛІГІН БАҒАЛАУ

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Өзектілігі: *Сүт безі қатерлі ісігі (СБҚІ) – әйелдер арасында ең көп тараған қатерлі ісік. Жергілікті таралған СБҚ ісігін заманауи емі көпсалалы, оның бірі – жергілікті ягни хирургиялық және сәулелік терапияны қолдану арқылы болса, екіншісі дәрі-дәрмектердің кең спектрін қамтитын жүйелі ем. Жүйелік терапияның маңыздылығы бүкіл денеге таралу әлеуеті бар микрометастаздарды бақылауға негізделген рецидивсіз өмір сүруді жақсарту болып табылады.*

Жүйелік терапия адъювантты терапия мен неоадъювантты терапияны қамтиды. Гормондық терапия, химиотерапия және таргетті терапия жүйелік терапия ретінде қолданылады, оларды жекелей немесе басқа әдістермен бірге тағайындауға болады.

СБҚІ тиімді емдеу үшін биологиялық маркерлердің экспрессиясына сәйкес ісіктерді кіші түрлерге жіктеу қолданыла-ды. Эстроген рецепторының (ER), прогестерон рецепторының (PR), адамның эпидермиялық өсу факторы рецепторының 2 (HER2) экспрессиясының болуы және Ki67 индексін анықтау арқылы ісік жасушаларының бөліну жылдамдығы анықтала-ды.

Неоадъювантты химиотерапияның (НХТ) жергілікті дамыған және сүт безі қатерлі ісігінің оталық емес түрінде клиникалық маңызы бар екені белгілі. НХТ ағзаны сақтау операцияларының жиілігін арттырады, сонымен қатар ісіктің толық патоморфологиялық регрессиясына (pCR) жеткенде жалпы өмір сүруді арттырады.

Зерттеудің мақсаты *– сүт безі қатерлі ісігінің неоадъювантты химиотерапиясының тиімділігі мен орындылығы ту-ралы бұрын жарияланған басылымдарға әдеби шолу жасау.*

Әдістері: *ғылыми жарияланымдарды іздеу және талдау web of Science, Pubmed, Scopus дерекқорларында 10 жыл, ягни 2013 жылдан бастап жүргізілді. Іздеу нәтижесінде 3000-ға жуық мақала қамтылды, сәйкес іріктеу кезінде қосу және алып тастау критерийі 39 дерекқоз қалдырылды.*

Нәтижелері: *Сүт безі обыры бар науқастарда әртүрлі иммунофенотиптерге байланысты НХТ қолдану тиімділігі анықталды. Ісік реакциясы RECIST критерийлері бойынша бағаланды. Патологиялық толық жауап сүт безі қатерлі ісігінің агрессивті түрлерінде, ягни HER2 оң және үштік негативті қатерлі ісігінде жиі байқалатыны анықталды. pCR мен ұзақ мерзімді нәтижелер, оның ішінде жалпы өміршендік пен асқынусыз өміршенділік арасындағы байланыс бар екені расталды.*

Қорытынды: *Неоадъювантты химиотерапия – бұл сүт безі обырын жүйелі емдеу. Оның негізгі мақсаты ісік мөлшерін азайтып, зақымдалған ағзаны сақтайтын операцияны орындау мумкіндігі, сондай-ақ жалпы және асқынусыз өмір сүру деңгейін арттыру болып табылады. НХТ артықшылығы- емнің in vivo тиімділігін бағалау және сәйкесінше ісіктің емге жауабы болмаған жағдайда, емдеудің балама режимдерін қолдану.*

Түйінді сөздер: *сүт безі қатерлі ісігі, неоадъювантты химиотерапия.*

АННОТАЦИЯ

ОЦЕНКА ЭФФЕКТИВНОСТИ НЕОАДЪЮВАНТНОЙ ХИМИОТЕРАПИИ ПРИ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ

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Актуальность: *Рак молочной железы (РМЖ) является самым распространенным онкологическим заболеванием среди женщин. Современное лечение местнораспространенного РМЖ требует мультидисциплинарного подхода, которое включает в себя местную, то есть хирургическую и лучевую терапию, а также системное лечение, включающее широкий спектр лекарственных препаратов. Важность системной терапии состоит в улучшении безрецидивной выживаемости (БРВ), основанной на контроле микрометастазов с потенциалом распространения по всему организму.*

Системная терапия операбельного РМЖ включают адъювантную терапию и неоадъювантную терапию. В качестве системной терапии используют гормональную терапию, химиотерапию и таргетную терапию.

Для наиболее эффективного лечения РМЖ используется классификация опухолей на подтипы, в соответствии с экспрессией биологических маркеров. Определяются наличие экспрессии рецептора эстрогена (ER), рецептора прогестерона (PR), рецептора

эпидермального фактора роста человека 2 (HER2) и скорость, с которой делятся опухолевые клетки, посредством определения индекса Ki67.

Неоадъювантная химиотерапия (НХТ) имеет клиническое значение при местнораспро-страненном и неоперабельном РМЖ. НХТ увеличивает частоту органосохраняющих операций (ОСО), а также увеличивает общую выживаемость (ОВ) при достижении полного патоморфологического регресса опухоли (pCR).

***Цель исследования** – оценить эффективность неоадъювантной химиотерапии рака молочной железы.*

***Методы:** Поиск и анализ научных публикаций проведен в базах данных Web of Science, Pubmed, Scopus в период 10 лет, с 2013 года. В результате поиска было найдено около 3000 статей, в ходе отбора согласно критерий включения и исключения оставлено 39 ис-точников.*

***Результаты:** Установлена эффективность применения НХТ в зависимости от различного иммунофенотипа у пациентов РМЖ. Ответ опухоли был оценен согласно критериям RECIST. Выявлено, что патологический полный ответ чаще наблюдался при более агрес-сивных подтипах РМЖ – Her2-позитивном и тройном негативном раке. Также установлена взаимосвязь между pCR и отдаленными исходами – ОВ и БРВ.*

***Заключение:** НХМ – это системное лечение РМЖ, основной целью которого является уменьшение размера опухоли для возможности выполнения ОСО, а также увеличение показа-телей ОВ и БРВ. Преимуществом НХТ является оценка эффективности терапии in vivo и, соответственно, применение альтернативных схем лечения при отсутствии ответа опухоли на проводимую терапию.*

***Ключевые слова:** рак молочной железы (РМЖ), неоадъювантная химиотерапия (НХТ).*

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