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EVALUATION OF THE SYSTEMIC AND REGIONAL ANTIBIOTIC THERAPY EFFECTIVENESS AS PART OF COMPLEX THERAPY IN PATIENTS WITH LOCALLY SPREAD BREAST CANCER

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Abstract

In recent years, breast cancer is the most common oncologic pathology and the most common cause of disability among women in developed countries.

The aim of the study. To improve direct and long-term results of treatment in patients with locally spread forms of breast cancer (LSBC) by accelerated regression of perifocal inflammatory changes using selective intraarterial application of antibiotics; improving patients' quality of life.

Materials and methods. The main sample consisted of 109 patients.The control group included 65 (61 %) clinical cases of LSBC who were performed series of courses of intravenous systemic polychemotherapy (SPHT) as neoadjuvant therapy accompanied by systemic intravenous antibiotic therapy. The study group consisted of 42 (39 %) patients who were performed selective intraarterial neoadjuvant polychemotherapy course with simultaneous regional use of antibiotic therapy in the intraarterial administration.

Results. The regional administration of antibiotics as a part of the complex neoadjuvant therapy, along with the method of selective intraarterial polychemotherapy, has a positive effect on the linear and chronometric regression of perifocal inflammatory changes around the focus of the primary inoperable LSBC, which positively affects the somatic and psychological patient's state and increases the quality of his life.

Conclusions. The complex regional impact on the affected organ has a statistically confirmed better effect with bright holistic features, demonstrating the additive synergism of selective techniques.The selective intraarterial antibiotic therapy does not require additional time and material costs while increasing the efficiency of the method. The versatile advanced approach positively affects the somatic and psychological state of the patient.

Keywords: locally spread breast cancer, complex treatment, intraarterial polychemotherapy, antibiotic therapy, quality of life.

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1. Introduction

Since the beginning of the twenty-first century, breast cancer (BC) has been introduced into the register of registers of most developed countries as the most widespread oncology process in the female population with a huge disability and potential mortality, and is one of the key issues that focuses on the public and the scientific community in the field of health and medicine [1].

A rather large and heterogeneous spectrum of etiological factors is kept for a long time at a certain level of a wide window of a set of factors, none of which can accurately detect a clear correlation with the risk of breast cancer [2, 3]. The classical approach to the study of most diseases with the definition of exogenous and endogenous risks at the end of the last century in a number of specialized scientific works has resolved the fate of external influence as a set of individual and socially behavioural trigger factors of passively aggressive nature with the necessary prolonged exposure, leaving a decisive role in understanding the key moments of treatment for research the pathology of the genome and the immunohistochemical profile of cells [4]. On the other hand, breast cancer is a fairly conventional name for heterogeneous number of tumors, different genotypic and phenotypic on properties, as a temporary consequence of defective and study sub-cellular substrate unstructured problems [5, 6]. Thus, the etiological and pathogenetic sets for the breast cancer form

a non-objective representation of the correspondences [7, 8]. All this explains the increased costs of maintaining and improving diagnostic and therapeutic measures by public and private insurance institutions and the growing equity of clinical and academic interest in understanding the key issues in the management of breast cancer [9].

Medical and economic feasibility, tactics of individualization and rationalization create preconditions for the development and implementation of optimal therapy, taking into account typical accents. In view of this, it is strategically important for the more effective treatment of a variety of forms of oncological processes to develop a variety of targeted therapies in the context of the oncology specialty, in particular methods for the mechanical vectorization of chemotherapeutic effects on the hearth of locally common types of breast cancer [10, 11]. An adequate combination of methods for influencing the array of tumors and the body as a whole is a topical issue, given the inadequate theoretical and practical effectiveness of the system approach [12]. The ultimate goal of polychemotherapy in breast cancer, the pathogenetic aspects of the application of therapeutic efforts, the composition of the panel of active substances is now a metastable subject of discussion in a wide range of journalism and narrow work of specialists [13, 14].

Regional methods of doping (intraarterial) are one of the modern surgical ways of solving the question of a selective approach to spatially limited processes [15, 16]. In general, the essence of selective intraarterial polychemotherapy (SIAPHT) as the main element of this type of regional complex effects on the tumour consists in an artificially controlled short-term increase in the peak concentration of active substances in the microcirculatory channel of the target area by saturation of the afferent backbone blood flow with active molecules. This strategy is implemented by catheterization of the internal thoracic artery on the side of the localization of formation and isolated potentiated perfusion of the affected area by chemotherapy drugs (CHT) [17, 18]. The фшь is to achieve common results for all targeted methods: increasing local exposure and reducing the systemic toxic response. The time of the operation and the chemotherapeutic stage does not limit the possibility of solving additional tasks, in particular antibiotic-therapeutic effects on the affected area.

The idea of the effectiveness of the mechanical vascularly associated methods of addressing the drugs to the sites of the body largely depends on the chosen method of isolation of the target area, which in the rest of the way determines the key parameters for achieving almost all the theoretical goals of treatment: the plateau concentration of active substances in the regional blood flow, the rate and uniformity of distribution , exposure of drugs on target cells, elimination of active molecules into the systemic circulation [17]. For known reasons, regional perfusion of the mammary gland is carried out through a contour with a semi-closed entrance, an uncontrolled pressure delta in the system of microcirculation and complete drainage into the central venous flow. Anatomical features of the distribution of arterial and venous segments of the mammary gland limit the ability to overcritically increase the concentration of CHT drugs with the subsequent elimination of the bulk of supersaturated blood, as well as limit the ability to control the redistribution of substances among metabolic cells [19]. Nevertheless, the main role in the theoretical model of this type of partial artificial modification of the qualitative composition of tissue perfusion devotes to the “shock wave” effect, which allows simultaneously to increase the peak concentration of the solution of preparations in the system of blood flow of the tumour, the calibre of the vessel, minimizing the histotoxic effect on the surrounding tissues, and the speed Infusion, which provides exposure and reduces the amount of preparation at the exit from the body.

2. Aim of the work

Improve the immediate and long-term results of treatment of patients with locally advanced BC forms by accelerated regression of perifocal inflammatory changes through selective intra-arterial use of antibiotics, improving the quality of life of patients.

3. Materials and methods

The present study was based on data from a randomized analysis of the cardiac pacients of 107 patients with regional breast cancer (RBC) class T4A-DN0-3M0 who received comprehensive specialized treatment based on selective intraarterial therapy based on the Donetsk re-

gional antitumor centre and the University Clinic of Odessa National Medical University in the period 2000–2017. Before entering the patient in the study protocol, a written voluntary consent to participate in the study was obtained in accordance with the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, 2013 form (protocol of the meeting of the Bioethics Commission of the Odessa National Medical University No. 117A dated 12.05.2017 year).

For the study, clinical cases with primary inoperable BC forms were selected for which in the framework of the integrated approach, individual schemes of neoadjuvant complex therapy were developed and applied to achieve operable status by reducing the linear size of the tumor, reducing the perifocal inflammatory response, and reversing skin changes over the tumor. As a material for studying, the use of selective intraoral polymer chemotherapy with the subsequent regional or systemic application of antibiotic therapy has been selected, on the basis of which the primary cohorts of the study have been formed. On the basis of further intra-group standardization, a final sample of 109 patients was formulated based on clinical and age parameters.

Analysis of the age composition, the prevalence of the tumour process, the presence of concomitant illnesses in patients showed that the composition of the control and study groups was homogeneous.

All patients were fully acquainted with the research objectives, the program of treatment and diagnostic measures and gave their written voluntary informed consent to this type of treatment.

65 (61 %) clinical cases of RBC were included in the control category, and a series of courses of systemic intravenous polychemotherapy (SIPCHT) using systemic intravenous antibiotics after the first course of PCHT was performed as a neoadjuvant therapy.

The study group consisted of 42 (39 %) patients who performed a series of courses of selective intraarterial polychemotherapy (SIAPHT) as a neoadjuvant therapy, simultaneous regional use of antibiotic therapy in the mode of intra-arterial administration after the first course of PCT.

Scheme of antibiotic therapy during the first course of PCHT:

– for systemic use: cephalosporin preparation of III generation (Ceftriaxone) by 1.0 in terms of dry substance twice a day by bolus administration for 7 days;

– for regional use: a similar drug in equivalent dosage was used twice a day as a continuous intraarterial infusion with a flow rate of 20 ml/h using infusomat for 1 week.

Protocol for using the CAIM scheme in SIAPHT mode:

– Cyclophosphamate: first, fourth, seventh day – 600 mg;

– Methotrexate: second, fifth, and eighth day intravenously – 30 mg/h;

– Doxorubicin: the ninth day iv/y – 80 mg;

– Fluorouracil: the third day – 800 mg, the sixth, the ninth day – 600 mg.

Total course doses of chemotherapeutic agents corresponded to calculated BSA criteria.

According to the protocol on the chemotherapeutic intervention stage, precision microsurgical catheterization of the internal trunk artery was carried out. Saturation of the afferent arterial bed was carried out by means of infusion infusion with a constant controlled rate of 0.3 ml/min using infusomat. Course dose of drugs was administered according to the indicated procedure at intervals of 21 days. The number of cycles of chemotherapy was determined based on the following parameters: evaluation of treatment efficacy, general condition of patients, presence and degree of severity of intoxication syndrome. The preponderant number of subjects received 2–4 cycles of PCHT in a neoadjuvant mode to achieve a clinical effect (resectability of the tumor).

For characterization of therapeutic efficacy in the process, RECIST (Response Evaluation Criteriain Solid Tumors) was used. In all cases, the largest linear size of all centres of tumour growth was determined, which was selected for the assessment of individual dynamics.

Criteria for RECIST Scale:

– Complete response – the disappearance of all the lesion cells for a period of at least 4 weeks;

– Partial effect – reduction of focal points by 30 % or more;

– Progression – an increase of 20 % of the smallest amount of lesion centers registered during observation, or the emergence of new foci;

– Stabilization – there is no reduction sufficient to evaluate either a partial effect or an increase that can be evaluated as progression.

During the evaluation of the therapeutic effect, the dynamics of the objective state of patients, the results of instrumental imaging (mammography) and the pathologic analysis (dynamic needle core biopsy to evaluate the therapeutic pathomorphism of the tumour after CHT) were taken into account.

Measurement of linear sizes of perifocal focal infiltrative changes and their dynamics on control mammographic photographs was carried out using a dial calliper with a price of 1 mm divisions. The initial size before each course SIAPHT was considered zero and converted to the maximum mark of the conventional 100 % scale. Further dynamics was estimated as a percentage reduction.

The study of the quality of life of patients was conducted within the framework of the International Protocol of the European Organization for the Study and Treatment of Cancer, using questionnaires for the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30), which have been tested in numerous foreign studies and meet the criteria for reliability, validity and performance.

To evaluate the immediate results of the treatment, two and seven days after the first course of polychemotherapy were selected as the control points for mammographic time control. Additionally, during the first week, patients were undergoing ultrasound screening of the affected area with orientation to echogenic signs of acute inflammation and appropriate graphic markers. The linear characteristic of the hearth was considered to be the estimate of the two largest perpendicular sizes. The obtained data were used as reference points for modelling the projection graphs of the dynamics of regression of infiltrative changes of perifocal tissues of the mammary gland.

Data processing was carried out using standard statistical formulas: the intragroup characteristic of changes was carried out using statistics of dynamic series, and when comparing the quality of life indicators in the study groups, the p-level indicator was used.

4. Results

In the first group, the first course of polychemotherapy was accompanied by the systematic use of an antibacterial drug for therapeutic purposes within a seven-day period – regardless of the individual dynamics of positive changes in local status. Regression of the reaction of inflammation during the first days of the post-cytomegalatory period had an even downward trend in the schedule and the achievement of the half-reduced tumour in the second half of the control week (**Fig. 1**).

In the second group, the first course of SIAPHT was accompanied by additional infusion of an antibiotic solution in the inner thorax for 1 week. During the first days (according to ultrasound screening) there was a rapid decrease in the volume of paracancerous inflammation with the achievement of a two-fold decrease in the focal point for 2–3 days, as reflected in (**Fig. 1**) in the form of exaggeration the tumour size change curve in the second group.

According to the absolute numerical data of mammographic control, the following values were obtained: the second day of the first postinfusion period in the first group, measured by the measurements of the two largest linear perpendicular sizes of volume reduction, was 84±3.9 percent, while for the second group, there was a significantly better dynamics – up to 58±4.1 percent, which according to the statistical estimation has a reliable value with the dimensionality of the criterion χ^2=16.416 and p<0.001 (at the critical level of 6.635 at p=0.01). After the second measurement on the seventh day, the infiltration volume around the tumour centre was 57±3.8 % in the first and 37±1.9 % in the second group, which maintained a significant level with the Pearson parameter =8.029 and p=0.005 (if necessary, 3.841 and p<0.05).

Assessment of medical pathomorphosis (according to the morphological study of biopsy material after the third course of treatment): control group: medical pathomorphosis 1 item. – 8 (12 %) persons; curative pathomorphosis 2 st. – 28 (43 %) persons; therapeutic pathomorphosis 3 st. – 26 (40 %) persons; therapeutic pathomorphosis 4 st. – 3 (5 %) persons. Investigated group: curative pathomorphosis 1 st. – 1 (2 %) patient; medical pathomorphosis 2 st. – 12 (29 %) persons; therapeutic pathomorphosis 3 st. – 22 (52 %) persons; therapeutic pathomorphosis 4 st. – 7 (17 %) persons.

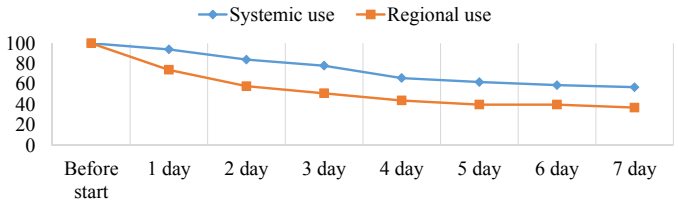

Fig. 1. Dynamics of linear sizes of paracancerous infiltration after antibiotic therapy in system and regional regimes

Differences in the distribution of assessing the effectiveness of treatment for patients in the control and study groups on the RECIST scale are statistically significant in the proportion of cases of achieving 4 degrees of medical pathomorphism among patients in group 2 (p=0.037).

The general condition of patients before neoadjuvant chemotherapy was due to objective (presence of tumour neoplasms and their complications: intoxication syndrome, syndrome of tumour decay, adherence of secondary infection) and subjective (psychological and emotional) factors. At the same time, the quality of life indicator did not differ significantly in the control group (54±11.3 points) and the subjects (53±7.4 points) in the groups (at p=0.888, χ^2=0.02). After the completion of the first course of chemotherapy, the IQ index decreased in both groups: 11.1 % (46±4.3 points) in the first group, by 3 % (50±3.7 points) in the second, but the difference remained statistically insignificant (p=0.572). Among the patients in the control group, 3 (4.6 %) developed a severe intoxication syndrome, after which they refused to further participate in the study. The negative dynamics, according to the authors, is related to the lack of obvious subjective improvement of the state, the lack of expected reduction of the size of neoplasms by the patients, the preservation of intoxication syndrome. After the second course of chemotherapy, the patients with the test parameter increased by 13 % (52±2.3 points) in the control group and by 56 % (78±7.1 points) in the study groups as a result of the positive evaluation of patients with their own general condition, the state of the tumour and the achievement of the expected result in themselves and other study participants. The ultimate goal was achieved in 16 (26 %) patients in the first group and in 19 (46 %) of the second. At this stage, convincingly reliable data were obtained in favour of the regional CHT (p<0.001). After the 3rd year of PCHT, the rates decreased by two to four points in both groups (50±4.4 and 74±2.3 points respectively), which was due to the depletion of the patients and their dissatisfaction with the systematic deterioration of the state after each administration of the drugs. Despite this, the statistical difference in favour of SIPCHT remained significant (p <0.001). Resectable tumour status was achieved in 28 (45 %) women in the first group and 23 (54 %) in the second. After conducting the 4th course of PCHT in the first group, a clinical effect was observed in 16 (26 %) women; in spite of the positive result, their assessment of their own quality of life has not changed compared with the previous indicator. Unfortunately, the resectable state of RBC did not reach 2 (3 %) patients in the control group; they were offered a system of professional assistance and support for cancer patients and symptomatic therapy in an oncologic dispensary (**Fig. 2**).

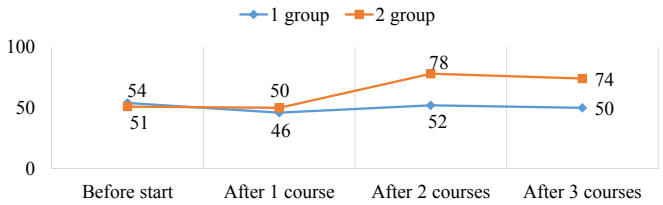

Fig. 2. Patients before and after polychemotherapy + antibiotic therapy in system and regional regimens

5. Discussion

Integrated therapy of primary inoperable, locally common forms of breast cancer is intended to reduce the quantitative and qualitative parameters of the tumour with bringing it to the morpho-functional state, in which it is possible to carry out operative intervention in a radical vol-

ume. Intraarterial selective polychemotherapy in neoadjuvant mode shows the highest efficacy in achieving the goal of tumour reduction in size, reducing its local aggression to a greater extent and in shorter time than the system and intra lymphatic routes of administration.

Standard protocol circuits create a combined effect, but in a small measure, the excessive area of the toxic blow overlaps surrounding tissues. Paracancerous mastitis, occurring in almost all cases of RBC, is a typical immune response of the compromised conditionally healthy tissue to the aggressive behavior of the tumor with the subsequent acquisition of the infectious process or the primary bacterial inflammation of the immunosuppressed organ prior to treatment. During chemotherapy, due to the overlap-effect, the perifocal tissue block is subject to histotoxic effects similar to the tumour, which in theory should deepen dysmetabolic and immunopathological changes. And in that, and in another case, the effectiveness of using antibiotics with a therapeutic and prophylactic purpose is theoretically substantiated and practically verified.

According to the results of the study, it was found that combined infusion of substances with cytotoxic and antibacterial activity spectra forms a favourable front for the patient's body in the part of conditionally healthy tissues, creating conditions for a faster and more efficient separation of the neoplastic process. The use of the method of artificial mechanical vectorization of influence in comparison with the method of primary systemic saturation of the body has statistically better results in terms of the linear reduction of the pericancrotic inflammation center. Also, there is a significant chronometric advantage in achieving the result of a semi-reduction of the inflammatory process in favour of the regional delivery of substances. At the same time, the expansion of the working substance panel does not require additional manipulations with the operating field and does not require additional time and material costs, increasing the efficiency of achieving the goal set before the methodology and the integrated scheme in general.

The use of the regional method of neoadjuvant preparation based on selective intraarterial polychemotherapy can be effectively supplemented by the simultaneous use of broad spectrum antibiotics to achieve faster and more efficient reduction of the inflammation process. It is worth noting that the use of modified antibiotic therapy does not have theoretical grounds and practical confirmation in the dynamics of intermediate results (quantitative and chronometric efficacy in reaching the ultimate goal – resectable tumour status) and remote indicators of three and five years of survival.

6. Conclusions

1. The use of antibiotics with a regional introduction through a complex neoadjuvant preparation of the tumour and the body to radical interference along with the method of selective intraarterial polychemotherapy has a positive effect on the geometric and chronometric regression of perifocal inflammatory changes around the centre of the primary inoperable RBC, statistically significantly better than the systemic version.

2. Increased efficiency of the complex treatment method to the local status of the patient positively affects her somatic and psychological state at the stage of neoadjuvant treatment, which increases the quality of life of the patient.

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