«I approve»
Acting Chief Physician
Communal institution "Rivne oncological dispensary"
(*signature, seal***) Maksimyak G.I.**
«___»_____2018

«УТВЕРЖДАЮ»
И.о. главного врача
КУ «Ровенский областной онкологический диспансер»
_____ Максимяк Г.И.
«____» _____ 2018 г.

REPORT
about the clinical study

"An open study to study the efficacy and tolerability of the drug Donovit-VS®, a tablet manufactured by Astrapharm LLC, used in patients with breast cancer on the background of chemotherapy in comparison with a group of patients receiving only chemotherapy"

Research phase – II

Study code - AF-DN-3/f .2/10.14
Protocol version No. 1 dated March 14, 2015

Sponsor of the study - LLC «NPF Aksomed LTD»

Location of the study - Communal Establishment "Rivne Regional Oncological Dispensary", Department of Breast and Head-Neck Tumors
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(подпись)

CONTENT

1. BRIEF SUMMARY OF THE REPORT (SUMMARY)

Title of the study: "An open study on the effectiveness and tolerability of the drug Donovit-VS®, a tablet manufactured by Astrapharm LLC, used in patients with breast cancer on the background of chemotherapy compared to a group of patients receiving only chemotherapy"

Research phase - II

Research code - AF-DN-3/f .2/10.14

Version of the protocol - No. 1 dated 03/14/2015.

The beginning of the study: 13.06.2016

End of the study: 09/04/2017

The aim of the study. Evaluation of the effectiveness and tolerability of the drug Donovit-VS®, tablets produced by Astrapharm LLC, used in patients with breast cancer on the background of chemotherapy compared to a group of patients receiving only chemotherapy.

Objectives of the study:

- to study the influence of the researched drug on the level of toxicity of chemotherapy;
- to study the effect of the researched drug on the patient's quality of life;
- to study the influence of the researched drug, which is used against the background of HT, on the dynamics of the size of the tumor formation;
- to compare the results of treatment obtained in the main and control groups in order to establish the superior effectiveness of treatment in the group of patients receiving chemotherapy + Donovit-VS ® comparison with the group of patients receiving only chemotherapy.

Research design: open, comparative, randomized and parallel.

The duration of the patient's participation in the study is 3 months + (3-7) days.

Contingent of subjects. Patients aged 18 to 65 years with a diagnosis breast cancer ($T_1N_{1-3}M_0$, $T_2N_{0-3}M_0$, $T_3N_{0-3}M_0$), who are indicated for non-adjuvant chemotherapy.

Number of patients: Planned number: 60 patients (30 patients - main group and 30 patients - control group).

The number of patients randomized to the study is 60.

The number of patients who completed the study according to the protocol is 60.

Inclusion criteria:

- women aged 18 to 65;
- diagnosis: breast cancer ($T_1N_{1-3}M_0$, $T_2N_{0-3}M_0$, $T_3N_{0-3}M_0$), confirmed by histological or cytological examination data ;
- patients prescribed neoadjuvant polychemotherapy;
- the presence of tumor formation, which can be objectively assessed in two dimensions;
- the functional state of the patient according to the ECOG scale – 0-2 points;
- expected life expectancy of at least 12 weeks (3 months);
- for women of reproductive age - a negative pregnancy test result, as well as the use of reliable contraceptives during the study;
- informed written consent of the patient to participate in the study.

Non-inclusion criteria:

- known hypersensitivity to the components of the studied drug;
- pregnancy; lactation;
- other malignant diseases (except basal cell carcinoma or cervical cancer in situ);
- the number of leukocytes $<2.0 \times 10^9$ cells/l;
- the number of neutrophils $< 1.5 \times 10^9$ cells/l;
- the number of platelets $<100 \times 10^9$ cells/l;
- hemoglobin level < 100 g/l;
- creatinine exceeds the upper limit of normal by more than 1.25 times;
- transaminases (AST, ALT) and alkaline phosphatase exceed the upper limit of normal by more than 2.5 times; total bilirubin exceeds the upper limit of normal by more than 1.5 times;
- atrial or ventricular arrhythmias in history that were clinically significant or required treatment;
- heart failure, in particular. in the anamnesis;
- a history of myocardial infarction within the previous 12 months;

- any unstable therapeutic or psychiatric condition that, in the opinion of the investigator, may impair the patient's ability to complete the study or prevent participation in the study;
- the need to take drugs that are not recommended (see section 8.2);
- participation in any other clinical trial.

Randomization and treatment scheme: All patients included in the study were divided into 2 groups in a ratio of 1:1, 30 people each, by the method of simple randomization. The allocation of female patients to the group was carried out on the basis of a randomization scheme formed on the basis of a table of random numbers obtained using the generation of random numbers in the MS Excel program.

Patients **of the main and control groups** received neoadjuvant polychemotherapy in accordance with international standards for the treatment of breast cancer according to the AS scheme (doxorubicin 60 mg/m^2 plus cyclophosphamide at a dose of 600 mg/m^2) in the form of 4 courses with an interval of 3 weeks.

In addition, patients **of the main group** on the background of CT received the study drug Donovit-VS®, tablets manufactured by Astrapharm LLC, 1 tablet 3 times a day for 3 months.

Concomitant treatment. To prevent nausea/vomiting, patients were prescribed ondansetron 8 mg IV 30 minutes before chemotherapy and dexamethasone 12 mg IV 30 minutes before chemotherapy on day 1, followed by ondansetron 8 mg daily. internally on days 2-4. According to indications, cardioprotectors and hepatoprotectors were prescribed.

Performance evaluation criteria:

Main variable:

- the degree of toxicity of chemotherapy in the course of treatment (the assessment was carried out in accordance with WHO recommendations, according to the CTC *NCIC* toxicity scale).

Secondary variables:

- the dynamics of the patient's quality of life during treatment (the assessment was carried out according to the questionnaire of the European Organization for Research and Treatment of Cancer EORTC QLQ – C 30);
- dynamics of the size of tumor formations before the end of the course of treatment (according to mammography data).

Portability Variables:

- the presence and nature of adverse events, their connection with the researched drug;
- dynamics of vital indicators (BP, heart rate, body t);
- dynamics of ECG data;
- dynamics of laboratory indicators (general blood test, general urine test, biochemical blood test).

Statistics.

When analyzing the study data, descriptive statistics methods were used (for quantitative variables, indicators were calculated - n, arithmetic mean, median, standard deviation, minimum and maximum, and for categorical variables - frequency and proportion in%), graphical methods, interval estimation methods (construction of confidence intervals for arithmetic means or medians, depending on the agreement of data with the normal distribution law), methods of two-way analysis of variance followed by the use of contrast analysis. The Mann-Whitney test or Student's t-test for independent samples (depending on the normality of the data distribution) was used to assess the significance of differences between the two groups, the Wilcoxon signed-rank test or Student's t-test for related samples was used to compare the values of indicators before and after treatment.

For performing comparisons, the level of significance was taken equal to 0.05. To analyze the consistency of the data distribution with the normal distribution law, the Shapiro-Wilk test was used at a significance level of 0.01.

Performance evaluation results.

Based on the results of the analysis, it can be concluded that there are statistically significant differences between the groups, which prove that the positive effect in preventing toxic reactions of chemotherapy and reducing the degree of their severity in patients who received neoadjuvant antitumor chemotherapy compared to the studied group exceeds the **positive** effect patients who received only chemotherapy.

1) A more pronounced decrease in the level of leukocytes and neutrophils (abs. count) was revealed, starting from the 1st course of chemotherapy in patients of the control group, compared to the main group.

2) A more pronounced decrease in the level of platelets was found starting from the 3rd course of chemotherapy in patients of the control group compared to the main group.
3) A significantly higher frequency of leukopenia and neutropenia was found in patients of the control group compared to the main group.
4) A statistically significantly higher number of patients in the control group compared to the main group experienced chemotherapy-induced nausea/vomiting.
5) A significantly more significant decrease in quality of life was established on the scale of "assessment of the general state of health" and the scale of "assessment of the quality of life" according to the data of the EORTC QLQ-C30 questionnaire, in patients of the control group compared to the main one at all stages of treatment.
6) It can also be stated that the groups in the course of treatment differed statistically significantly in the evaluation of the general condition according to the ECOG scale in favor of the patients of the main group.

The above confirms the conclusion about the superior effectiveness of the treatment in the group of patients who received, against the background of neoadjuvant antitumor chemotherapy, the study drug Donovit-VS®.

The results of the tolerability assessment.

The data obtained during the research also allow us to conclude about the good tolerability of the studied drug. In the course of the study, no allergic and anaphylactic reactions, significant fluctuations in hemodynamic parameters were recorded in the group of patients taking the study drug. None of the patients taking the study drug had serious AE/AR, and none of the patients dropped out of the study due to AE/AR.

All AE/AR registered during the study were directly related to chemotherapy and corresponded to the toxicity profile of the chemotherapy drugs used. In no case did the researcher establish a connection between the observed AE/AR and the study

drug. It should also be taken into account that in the group of patients taking the study drug Donovit-VS® , the number of AE/AR was significantly lower than in the group of patients not taking Donovit-VS® (the number of AE/AR: 132 in the main group and 173 - in the control room).

Based on the above, it can be assumed that the tolerability of the study drug Donovit-VS® was good in all 100% of patients.

Conclusions and recommendations.

1. Based on the data of a clinical study, it was proven that the treatment of patients with breast cancer was more effective in the group that received, against the background of antitumor chemotherapy, the researched drug Donovit-VS®, tablets manufactured by Astrapharm LLC, compared to the group of patients that received only chemotherapy, the main variable. This was manifested in a decrease in the severity and frequency of such chemotherapy complications as: leukopenia, neutropenia, as well as in a decrease in the severity and frequency of nausea and vomiting.
2. It was established that patients who took the study drug Donovit-VS® had a higher quality of life during chemotherapy treatment, according to the EORTC QLQ-C30 questionnaire, compared to patients who did not take Donovit-VS®.
3. The study drug Donovit-VS®, tablets produced by Astrapharm LLC, was well tolerated by all 100% of patients. In the course of the study, no allergic and anaphylactic reactions, significant fluctuations in hemodynamic parameters were recorded in the group of patients who took the drug Donovit-VS®. No serious AE/AR were reported in any of the study drug patients, and none of the patients dropped out of the study due to AE/AR. It should be noted that in the group of patients who took the study drug Donovit-VS®, the number of AE/AR was significantly lower than in the group of patients who did not take Donovit-VS® (the number of AE/AR: 132 in the main group and 173 - in the control room).
4. Based on the data obtained during the clinical study, the researched drug Donovit-VS®, tablets produced by Astrapharm LLC can be recommended for medical use in patients with breast cancer as an accompanying drug during a

course of chemotherapy, in order to prevent and reduce the severity of toxic reactions chemotherapy and improving the quality of life. Recommended regimen: 1 tablet 3 times a day for 3 months.

The report contains: 138 pages, 73 tables, 16 figures, bibliography - 29 sources.

2. LIST OF ABBREVIATIONS AND TERMS

AP - arterial pressure
ALT - alanine aminotransferase
AST - aspartate aminotransferase
ASA - acetylsalicylic acid
VGN - the upper limit of the norm
WHO - the World Health Organization
SEC - State expert center of the Ministry of Health of Ukraine
DBP - diastolic blood pressure
IRF - an individual registration form
IU - international units
MTD - maximum tolerated dose
NSAIDs - nonsteroidal anti-inflammatory drugs
OAC - organs of the abdominal cavity
CO - chest organs
AR - side reaction
AE - side effect
PCT - polychemotherapy
BC - breast cancer
RN - randomization number
SBP - systolic blood pressure
HF - heart failure
SNR - standard normal distribution
VA - variance analysis
SD - standard deviation
ESR - erythrocyte sedimentation rate
Ultrasound - ultrasound examination
LVEF - left ventricular ejection fraction
CT - chemotherapy
HR - heart rate
ECG - electrocardiography
CBEP - central body of executive power

GCP - Good Clinical Practice

ICH - International Conference on Harmonization

t^0 - body temperature

EORTC - European Organization for Research and Treatment of Cancer

EORTC QLQ - C 30 - European Organization for Research and Treatment of Cancer quality of life questionnaire

CTC *NCIC - Common Toxicity Criteria* National Cancer Institute - *toxicity assessment scale of the National Cancer Institute*

3. ETHICAL AND LEGAL ASPECTS OF RESEARCH

3.1. Approval of the protocol by official bodies

Before the start of the study, the sponsor of the study provided the clinical study protocol, a sample of IRF, written information for the patient and an informed consent form to the Central body of executive power (CBEP) and the Ethics Committee of the Rivne Regional Oncology Dispensary. This study was started only after receiving the decision of the CBEP to conduct a clinical trial and approval of the protocol by the Ethics Committee.

3.2 Ethical aspects of research

This clinical study was conducted in accordance with the ethical principles of the Declaration of Helsinki in its latest edition, adopted at the 64th General Assembly of the World Medical Association (World Medical Association - WMA), Fortaleza, Brazil, October 2013, international ICH GCP), current regulatory documents and legislation of Ukraine.

3.3. Procedure for obtaining informed consent

Written informed consent to participate in the study was obtained from each potential participant prior to any screening procedures.

Information about this clinical study was provided in a form accessible to patients by the principal investigator (or researcher) on the basis of written information and an informed consent form. The content of the information related to the nature of the clinical study, the properties of the researched drug, as well as the possible risk associated with the use of the drug, the rights and responsibilities of the patient participating in the study.

Written information was provided to the patient, at her request, in Russian or Ukrainian.

Patients were informed that they could refuse to participate in the study at any time, without prejudice to further treatment.

Patients were also familiarized with the conditions of confidentiality and use of their personal data, including the need for access to them by authorized persons (in case of audit, inspection, etc.).

Each patient was given sufficient time to consider the possibility of her participation in the study and to ask the researcher what she was interested in. The researcher did not put pressure on the patient to influence her decision.

If the patient decided to participate in the study, she filled out and signed the Informed Consent Form in her own hand, in 2 copies, one copy of which was given to the patient with information about participation in the clinical study, as well as information about her mandatory insurance contract life. and health, as participants in a clinical study, the 2nd copy of this form remained in the research center for further storage for 15 years.

3.4. Privacy

All documentation of the study was conducted in compliance with the conditions of strict confidentiality. The researcher and the Sponsor have ensured the protection of personal data of the patients participating in the study. The necessary personal data of the research participants (for example, socio-demographic parameters) were used exclusively to achieve the research goals.

3.5. Insurance

This clinical study was insured by the Study Sponsor before its commencement in accordance with the current legislation of Ukraine. All patients who signed the informed consent form were covered by insurance.

The terms and procedure for payment of the insurance amount in the event of damage to the patient's health as a result of treatment with the researched drugs are set forth in the insurance contract, a copy of which was provided to the researcher by the Sponsor.

4. RESEARCHERS AND RESEARCH ADMINISTRATIVE STRUCTURE

Research sponsor Aksomed LTD NVF LLC 04210, Kyiv, avenue Heroes of Stalingrad 6 building 4. tel. (044) 537-78-41	
Director	Ph.D., associate professor G.N. Aksonov
Scientific consultant	Doctor of Medicine, Honored Doctor of Ukraine V.V. Sobetskyi

Place of research	
Communal establishment "Rivna Regional Oncology Dispensary", Department of Breast and Head and Neck Tumors 33013, Rivne, st. Oleksandra Olesya, 12 (036) 268-36-69	
Responsible executor	Chief division of breast and head and neck tumors Yakymchuk P.M.
Researchers	Maksym'yak G.I. Yakymchuk M.P.

5. INTRODUCTION

5.1. State of the problem

Malignant tumors of the breast occupy the first place in the structure of oncological morbidity and mortality from oncology in the female population worldwide. Every year, more than 1 million women are registered with breast cancer for the first time, and every year more than 600 thousand patients die from this disease. In recent years, approaches to the treatment of breast cancer have changed significantly. These changes mainly affected the early diagnosis of the disease and the wider use of chemotherapy (CT), which occupies a prominent place in the modern therapy of cancer patients. The success of modern CT has made it possible to achieve positive results in the treatment of many malignant neoplasms that were previously considered fatal. Malignant formations of the breast were found to be sensitive to most modern anticancer drugs, primarily to doxorubicin (effective in 40% of patients), cyclophosphamide (35%) and fluorouracil (25%). According to many researchers, the inclusion of CT in the treatment regimen of breast cancer patients reliably reduces disease recurrence rates by 23.8%, and mortality rates by 15%. However, the negative side of CT is the side effects of anticancer drugs caused by the low selectivity of most cytostatics, which is a serious limitation in achieving the maximum therapeutic effect.

Side effects of CT are distinguished by the time of occurrence after the start of administration. Conditionally, immediate, immediate and delayed side effects are distinguished. Nausea, vomiting, fever, and increased body temperature are among the immediate side effects that appear immediately or during the first day. The closest side reactions appear within 7-10 days (suppression of bone marrow hematopoiesis, decrease in the level of leukocytes, erythrocytes, dyspeptic syndrome, neurological disorders, toxic damage to organs). Delayed side effects are possible several weeks or more after the end of the course of treatment.

In the structure of complications of CT, one of the leading places, according to the data of various authors, are toxic effects manifested on the myeloid germ of hematopoiesis. Various CT schemes reduce the content of granulocytes (neutrophils)

in peripheral blood to one degree or another. Neutropenia is the most common hematological complication of CT in cancer patients, caused by damage to the granulocytic bud of hematopoiesis. The presence of neutropenia is associated with a high risk of bacterial infection. The appearance of fever in these patients is directly correlated with the intensity of CT. *So-called febrile neutropenia* develops in 10–40% of patients with solid tumors who received CT in standard doses. More than 20% of patients with febrile neutropenia register bacteremia when the number of neutrophils in the blood decreases to less than 1.0×10^9/l. This condition is life-threatening for patients because, if not treated properly, it can lead to septic shock and death. III-IV degree neutropenia is the main limiting factor that prevents the initiation of CT and causes the need to reduce doses of chemotherapy drugs, delay and/or cancel treatment courses. Thrombocytopenia as a complication of CT also represents a clinical problem, the most threatening manifestations of which are hemorrhages, which are often fatal, especially in the presence of concomitant infection. Anemia can significantly impair quality of life and tolerability of CT.

It is assumed that the inclusion of the researched drug Donovit-VS® as an "accompanying" drug in the main treatment regimens will reduce the toxic effect of chemotherapy on internal organs and contribute to the normalization of bone marrow hematopoiesis, stabilization of hemodynamic indicators and improvement of the patient's general well-being.

5.2. Description of the studied drug

The researched drug Donovit-VS®, tablets produced by Astrapharm LLC, is an original development of the research and production company Aksomed LTD, presented for clinical study in order to resolve the issue of the possibility of registering the drug in Ukraine as a medicinal product.

The drug Donovit-VS® belongs to anticancer drugs. The composition of the drug includes an extract of the rhizome of aconite (wrestler) - 1 tablet contains 10 μg of alkaloid aconitine, auxiliary substances - lactose, calcium stearate.

Pharmacological action.

Donovit-VS exhibits pronounced antitumor activity against solid tumors with angiogen-dependent growth. The drug also significantly suppresses the process of metastasis, reducing both the number of metastases and their volume. The antitumor and antimetastatic effect is dose-dependent and due to the implementation of two mechanisms: antivascular (at total doses of the order of MTD/2) and antiangiogenic (at total doses less than MTD/20). The anti-angiogenic mechanism of action determines the anti-tumor and anti-metastatic effect only in relation to malignant neoplasms with angiogenic-dependent growth.

Possible indications for use.

The drug is intended to be used in the treatment of oncological diseases, as a therapy "accompaniment" of the main treatment, treatment of the consequences of toxic and radiation reactions, as a supportive (symptomatic) therapy of late complications of tumor processes.

The drug is intended to be used at the I-III stage of the tumor process with:

- brain tumors (astrocytomas, glioblastomas, medulloblastomas, melanoma metastases to the brain);
- breast tumors;
- prostate cancer;
- lung cancer;
- uterine cancer;
- bowel cancer

Contraindications are possible.

Hypersensitivity to the components of the drug. The nature of contraindications will be specified in the course of clinical trials.

Special warnings.

Patients with severe kidney and/or liver dysfunction should reduce the daily dose by half. The drug contains lactose, so it should not be prescribed to patients with rare hereditary forms of galactose intolerance and lactase deficiency.

Method of application and dosage.

1 tablet 3 times a day for 3 months. A combination with radiation and chemotherapy is possible.

Possible schemes for prescribing the drug under study will be specified in the course of clinical trials.

Adverse reactions.

The appearance of a hypersensitivity reaction in the form of rashes, urticaria, a feeling of heaviness in the epigastric area is possible. The nature of adverse reactions will be clarified in the course of clinical research.

Overdose.

The use of too high doses of the drug leads to the appearance of nausea, shortness of breath, headache, facial hyperemia. One of the first signs of an overdose is numbness of the tip of the tongue and lips, sometimes a feeling of numbness of the scalp.

Features of application.

The drug should not be used at night, as it may cause insomnia in some patients.

Use during pregnancy and lactation. There are no data.

Interaction with other medicinal products. There are no data.

5.3. Preclinical studies of the drug Donovit -VS®

Preclinical studies of the drug "Donovit-VS" (VS-1 test agent), conducted by the Institute of Experimental Pathology, Oncology and Radiobiology named after RE. Kavetsky National Academy of Sciences of Ukraine. The research was conducted on three types of animals: mice, rats and pigs of the "Vietnamese flat-bellied" breed. As a result of the conducted research, the following reports were prepared:

1. "Study of the specific antitumor activity of the VS-1 agent (the name of the drug Donovit-VS at the preclinical stage) against Lewis lung carcinoma with low metastatic potential (LLC/R9)."

2. "Comparative study of the specific antitumor activity of the VS-1 agent in relation to variants of Lewis carcinoma LLC and LLC/R9 with different dependence on angiogenesis"

3. "Study of the specific pharmacological activity of the drug VS-1 in relation to melanoma B16"

4. "Investigation of the specific antitumor activity of the VS-1 agent in relation to variants of Geren's carcinoma of rats with high and low rates of tumor growth"

5. "Study of antitumor and antimetastatic activity of VS-1 in relation to tumor models: Lewis lung carcinoma LLC/R9, sarcoma (S 180) and lymphoid leukemia L1210"

6. "Investigation of the specific antitumor activity of the VS-1 agent in relation to rat brain glioma"

7. "The effect of VS-1 on the life span of mice with Lewis carcinoma"

8. "Comparative study of the antitumor activity of VS-1 in relation to ascites and solid forms of Ehrlich's sarcoma"

9. "Determination of the maximum tolerated dose (MTD) and analysis of the acute toxicity of the VS-1 agent in mice and rats"

10. "Study of the cumulative properties and chronic toxicity of the VS-1 agent on mice"

11. "Study of immunotoxicity of VS-1 in mice"

12. "Investigation of the cumulative properties and chronic toxicity of the VS-1 agent on Vietnamese flat-bellied pigs"

The conducted research made it possible to draw the following conclusions:

A) VS-1 has a pronounced antitumor effect on malignant neoplasms with angiogenesis-dependent growth and is ineffective against tumors with an unexpressed vascular network. This indicates the **antiangiogenic** mechanism of the antitumor effect of this agent.

B) VS-1 has an antitumor effect on malignant brain neoplasms (for example, rat glioma), which is manifested in an increase in life expectancy by more than 19%.

C) VS-1 has no antitumor effect on the ascites form of Ehrlich's carcinoma. At the same time, the solid form of this tumor model is sensitive to the action of VS-1,

which is manifested in the pronounced stabilization of tumor growth, which provides inhibition of tumor growth by more than **77%.**

D) Metronomic administration of VS-1 in a total dose of MTD/2 leads to a **73%** increase in the lifespan of mice with **Lewis carcinoma.**

E) VS-1 has a pronounced anti-metastatic effect on LLC/R9 tumor cells during passive and spontaneous metastasis. As a result of the experiment, it was established that VS-1 has a pronounced antimetastatic effect in relation to Lewis carcinoma resistant to cis-DDP. The percentage of inhibition of metastasis, estimated by the average number of metastases in the group, is **92.2%.**

F) The proposed hypothesis that VS-1 has **a high antitumor effect on fast-growing tumors** was confirmed in experiments on two variants of Geren's **carcinoma**.

G) The use of the test agent VS-1 in a dose of MTD/2 was **not effective** against the tumor model **L1210 of lymphoid origin**.

H) VS-1 at a dose of MTD/2 showed antitumor activity against **S 180** sarcoma , which was expressed in inhibition of tumor growth by **60% on the 19th day,** after resection of the tumor.

I) The tested test agent at a dose of MTD/2 showed antitumor and antimetastatic activity against **Lewis LLC lung carcinoma** , which was expressed in the treatment of **40%** of animals and in the absence of metastases in **37%** of animals of the experimental group.

The results of preclinical studies are published in the article: ANTICANCER ACTIVITY OF ACONITINE-CONTAINING HERBAL EXTRACT BC1. Exp Oncol 2004 26,4, 307-311.

In 2003, the drug Donovit-VS was registered in Ukraine as a biologically active dietary supplement. For several years, in the Main Military Clinical Hospital of the Ministry of Defense of Ukraine, the Kyiv City Oncology Clinic and the "Medicom" clinic, Donovit-VS was used as part of the complex therapy of immunodeficiency states, persistent viral infections, as well as tumor diseases of the III-IV clinical stage as a monotherapy of accompanying therapy - after PCT and radiation therapy of tumors of various genesis.

In the treatment of oncological diseases of the III-IV clinical stage, Donovit-VS was included in the treatment schemes, as: therapy "accompaniment" of the main treatment; treatment of the consequences of toxic and radiation reactions; supportive (symptomatic) therapy of late complications of tumor processes. The terms of treatment ranged from 2 months to 2.5 years. The improvement was determined by the general well-being of patients, stabilization of hemodynamic parameters, reduction of manifestations of compressive, edematous and dyspeptic syndromes. The time of onset of primary effects is from 2 weeks to 1 month. Treatment courses were continuous with periodic consolidation of the effect. A particularly pronounced effect, with prolongation of survival, was observed in patients with brain and lung tumors. Thus, the number of positive reactions to treatment was 70%,

The use of dietary supplements Donovit-VS in COPD, bronchial asthma, osteochondrosis, depressive syndromes increased the effect of basic drugs, their dose was reduced, which made it possible to achieve a clinical effect in a short time.

Side effects when using the drug Donovit-VS were not observed in any case. Treatment avoidance was not accompanied by a withdrawal syndrome. Detailed information about the clinical observations of the drug is presented on the website of the Aksomed Foundation: aksomed.kiev.ua and donovit.com

5.4. Results of the first phase of the clinical trial of the drug Donovit-VS®.

The first phase of the clinical study of the drug Donovit-VS® tablets manufactured by Astrapharm LLC was conducted on the basis of the Rivne Regional Oncology Dispensary. The study included 20 male and female patients aged 18 to 65 with a diagnosis of colorectal cancer, T_{2-4} N_{0-2} M_0 after surgical resection of the tumor and 4 courses of polychemotherapy. All included patients, by the method of simple randomization, were divided in a ratio of 1:1 into 2 groups of 10 people. Patients of each group received the study drug according to different schemes: I group - 1 tablet 2 times a day for 28 days; II group - 1 tablet three times a day for 28 days. The objectives of the study were:

assessment of tolerability and identification of possible adverse reactions to the study drug, and comparison of the tolerability of two different regimens of treatment with the study drug.

The data obtained in the study made it possible to conclude about the good tolerability of the drug under study in all treatment regimens under study. The drug did not affect the results of objective clinical and laboratory studies, which made it possible to express a generalized assessment of the tolerability of the treatment as "good" in both compared groups.

6. PURPOSE AND OBJECTIVES OF THE RESEARCH

The purpose of this study was to evaluate the effectiveness and tolerability of the drug Donovit-VS®, a tablet produced by Astrapharm LLC, used in patients with breast cancer on the background of chemotherapy compared to a group of patients receiving only chemotherapy.

Objectives of the study:

- to study the influence of the researched drug on the level of toxicity of chemotherapy;
- to study the effect of the researched drug on the patient's quality of life;
- to study the influence of the researched drug, which is used against the background of CT, on the dynamics of the size of the tumor formation;
- to compare the results of treatment obtained in the main and control groups, with the aim of establishing the superior effectiveness of treatment in the group of patients receiving chemotherapy + Donovit-VS® comparison with the group of patients receiving only chemotherapy.

7. DESCRIPTION OF CLINICAL RESEARCH METHODOLOGY

7.1. Study design

This study was conducted as an open comparative randomized in parallel groups.

7.2 Number of patients (planned and analyzed)

The planned number: 60 patients (30 patients - the main group and 30 patients - the control group).

The number of patients randomized to the study is 60.

The number of patients who completed the study according to the protocol is 60.

7.3. General description of the study

60 patients who are being treated in the Department of Breast and Head and Neck Tumors of the Rivne Regional Oncology Clinic took part in the study and met the inclusion/exclusion criteria described in the study protocol. The patients included in the study were diagnosed with breast cancer ($T_1N_{1-3}M_0$, $T_2N_{0-3}M_0$, $T_3N_{0-3}M_0$), confirmed by the data of a histological or cytological examination. All patients were prescribed neoadjuvant polychemotherapy according to the AS scheme (doxorubicin 60 mg/m^2 plus cyclophosphamide at a dose of 600 mg/m^2).

After the clinical evaluation, the eligible candidates were provided verbal and written information about the investigational drug and the study. All potential research participants were given time to consider their participation in the study and an opportunity to ask questions of the researcher. All potential study participants provided written informed consent prior to initiation of any study procedures.

Potential patients underwent screening procedures at visit 1. Screening lasted up to 7 days.

If the patient met all inclusion/non-inclusion criteria, she was assigned by simple randomization to one of the treatment groups: main or control. Patients of the main and control groups received neoadjuvant polychemotherapy in accordance with international standards for the treatment of breast cancer according to the AS scheme (doxorubicin 60 mg/m^2 plus cyclophosphamide at a dose of 600 mg/m^2). In addition, patients of the main group on the background of CT received the study drug Donovit-VS®, tablets produced by Astrapharm LLC.

Table 1 - Therapy plan in the main and control groups

V 1	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**
D (- 7-0)	**D0**	**D21**	**D42**	**D63**	**D90(±3)**
Screening	**Randomization**				**Final visit**
	Main group Chemotherapy + Donovit- **VS®**				
	1st course of chemotherapy	2nd course of chemotherapy	3rd course of chemotherapy	4th course of chemotherapy	
	↓↓	↓↓	↓↓	↓↓	↓
	Control group Chemotherapy				
	↓	↓	↓	↓	
V - visit D - day					

Four courses of chemotherapy were planned for each patient. Patients who received less than 4 courses of chemotherapy could continue to participate in the study, regardless of which group, the main or the control, they belonged to. Patients who received at least 2 courses of CT were included in the efficacy analysis.

Registration of patient examination data (Visits) was carried out at the following time points: before the start of treatment, then every 3 weeks (after the next course of CT) for 3 months. The last, final visit was carried out on the 90th day from the start of treatment, regardless of how many courses of CT the patient took.

Before the start of the study, each patient underwent a physical examination, chest x-ray, ultrasound of the abdominal cavity, general blood analysis, biochemical blood analysis, general urinalysis, ECG at rest, pregnancy test, functional status was determined according to the ECOG scale. Baseline assessment before starting treatment also included assessment of tumor size based on mammography data.

All patients included in the study had an ECOG functional status of 0 to 2 and a life expectancy of at least 12 weeks. Additional criteria included sufficient bone marrow reserve (leukocyte content $\geq 2.0 \times 10^9$ cells/l, neutrophils $\geq 1.5 \times 10^9$ cells/l; platelets $\geq 100 \times 10^9$/l, hemoglobin level ≥ 100 g/l), as well as sufficient liver and

kidney function (AST, ALT did not exceed the upper limit of normal by more than 2.5 times; total bilirubin did not exceed the upper limit of normal by more than 1.5 times creatinine did not exceed the upper limit of normal by more than 1.25 times). Patients were excluded from the study if they had a history of clinically significant atrial or ventricular arrhythmias, heart failure, myocardial infarction within the previous 12 months, as well as any unstable therapeutic or psychiatric condition that, in the opinion of the researcher, could impair the patient's ability to prevent participation in it. Pregnant or breastfeeding women could not participate in the study.

In the course of the study, after each course of chemotherapy, the patients underwent a physical examination, subjective complaints were recorded, a general comprehensive blood test, biochemical blood test, urinalysis, ECG were performed, and functional status was determined according to the ECOG scale. In addition, at Visits 1, 4 and 6, patients filled out the EORTC QLQ - C 30 quality of life questionnaire. After each course of CT, chemotherapy toxicity was assessed according to WHO criteria on the CTC *NCIC* scale .

3 months after the start of therapy, at the visit, 6 patients underwent mammography in order to assess the response of the tumor to treatment.

The main variable in this study was the degree of chemotherapy toxicity during treatment. Secondary variables are the level of the patient's quality of life during treatment and the size dynamics of tumor formations before the end of the treatment course (according to mammography data).

Tolerability variables were the presence and nature of adverse events, their relationship with the study drug, dynamics of vital indicators (BP, heart rate, body t), dynamics of ECG data, dynamics of laboratory indicators (general blood test, general urine test, biochemical blood test) .

All patients who received at least two courses of treatment were considered suitable for evaluating the effectiveness of treatment with the study drug. All randomized patients who received at least one dose of the study drug were evaluated for tolerability.

The results of all the patient's examinations conducted were registered in the primary and secondary medical documentation (IMD).

7.4. Randomization

Allocation of patients to treatment groups was carried out on the basis of a randomization scheme formed on the basis of a table of random numbers obtained by means of the generation of random numbers of the MS Excel program.

To carry out the allocation procedure to the treatment groups, the Sponsor provided the investigator with envelopes numbered according to the randomization scheme. The patient's randomization number (from 01 to 60) was marked on the envelopes, and the group to which the patient should be allocated was in the envelope. Randomization numbers were given to patients in chronological order according to the assignment of screening numbers to them. On the envelope, the researcher indicated the initials of the patient and the date of randomization. In the process of the study, a log of screening/randomization of patients was kept.

7.5. The duration of the patient's participation in the study

The duration of the patient's participation in the study was 3 months + (3-7) days, of which: up to 7 days were screening and 3 months - treatment.

` 7.6. Schedule of research procedures

Registration of the studied indicators was carried out before the start of treatment, then before the start of the 2nd, 3rd, and 4th courses of CT and 90 days after the start of CT.

Periodicity of examination of patients and registration of the received data was carried out in accordance with the following schedule:

Table 2 – Schedule of research procedures

Data registration points	Screening	1st course CT	2nd course CT [1]	3rd course CT [1]	4th course CT [1]	27-30 days after the 4th course of CT
Days	**D (-7-0)**	**D0**	**D 21**	**D 42**	**D 63**	**D 90 (±3)**
Visits	**1**	**2**	**3**	**4**	**5**	**6**
Anamnesis	*					
Obtaining written informed consent	*					
Pregnancy Test	*					
Mammography	*					*
R-graph of chest organs	*					
Ultrasound of abdominal organs	*					
EKG	*		*	*	*	*
Objective examination	*		*	*	*	*
- general analysis of urine - general blood test - biochemical blood analysis	*		*	*	*	*
Assessment of the functional state of the patient according to the ECOG scale	*		*	*	*	*
Evaluation of the degree of toxicity of therapy according to the CTC *NCIC scale*			*	*	*	*
Evaluation of the quality of life according to the EORTC QLQ scale – C 30	*			*		*
Assessment of the patient's compliance with inclusion/exclusion criteria.		*				
Randomization, treatment assignment		*				
Issuance of the researched drug		*	*	*	*	
Identification and registration of possible AE/AR			*	*	*	*

[1] *Examination of patients and data registration were carried out 1-2 days before the start of each course of CT.*

7.7. Plan of visits

Visit 1 (screening):

- registration of demographic and physical data (age, height, body weight);
- collection of anamnesis (including information about concomitant diseases and taking concomitant medications);
- pregnancy test (for women of reproductive age);
- objective examination;
- measurement of blood pressure, heart rate, body t;
- mammography;
- Ultrasound of abdominal organs;
- X-ray of chest organs;
- ECG at rest;
- assessment of the patient's functional state on the ECOG scale;
- assessment of the patient's quality of life according to the EORTC QLQ scale – C 30;
- general blood test;
- general analysis of urine;
- biochemical blood analysis.

Visit 2 (before the 1st course of CT):

- determination of the patient's compliance with inclusion/non-inclusion criteria;
- randomization;
- appointment of treatment;
- dispensing of the researched drug.

Visit 3 (before the 2nd course of CT):

- objective examination;
- measurement of blood pressure, heart rate, body t;
- registration of therapy, including concomitant therapy;
- ECG at rest;
- assessment of the patient's functional state on the ECOG scale;
- assessment of the degree of toxicity of therapy according to the CTC *NCIC* scale ;
- general blood test;
- general analysis of urine;
- biochemical blood analysis;
- registration of AE/AR;

- issuance/accounting of the researched drug.

Visit 4 (before the 3rd course of CT):

- objective examination;
- measurement of blood pressure, heart rate, body t;
- registration of therapy, including concomitant therapy;
- ECG at rest;
- assessment of the patient's functional state on the ECOG scale;
- assessment of the degree of toxicity of therapy according to the CTC *NCIC* scale;
- assessment of the patient's quality of life according to the EORTC QLQ scale C 30;
- general blood test;
- general analysis of urine;
- biochemical blood analysis;
- registration of AE/AR;
- issuance/accounting of the researched drug.

Visit 5 (before the 4th course of CT):

- objective examination;
- measurement of blood pressure, heart rate, body t;
- registration of therapy, including concomitant therapy;
- ECG at rest;
- assessment of the patient's functional state on the ECOG scale;
- assessment of the degree of toxicity of therapy according to the CTC *NCIC* scale ;
- general blood test;
- general analysis of urine;
- biochemical blood analysis;
- registration of AE/AR;
- issuance/accounting of the researched drug.

Visit 6 (final, 27-30 days after the 4th course of CT):

- objective examination;
- measurement of blood pressure, heart rate, body t;
- registration of therapy, including concomitant therapy;
- mammography;
- ECG at rest;
- assessment of the patient's functional state on the ECOG scale;
- assessment of the degree of toxicity of therapy according to the CTC *NCIC* scale ;
- assessment of the patient's quality of life according to the EORTC QLQ scale C 30;

- general blood test;
- general analysis of urine;
- biochemical blood analysis;
- registration of AE/AR.

7.8. Procedures and methods of research

1). Acquisition of informed consent.

Written informed consent to participate in the study was obtained from all potential participants prior to the initiation of any diagnostic and treatment procedures related to this study.

Each patient filled out and signed the Informed Consent Form in her own hand, in 2 copies, one copy of which was given to her, the other remained in the research center for further storage for 15 years.

The fact of discussing the informed consent was recorded in the medical history and IRF with the date of signing.

2). History collection.

Life and disease anamnesis was conducted according to the generally accepted methodology and included: mammography data, tumor characteristics, stage of the disease, results of R-graphy of chest organs and ultrasound of abdominal organs, concomitant diseases, therapy that the patient received during the last 3 months. The anamnesis of the patient's life and illness was reflected in the primary documentation and IRF.

3). Pregnancy Test.

It was carried out with the help of test strips in the urine. Women of reproductive age, at the time of inclusion in the study, used adequate methods of contraception and agreed to continue their use throughout the study and 30 days after the last administration of the study drug. Acceptable methods of contraception were: intrauterine spiral, barrier method (condom, contraceptive cap, cervical cap or spermicide), hormonal contraception, previously performed surgical sterilization.

4). Objective review.

It included an assessment of the patient's general condition, an examination of organs and systems. In the primary documentation and IRF, the result of the

examination of each system at the first visit was noted. At subsequent visits, data on the changes recorded during the examination were entered into the primary documentation and IRF. Identified changes were given a brief assessment of their compliance with the FP/PR.

5). Measurement of heart rate, blood pressure and body temperature.

Heart rate, blood pressure, and body temperature were measured at each visit during the study. Blood pressure was measured according to the standard method, after the patient had rested for 15 minutes, three times with breaks between measurements of at least 10 minutes. In the IRF, the average values of the results of three measurements were recorded. Heart rate was measured once.

Body temperature was measured in the armpit with a mercury thermometer.

6). A resting ECG was performed before starting treatment, then before each course of CT and at the final visit.

In case of significant ECG changes, echocardiography, daily ECG monitoring, and consultation with a cardiologist were provided.

7) R-graphy of chest organs and ultrasound of abdominal organs were carried out at the screening stage or the results of studies carried out no earlier than 4 weeks before screening were taken into account.

8). Assessment of the functional state according to the ECOG scale, designed to determine the working capacity of oncology patients according to degrees from 0 to 4, where 0 - the patient maintains full activity; 4 – cannot perform self-service.

Table 3 - ECOG scale

Mark	Sign
0	No symptoms
1	There are symptoms, but daily activities are preserved
2	Spends less than half of the day in bed
3	Spends half of the day or more in bed
4	Does not get up, requires care

9). Chemotherapy toxicity was assessed using *the Common Toxicity Criteria NCIC* (CTC *NCIC*) toxicity assessment scale.

The scale shows the objective and subjective manifestations of various types of chemotherapy toxicity in 5 grades: 0 – no toxicity, 1 – low toxicity, 2 – moderate toxicity, 3 – severe toxicity and 4 – life-threatening toxicity.

Evaluation of the toxicity of chemotherapy according to the scale was carried out after each course of CT, as well as at the final visit.

Table 4 - Chemotherapy toxicity rating scale

Indicator	Degree of toxicity				
	0	1	2	3	4
Hemoglobin, g/l	>110 g/l	95-109 g/l	80-94 g/l	65-79 g/l	<65 g/l
Leukocytes 10^9 /l	>4.0	3-3.9	2-2.9	1.0-2.0	<1.0
Neutrophils 10^9 /l	>2	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Platelets 10^9 /l	>100	75-99	50-74	25-49	<25
Bleeding	absent	Weak petechiae	Do not require treatment or transfusion. of blood	Expressed, requires a blood transfusion up to 4 times of 500 ml each.	It is necessary to transfuse. of blood > than 4 times for 500 ml
Bilirubin	<1.25 x N[a]	1.25-2.5 x N[a]	1.25-5.0 x N[a]	5.1-10.0 x N[a]	> 10.0 x N[a]
AST, ALT	<1.25 x N[a]	1.25-2.5 x N[a]	1.25-5.0 x N[a]	5.1-10.0 x N[a]	> 10.0 x N[a]
Diarrhea	absent	Disappears in less than 2 days	Tolerate more than 2 days	Intolerable, needs treatment	Hemorrhages and dehydration, requiring intravenous fluids
Nausea vomiting	Absences.	Nausea	Vomiting that passes	Vomiting that needs treatment	Unbearable vomiting
The state of the oral cavity	Unchanged	Itching, heartburn, erythema	Erythema, ulcers, free food	Ulcers, difficulty in taking food, only liquid food is needed	It is impossible to take food
Proteinuria	Parents	1+<0.3 g/l	2-3+<3-10 g/l	4+<10 g/l	Nephrotic syndrome
Hematuria	Absences.	Microscopic	Macroscopic	Macroscopic + clots	Obstructive uropathy
Light changes	Absences.	X-ray changes are minimal	Moderate symptoms that	Periodic shortness of	Shortness of breath is

			do not require special treatment	breath at rest	constant, requires constant stay in bed
Temperature	Normal	At least 38°C	38°C-40°C	More than 40°C	An increase in temperature with a decrease in blood pressure/collapse
Allergic reactions	Absences.	Dermatitis or edema	Bronchospasm that does not require treatment	bronchospasm, which requires treatment	Anaphylactic shock
Skin manifestations	Absences.	erythema	Dry peeling, vesicles, itching	Wet peeling, ulcers	Necrosis requiring surgical intervention, dermatitis with peeling
Hair	Unchanged	Minimal hair loss	Moderate alopecia areata	Complete but reversible alopecia	Complete, but irreversible alopecia
Infection	Absences.	local	Medium grade	Heavy	Threatening, sepsis
Violation of heart rhythm	Absences.	Sinus tachycardia > 100 bpm at rest	Unifocal ventricular extrasystole, atrial fibrillation	Multifocal extrasystole	Ventricular tachycardia
Violation of heart function	Absences.	Asymptomatic disorders of cardiac activity	Symptomatic dysfunction that resolves does not require treatment	Symptomatic dysfunction corrected by treatment	Symptomatic dysfunction not corrected by treatment
Pericarditis	Absences.	Asymptomatic fluid accumulation	Symptomatic disorders that do not require treatment	Tamponade requiring treatment, myocardial function	Tamponade requiring surgical intervention
Neurotoxicity: state	Alertness	Drowsiness that passes	Drowsiness/time without sleep <50%	Drowsiness/time without sleep >50%	Coma
Peripheral neuropathies	Absences.	Paresthesias/or decreased tendon reflexes	Severe paresthesias, moderate weakness	Intolerable paresthesias, loss of motor reactions	Paralysis
Constipation [b]	Absences.	Rare	Moderate	Abdominal itching	Bloating, vomiting
Pain [c]	Absences.	weak	moderate	Strong	Intolerable, which requires

					the use of drugs

N^a is the upper limit of normal indicators.
b - constipation associated with the use of drugs.
c – pain associated with treatment, not with the disease.

10). Quality of life was assessed using the questionnaire of the European Organization for Research and Treatment of Cancer EORTC QLQ – C 30 (Appendix B).

The EORTC QLQ - C 30 questionnaire consists of 9 main scales: 5 functional scales reflecting physical, role, cognitive, emotional, social functioning; 3 symptom scales including fatigue, pain, nausea and vomiting; a scale of general health and quality of life. The questionnaire also includes additional symptoms (shortness of breath, sleep disturbances, decreased appetite, constipation, diarrhea, and financial difficulties caused by the disease itself and its treatment). The condition according to each of the scales was evaluated within 4 gradations: no - 1 point; rather no than no - 2 points; yes rather than no - 3 points; yes - 4 points.

To facilitate the interpretation of the obtained data, in accordance with the recommendations of the EORTC, all scales and individual questions were linearly transformed and measured in the range from 0 to 100 points (the maximum possible number of points is taken as 100).

In each specific case, the total score was calculated according to the following formula: $$S_y = \frac{S_x - S_{min}}{S_{max} - S_{min}} \cdot 100$$

The patient filled out the questionnaire herself. The researcher calculated the quality of life index for each of the scales.

11) Mammography was performed before the start of treatment and at the final visit.

We measured the two largest diameters of the tumor formation (mainly perpendicular to each other).

Mammological images were interpreted according to RECIST 1.1 criteria.

12). Laboratory tests were performed at screening, then before each course of chemotherapy (starting with the 2nd course) and at the final visit.

Laboratory studies were carried out according to the following indicators:

- general blood analysis (hemoglobin, erythrocytes, hematocrit, platelets, leukocytes, leukocyte formula, ESR);

- general analysis of urine (pH, specific gravity, protein, sugar, leukocytes, erythrocytes, epithelial cells, salts);

- biochemical blood analysis (ALT, AST, total bilirubin, creatinine, glucose).

In the event of a change in any of the laboratory indicators, the research doctor made a conclusion about its clinical significance.

13). Identification and registration of possible AE/AR.

Detection of AE/AR was carried out on the basis of patient complaints, objective examination data and laboratory research data.

The patient's survey regarding the occurrence of AE/AR was conducted by the researcher at each visit during the study.

14) Additional methods of examination.

In the process of conducting the research, the research doctor, if necessary, could use any other laboratory, instrumental and clinical examination methods for diagnosis and assessment of the patients' condition.

8. PATIENT SELECTION CRITERIA

8.1. Criteria for inclusion of patients in the study

Patients who meet the following criteria were included in the study:

- women aged 18 to 65;
- diagnosis: breast cancer ($T_1N_{1-3}M_{0,}$ $T_2N_{0-3}M_{0,}$ $T_3N_{0-3}M_0$), confirmed by histological or cytological examination data ;
- patients who are indicated for neoadjuvant polychemotherapy;
- the presence of tumor formation, which can be objectively assessed in two dimensions;
- the functional state of the patient according to the ECOG scale corresponds to 0-2 points;
- expected life expectancy of at least 12 weeks (3 months);
- for women of reproductive age - a negative pregnancy test result, as well as the use of reliable contraceptives during the study;
- informed written consent of the patient to participate in the study.

8.2. Criteria for not including patients in the study

Patients with at least one of the following criteria were not included in the study:

- known hypersensitivity to the components of the studied drug;
- pregnancy; lactation;
- other malignant diseases (except basal cell carcinoma or cervical cancer in situ);
- the number of leukocytes <2.0 x 10^9 cells/l;
- the number of neutrophils < 1.5 x 10^9 cells/l;
- the number of platelets <100 x 10^9 cells/l;
- hemoglobin level < 100 g/l;
- creatinine exceeds the upper limit of normal by more than 1.25 times;
- transaminases (AST, ALT) and alkaline phosphatase exceed the upper limit of normal by more than 2.5 times; total bilirubin exceeds the upper limit of normal by more than 1.5 times;
- atrial or ventricular arrhythmias in history that were clinically significant or required treatment;
- heart failure, in particular. in the anamnesis;
- myocardial infarction during the previous 12 months;
- any unstable therapeutic or psychiatric condition that, in the opinion of the investigator, may impair the patient's ability to complete the study or prevent participation in the study;
- the need to take drugs that are not recommended;
- participation in any other clinical trial.

8.3. Criteria for early withdrawal of patients from the study

Any patient could withdraw informed consent and stop participating in the study at any time and for any reason. In addition, the patient could be removed by the researcher from taking the study drug and from participating in the study under the following circumstances:

- the occurrence during the study of severe and/or unexpected AE/AR requiring discontinuation of the drug;
- significant deterioration of the patient's general condition during the study;

- the need to prescribe drugs inadmissible for use within the scope of this study;
- non-compliance by the patient with the treatment regimen;
- the patient's non-compliance with the procedures provided for in the protocol.

In case of premature withdrawal of the patient from the study, the researcher was recommended to conduct a visit to assess the safety of the researched therapy, during which it is necessary to carry out visit procedures 6.

9. THE INVESTIGATED DRUG: LABELING, RECEIVING, ACCOUNTING AND STORAGE

9.1. Investigated drug

Name: Donovit-VS®.

Pharmaceutical form: tablets.

Composition: aconite (wrestler) rhizome extract - 1 tablet of 10 mcg alkaloid aconitine, auxiliary substances - lactose, calcium stearate.

Pharmacotherapeutic group: Antitumor drugs.

Physico-chemical properties: Tablets of light brown color, flat-cylindrical shape with beveled edges or biconvex.

Packaging: 30 tablets in a blister, 3 blisters in a box.

Manufacturer: "Astrapharm" LLC.

9.2. Marking

The following information was given on the label/packaging of the studied drug: name of the manufacturer, address; name of the drug; storage; release form; serial number; storage conditions; issue date, expiration date (date, month, year); designation: "Keep out of the reach of children"; designation: "For clinical research."

9.3. Terms of transfer, accounting and return of the researched drug

The study drug was provided to the clinical base by the Sponsor (LLC SPF "Aksomed LTD"). The transfer of the drug was confirmed by the act of transfer. The act indicated the amount of the researched drug, the series and the date of transfer.

The study drug was used only for the purpose of conducting this clinical study in strict accordance with the protocol.

The study drug was given to the patient according to the randomization scheme at Visits 2, 3, 4 and 5 in the amount necessary for treatment for 3-4 weeks. Patients brought all used and unused packaging materials, as well as unused pills, to the clinic at each subsequent visit.

The researcher kept a journal of dispensing/returning the study drug. The journal indicated the amount of drug issued/returned, the date of issue/return, the patient's randomization number and initials, as well as the name of the person who issued the drug.

Counting of study drugs was documented throughout the study. Upon completion of the study, the investigator provided the Sponsor with a report on the use of the study drug.

9.4. Storage conditions

The drug under study was stored in a place protected from light, at a temperature of up to 25°C, in a room to which only the responsible researcher and a person authorized by him have access.

Patients receiving the study drug were instructed about its storage conditions.

10. TREATMENT

10.1. Scheme of treatment

Patients of the main and control groups received neoadjuvant polychemotherapy, in accordance with international standards for the treatment of breast cancer, according to the AS scheme (doxorubicin 60 mg/m^2 plus cyclophosphamide at a dose of 600 mg/m^2) in the form of 4 courses with an interval of 3 weeks.

In the course of treatment, modification of the dose of anticancer drugs was allowed, both in the direction of decreasing and increasing the dose, based on the monitoring of blood parameters and the assessment of other toxic effects of CT.

After the end of the course of treatment, the cumulative dose of each of the used CT drugs was calculated.

In addition, patients of the main group, simultaneously with CT, received the study drug Donovit-VS® tablets manufactured by Astrapharm LLC, 1 tablet 3 times a day for 3 months.

Four courses of chemotherapy were planned for each patient.

Patients who received less than 4 courses of chemotherapy continued to participate in the study, regardless of which group, the main or the control, they belonged to. The last, final visit was carried out on the 90th day from the start of treatment, regardless of how many courses of CT the patient took. Patients who received at least 2 courses of CT were included in the efficacy analysis.

10.2. Concomitant therapy

The AS regimen is highly emetogenic and requires prevention of nausea and vomiting. For this purpose, premedication with antiemetic drugs was carried out. Patients were prescribed the 5-CT3 receptor antagonist ondansetron 8 mg intravenously 30 minutes before the start of chemotherapy and dexamethasone 12 mg intravenously 30 minutes before the start of chemotherapy on day 1, followed by ondansetron 8 mg/daily internally on days 2-4.

As concomitant therapy, patients were prescribed cardioprotectors and hepatoprotectors as indicated.

In the course of the study, it was also allowed to take drugs that the patient was constantly taking for the treatment of concomitant diseases.

10.3. Prohibited treatment

During the study, patients were not allowed to use the following groups of drugs:

- means that have an immunomodulatory effect;
- immunosuppressants;
- biostimulants, bioinhibitors, adaptogens.

If it was necessary to prescribe "forbidden" drugs, the researcher had to exclude the patient from the study.

10.4. Control over the patient's adherence to the regimen of the drug being studied

The researcher monitored the patient's adherence to the study medication regimen by counting the number of tablets issued and returned (unused) by the patient.

Patients brought all used and unused packaging materials, as well as unused pills, to the clinic at each visit. Data on each dispensing and return of the study drug were entered into the study drug logbook.

After the end of the treatment course, the researcher determined the patient's "adherence to treatment" coefficient according to the formula:

$$K_{привлечению} = \frac{(A-B)}{A} \times 100\%$$

where:

A - the number of tablets that needed to be taken,

B - the number of returned pills.

"Adherence to treatment" of less than 80% was considered by the researcher as "unsatisfactory" and this patient should not have been included in the efficacy analysis.

In this study, the rate of "adherence to treatment" in all patients was more than 80%.

11. THERAPY EFFICIENCY ASSESSMENT CRITERIA

Main variable:

- the degree of toxicity of chemotherapy during treatment (according to the CTC *NCIC toxicity scale)* .

Secondary variable:

- the level of the patient's quality of life during treatment (according to the questionnaire of the European Organization for Research and Treatment of Cancer EORTC QLQ – C 30);
- dynamics of the size of tumor formations before the end of the course of treatment (according to mammography data).

The toxicity of chemotherapy was evaluated according to the clinical and laboratory indicators (individually) relevant for the used CT, such as: leukopenia,

neutropenia, anemia, thrombocytopenia, impaired liver function, diarrhea, nausea, vomiting, condition of the oral cavity, impaired cardiac activity, etc.

To evaluate the response of the tumor to treatment, the criteria for the effectiveness of solid tumor therapy according to the RECIST 1.1 scale were used:

The complete answer is the disappearance of all cells, in the absence of the appearance of new ones.

A partial response is a reduction of 30% or more in measurable tumor formations, provided there are no signs of the appearance of new metastases or the progression of old ones.

Stabilization of the process - there is no decrease sufficient to be assessed as partial regression, or an increase that can be assessed as progression.

Progression of the process involves an increase in the smallest number of lesions registered during observation by 20% or the appearance of new foci.

Clinically significant response was defined as complete/partial regression (confirmed) or stabilization of the process.

12. EVALUATION OF TOLERABILITY

12.1. Portability Variables

When evaluating the tolerability of the studied drug, the following were taken into account:

- the presence and nature of adverse events, their connection with the researched drug;
- dynamics of vital indicators (BP, heart rate, body t);
- dynamics of ECG data;
- dynamics of laboratory indicators

12.2. Methods and terms of assessment of tolerability indicators

In the course of the study, the patient's condition was carefully monitored. For this purpose, during each visit, the researcher asked the patient questions about her well-being, conducted a physical examination, and measured blood pressure, heart rate, and body t. Diseases, signs or symptoms and/or abnormal laboratory parameters

observed in the patient prior to inclusion in the study were not considered adverse reactions if they were detected during the trial, except for cases when there was a worsening of the intensity or frequency of their manifestation. Changes in laboratory indicators were considered side effects of the drug under study, if, in the opinion of the researcher, they were not a consequence of the chemotherapy being used.

Collection of information on AE/AR began after the patient signed the informed consent form and was administered the study drug and continued until the patient completed the study.

Information about all adverse events related and unrelated to the protocol procedures that occurred during the study, as well as about all clinically significant changes in laboratory parameters, was recorded in the medical history and in the IRF. For each case of AE/AR, the following were assessed: its duration, expressiveness, severity, cause-and-effect relationship with the studied drug. The actions taken, the accompanying treatment and the outcome of the phenomenon were described, as well as whether this AE/AR was the reason for the patient's premature termination of participation in the study.

12.3. Tolerability rating scale

The tolerability of the drug was assessed by the researcher according to the following categorical scale:

Table 5 - Tolerability rating scale

Category	Category description
Beautiful	An objective examination does not reveal any pathological changes or clinically significant deviations in the gradual dynamics; the patient does not note the appearance of AE/AR.
Satisfactory	An objective examination reveals minor changes in the dynamics that are transient and do not require additional medical measures and/or minor AE/AR are observed, which do not cause serious problems for

	the patient and do not require discontinuation of the drug.
Unsatisfactory	During an objective examination, pathological changes are revealed in the dynamics, which require the withdrawal of the drug and the implementation of additional medical measures. and/or there is an AE/AR, which has a significant negative impact on the patient's condition, which requires the withdrawal of the drug and the use of additional medical measures.

13. ADVERSE EVENTS/REACTIONS (AE/AR)

13.1. Definition of AE/AR

Adverse reaction (AR) - adverse reactions should include all negative or unexpected reactions associated with the administration of any dose of a medicinal product, provided that there is at least a minimal probability of a cause-and-effect relationship between the drug and side reaction, i.e. the relationship cannot be excluded.

Adverse effect (AE) – any unwanted medical manifestation in a research subject that does not necessarily have a causal relationship with the use of a medicinal product (changes in laboratory data, symptoms or diseases that coincide in time with the use of the researched drug).

Serious adverse reaction or serious adverse event - any unwanted medical manifestation when using the study drug (regardless of the dosage), which leads to death, is life-threatening, requires hospitalization or an increase in the duration of hospitalization; leads to long-term or significant loss of working capacity or disability; to congenital anomalies or developmental defects.

A minor adverse reaction is an unwanted reaction that falls under the category of serious.

Unanticipated adverse reaction - an adverse reaction whose nature or severity is not consistent with the available information on the medicinal product (with the investigator's brochure for an unregistered medicinal product or the package leaflet/summary of characteristics for a registered medicinal product).

13.2. Assessment of the degree of severity of AE/AR

- **mild** – transient phenomena that do not affect the patient's daily activity;
- **medium** - phenomena cause some inconvenience to the patient and may affect his daily activity;
- **expressed** - phenomena cause inconvenience to the patient and interfere with the performance of everyday activities.

13.3. The connection of AE/AR with the studied drug

The assessment of the cause-and-effect relationship of the observed AE/AR with the study drug was carried out according to the following scale:

- **cannot be assessed** - it is impossible to give an assessment due to the insufficiency or contradiction of the available data, as well as in cases where they cannot be verified or supplemented;
- **absent** - undesirable clinical manifestation or changes in laboratory parameters are not related to the use of the medicinal product;
- **possible** - there is a certain temporary relationship with taking the drug, but the development of AE/AR can also be explained by a concomitant disease and/or taking another drug;
- **probable** – there is a certain temporary relationship with taking the drug, but the probability that the development of AE/AR is due to a concomitant disease and/or taking another drug is low;

- **undisputed** - the side reaction occurs after a certain period of time after the administration of the drug, the reaction subsides after the withdrawal of the drug, the symptoms reappear after the repeated administration of the drug.

13.4. Results of AE/AR**:**

- **recovery without consequences** - side effects stopped (symptoms are absent and the patient is not treated to eliminate this AE/AR);
- **recovery with consequences** - AE/AR stopped, but its consequences remained;
- **no changes** - AE/AR did not disappear, symptoms persisted, despite medical measures taken to eliminate it;
- **deterioration** - there was an increase in the symptoms of AE/AR;
- **fatal outcome** - the patient died as a result of this AE/AR.
- **no data** - communication with the patient has been lost, as a result of which it is impossible to obtain reliable data about the patient's condition.

13.5. Actions to be taken in the event of an AE/AR

In the event of an AE/AR, the investigator had to take measures of a medical nature that buy the reaction. In the event of a patient's AE/AR, threatening health and/or life, the study drug should be stopped immediately.

All patients in whom AE/AR were registered during the study should be observed until the reaction or its clinically significant signs disappear.

13.6. Notification of AE/AR

In the event of an unforeseen and/or serious AE, the researcher had to notify the sponsor of the study within 24 hours by phone: (044) 537-78-41 and in writing by e-mail: agn1942@gmail.com. A full report, detailing all the details of the AE/AR, was to be provided within 5 days to the Sponsor and within 15 days to the Ethics Committee of the LLP.

The researcher was also required to notify the Sponsor of all other AE/AR and/or abnormal laboratory values within 5 calendar days from the date it became known to him.

In the event of the death of the subject or the occurrence of a threat to life as a result of taking the researched drug, the researcher had to provide information to the

Commission on Ethics at the medical prophylactic establishment within 7 calendar days from the date it became known to him. Additional information regarding these cases was to be provided to the Ethics Commission within the next 8 calendar days.

14. METHODS OF STATISTICAL DATA ANALYSIS

14.1. Substantiation of the number of test subjects

This parallel, two-group, equal-sized trial was conducted to demonstrate the superior efficacy of therapy including chemotherapy + Donovit-VS® to a group of patients receiving only chemotherapy.

The planned power of the test is 80% (the probability of making a type 2 error is 0.2), the two-sided probability of making a type 1 error is 0.05.

The main variables in this test are:

- the level of CT toxicity for relevant clinical and laboratory indicators according to the CTC *NCIC* scale .

Since all of the main variables assessing toxicity are quantitative, the following null hypothesis will be tested for each main variable for evidence of excess efficacy (assuming that the data are normally distributed):

H_0: $\varepsilon \leq \delta$ versus H_a: $\varepsilon > \delta$, (1),

where $\delta >= 0$, is the value of clinically significant differences, at which it can be assumed that the treatment scheme, which includes CT + Donovit-VS®, exceeds effectiveness of only CT; ε - is the difference between the groups predicted to be observed on this measure. In the case of a quantitative main variable:

$\varepsilon = \mu$ (main group) – μ (control group), (2),

where μ (main group) is the arithmetic mean of the corresponding main variable for the treatment regimen including Donovit-VS®, and m (control group) is for the control group (without Donovit-VS®).

Furthermore, any reduction in the level of toxicity in each of the main variables is assumed to be clinically important. Therefore, in this study, to confirm the greater effectiveness in the main group against the control group, d was taken equal to 0 (δ = 0).

The sample size for a study exceeding efficiency can be estimated using the following expression (for each main variable):

$$n_k = k \cdot n_m$$

$$n_m = \frac{(z_{\alpha/2} + z_\beta)^2 \times \sigma^2 \times (1+1/k)}{(\varepsilon - \delta)^2}, \qquad (3)$$

where: z_α and z_β - Corresponding percentage points of SNR; δ – value of clinically important differences; ε — differences between groups according to a certain main variable (difference of arithmetic mean groups assuming that the data are normally distributed); σ^2 - dispersion; k - coefficient with different number of patients in groups (subgroups); n_m and n_k the number of patients planned to be included in the main and control groups, respectively; α - limit value of error of the 1st kind (level of significance); β - the limit value of the error of the 2nd kind.

In this study, it is assumed that the number of patients in the compared groups will be the same (k =1).

The two-sided level of significance α is taken equal to 0.05 (5%).

The limit value of the error of the second kind β = 0.2 (which makes it possible to reach 80% of the statistical power of the study).

The calculation of the sample size according to formula (6) is given in the table below:

Table 6 - Output and sample size estimation results

Statistical indicator	Value
Significance level α	0.05
The value of β	0.2
SNR percentage point for α	1.96
SNR percentage point for β	0.84

Statistical indicator	Value
The previously estimated standard deviation σ	1.3 *
The previously estimated variance σ^2	1.69
The value of δ	0
The value of ε	1
Estimated sample size	27
Adjusted sample size for possible dropout of patients from the study	30
The standard deviation is based on the rule of 3σ, assuming that the scores will be normally distributed between 0 and 4 points.	

Thus, to prove the superior effectiveness of the treatment regimen used in the main group compared to the treatment regimen used in the control group for the main variable (CT toxicity level for relevant clinical and laboratory parameters according to the CTC *NCIC* scale), it is enough to include 30 patients group

Based on the above, this study is planned to include 60 patients (30 patients in the main group and 30 patients in the control group).

14.2. Statistical analysis plan

- Description of patients included in the study;
- The number of subjects who dropped out of the study;
- Analysis of initial homogeneity of groups;
- Analysis of effectiveness in groups;
- Comparison of efficiency between groups;
- Tolerability analysis;
- Number of unwanted/side effects;
- Evaluation exceeds efficiency;
- Statistical conclusions.

14.3. Analysis of initial homogeneity of groups

Analysis of homogeneity of groups by age, diagnosis, disease severity, comorbidity, efficacy and safety indicators. For this:

a) Descriptive statistics methods were used to describe the initial state of the main and control groups (for quantitative variables: n, arithmetic mean, median, standard deviation, minimum and maximum values; for categorical variables – frequency and share in percent).

b) To assess the homogeneity of the main and control groups by quantitative variables:

- the hypothesis regarding the normality of the distribution of relevant data in each group was tested using the Shapiro-Wilk test. If the data for any indicator are normally distributed in both groups, then the comparison of groups for this indicator was performed using the Student's test for independent samples, otherwise, the comparison of groups for this indicator was performed using the Mann-Whitney test.

c) To assess the homogeneity of groups according to categorical variables, they were compared using the Pearson chi-square test. If the reasons for using the chi-square test were not met, Fisher's exact test was used (to test a two-tailed hypothesis).

d) Statistical conclusions were made regarding the initial homogeneity of the groups according to the specified variables.

14.4. Analysis of effectiveness in groups

(a) For quantitative efficacy measures, descriptive statistics (n, mean, median, standard deviation, minimum and maximum value) were evaluated in each group at each visit.

In order to assess the dynamics of these indicators, variance analysis (VA) was performed using a mixed two-factor model (the dependent variable is the value of the analyzed indicator, the "visit" factor is fixed, and the "subjects" factor is random). Values at visits starting from the next with the initial visit for the analyzed variable were compared using contrast analysis (simple contrasts were used, the

initial level was the reference level). The normality of the distribution of VA residuals was checked. If the residuals were normally distributed, then the transformation of the corresponding indicator into ranks was performed and the analysis was performed in ranks.

The dynamics of the analyzed parameters are presented graphically.

14.5. Comparison of efficacy between groups

(a) For the main variable assessing toxicity (scores), comparisons were made between groups at each respective visit (according to the patient review schedule) using the Mann–Whitney test or the Student's t test for independent samples, depending on the normality of the distribution of the data sets being compared. Normality was tested using the Shapiro-Wilk test.

b) For other quantitative performance indicators (secondary variables that are measured quantitatively), groups were compared by $dT_{visit\ i} = T_{visit\ i} - T_{visit\ 1}$.

Individual differences $dT_{visit\ i}$ were calculated for each subject for each parameter.

If the groups did not differ statistically significantly at baseline, the comparison of groups by $dT_{visit\ i}$ was performed using the Student's test for independent samples or the Mann-Whitney test, depending on the normality of the distribution of the compared data sets.

If the groups differed statistically significantly in the initial state, then to compare the groups with $dT_{visit\ i}$, taking into account possible initial differences between the groups, a covariance analysis was performed at each time point T_i according to the scheme: dependent variable - dT_i for the corresponding parameter, factor "Group" - fixed (levels: main and control), covariate - the value of this parameter at the time $T_{visit\ 1}$. A contrast analysis was performed using simple contrasts between the levels of the "Group" factor. The normality of the distribution of the residuals of the covariate analysis was checked using the Shapiro-Wilk test. If the residuals were not normally distributed, the specified rank analysis was performed. Conclusions were made regarding the differences between the groups.

14.6. Tolerability analysis

a) Results of laboratory tests (indicators of general blood analysis, general urinalysis, biochemical blood test).

Descriptive statistics (n, arithmetic mean, median, standard deviation, minimum and maximum value) for each group and visit according to the patient examination pattern. The results of each visit were compared between the groups.

Each indicator was transformed into a categorical variable with categories: "normal", "outside the norm". The frequency and share in % were calculated for the transformed variables in each group and for each visit, according to the patient examination scheme, and their dynamics in each group were evaluated.

b) Results of measurement of heart rate, blood pressure, body temperature.

Descriptive statistics (n, arithmetic mean, median, standard deviation, minimum and maximum value) for each group and visit according to the patient examination pattern.

c) Data on AE/AR.

Indicators of descriptive statistics (frequency and percentage of each group).

d) Variable general tolerance.

Indicators of descriptive statistics (frequency and percentage of each group).

14.7. levels of significance

The level of significance for the Shapiro-Wilk test is 0.01, and for other criteria - 0.05.

14.8. Conclusion on exceeding therapeutic efficiency

The conclusion about the superior effectiveness of therapy including the study drug (main group) versus therapy without the study drug (control group) was made based on the presence of statistically significant differences compared to the main variable assessing the degree of toxicity.

14.9. Subjects included in the analysis, handling of missing data, ensuring data validity

Patients who received at least 2 courses of CT were included in the efficacy analysis. The treatment of patients who dropped out of the study due to the occurrence of AE/AR was considered ineffective. Patients who violated the requirements of this protocol (inclusion/exclusion criteria, treatment regimen, prescription of "forbidden" concomitant therapy, etc.) were not included in the efficacy analysis. The tolerability analysis included all patients who took at least one dose of the study drug and dropped out of the study due to the occurrence of AE/AR.

Work with data was carried out in accordance with the basic principles of data management in order to ensure their integrity and validity. For this, data entry was carried out in pre-designed EXCEL spreadsheets using the principle of "double entry" and subsequent cross-validation.

14.10. Software

Data analysis was carried out using the built-in statistical analysis tools of Microsoft Excel spreadsheets and the SPSS 13.1 application program package.

15. RESEARCH RESULTS AND THEIR DISCUSSION

15.1. Description of the patients included in the study

60 patients diagnosed with breast cancer ($T_1N_{1-2}M_0$, $T_2N_{1-3}M_0$, $T_3N_{1-2}M_0$), confirmed by the data of histological or cytological examination, took part in the study. In the vast majority of patients, the tumor was located in the upper outer quadrant of the breast. Axillary lymph nodes were affected in all patients, cervical lymph nodes in two patients. In all patients, the tumor node was radiographically visualized, the sizes varied from 8 to 50 mm.

Written informed consent to participate in the study was obtained from all patients prior to the initiation of any study procedures.

All patients included in the study had an ECOG functional status of 0 to 2 and a life expectancy of at least 12 weeks.

Patients who signed a written informed consent and met the selection criteria for this study were randomized to one of the treatment groups: main or control, 30 patients each. The randomization scheme is given in Appendix A, table. A.1.

Patients of the main and control groups received neoadjuvant polychemotherapy according to the AS scheme (doxorubicin 60 mg/m^2 plus cyclophosphamide at a dose of 600 mg/m^2) in the form of 4 courses with an interval of 3 weeks. In addition, patients of the main group, simultaneously with CT, received the study drug Donovit-VS® tablets manufactured by Astrapharm LLC, 1 tablet 3 times a day for 3 months.

All patients of the main and control groups received the planned course of chemotherapy. The average number of courses received by patients in the course of this study was 4 in the main and control groups. The average cumulative dose of doxorubicin was 393.3 mg/m^2 in the main group and 389.3 mg/m^2 in the control group.

In no case was there a reduction in the dose of chemotherapy drugs or a delay in the course of chemotherapy

Female patients aged 34 to 63 years (M = 52.15, SD = 6.9) with a body weight of 58 to 88 kg (M = 72.58 SD = 9.7) were included in the study. The description of patients by age and body weight is given in the table. 7.

Table 7 - Characteristics of female patients by age and body weight

Parameter	n	M	Me	SD	MIN	MAX
Age, years	60	52.15	50	6,860	39	63
Body weight, kg	60	72.58	73	9,683	54	88

15.2. The number of analyzed patients

In this study, there were no cases of premature withdrawal of patients from the study due to an adverse reaction that occurred or for any other reason.

All randomized patients, in the main and control groups, accepted the full course of chemotherapy and completed the study according to the protocol.

All 60 patients were included in the analysis of efficacy and tolerability.

15.3. Analysis of homogeneity of groups at the screening stage

15.3.1. Analysis of homogeneity of groups by demographic characteristics

The main group included patients aged 34 to 63 years. The control group included patients aged 37 to 62 years. The average age of patients in the main group was 51.53 years, in the control group - 52.84 years. The largest share in both groups (60% or more) was made up of subjects aged 50 and over.

The distribution of patients in groups by age categories is shown in **Table 8**.

Table 8 - Distribution of subjects by age categories (absolute quantity, %)

Age years	Main group n = 30	Control group n = 30
30-39	5 (16.7%)	4 (3.3%)
40-49	5 (16.7%)	8 (26.7%)
50-59	8 (26.7%)	6 (20.0%)
60-65	12 (40.0%)	12 (40.0%)

Analysis of patients by age and body weight, at the time of inclusion in the study, by methods of descriptive statistics (n, arithmetic mean (M0, median (Me), standard deviation (SD), minimum and maximum) is shown in **Table 9**. The results of checking the normality of data distribution using the Shapiro-Wilk test are given in **Appendix A, table. A.2** .

Table 9 - Results of descriptive analysis of patients by age and body weight at the time of inclusion in the study

Indicator	Group	n	M	Me	SD	MIN	MAX
Age, years	Main group	30	51,53	52	7,052	34	63
	Control group	30	52.84	55	6,453	37	62
Body weight, kg	Main group	30	71.67	70	8,494	60	88
	Control group	30	73.49	75	8,290	58	86

To compare groups by age and body weight, the Student's test for independent samples was used (**Table 10**), since the data were distributed normally in both groups (**Appendix A, Table A2**).

Table 10 - Results of comparison of groups by age and body weight using the Student's test for independent samples

Indicator	t-statistics	df	p-value	Difference of mean	Conclusion on homogeneity of groups *
Age	-0.751	58	0.456	-1.31	homogeneous
Body weight	-0.839	58	0.404	-1.82	homogeneous
** At a significance level of 0.05.*					

Conclusion. From the results of the analysis, we can come to the disappointing conclusion that the groups did not differ statistically significantly in terms of age and body weight.

15.3.2. Analysis of the initial homogeneity of the groups according to the stage of the disease and the general condition of the patients according to the ECOG scale

All patients were diagnosed with locally advanced breast cancer, disease stage: $T_1N_{1-2}M_0$, $T_2N_{1-3}M_0$, $T_3N_{1-2}M_0$.

The distribution of patients in groups depending on the stage of the disease is presented in **Table 11**.

Table 11 - Distribution of female patients in groups, depending on the stage of the disease (abs. in, %)

Stages of the disease	Main group (n=30)	Control group (n=30)	P-value *
I ($T_1N_0M_0$)	0	0	0.535
IIa ($T_1N_1M_0$)	5 (16.7%)	4 (13.3%)	
IIb ($T_1N_2M_0$; $T_2N_{1-2}M_0$)	15 (50.0%)	18 (60.0%)	
III ($T_2N_3M_0$ $T_3N_{1-2}M_0$)	10 (33.3%)	8 (26.7%)	
**Comparisons were made using Pearson's chi-square test*			

The general condition of patients before treatment corresponded to 0-1 points on the ECOG scale. The patients led a normal, physically active lifestyle.

The distribution of patients in groups depending on the general condition according to the ECOG scale is presented in **Table 12**.

Table 12 - Characteristics of the general condition of patients according to the ECOG scale before treatment (absolute quantity, %)

General condition (Points)	Main group (n = 30)	Control group (n = 30)	P-value *
0	12 (40.0%)	15 (50.0%)	0.604
1	18 (60.0%)	15 (50.0%)	
2	-	-	
3	-	-	
4	-	-	
**Comparisons were made using Pearson's chi-square test*			

Conclusion. According to the results of the statistical analysis of the data presented in **Tables 11-12**, it can be stated that initially the groups did not differ statistically significantly in terms of the severity of the disease and general condition.

15.3.3 Analysis of initial homogeneity of groups based on objective examination data, hemodynamics and body temperature indicators

Before the start of the study, an objective examination of the subjects was carried out, including an examination of the skin and visible mucous membranes; palpation and percussion of the abdomen, auscultation of the heart and lungs. The data of the objective examination showed the absence of exacerbation of chronic diseases, which prevent the subjects from participating in the study. None of the patients in the main and control groups had clinically significant pathology from the cardiovascular system, based on subjective complaints, anamnesis and objective examination.

Hemodynamic parameters (heart rate, blood pressure) of the subjects of both groups were within the norm or slightly exceeded the norm.

Hemodynamic parameters and body t did not differ significantly between patient groups before treatment. The results of the comparative analysis of groups before the treatment of these parameters by methods of descriptive statistics are given in **Table 13.**

Table 13 - Results of the analysis of the initial homogeneity of the groups according to the BP, heart rate and body t indicators using the methods of descriptive statistics

Indicator	Group	n	M	Me	SD	MIN	MAX
SBR, mm Hg Art.	Main group	30	131.24	130	12,336	100	145
	Control group	30	133.65	135	13,053	95	150
DBR, mm Hg Art.	Main group	30	79.99	80	6,569	60	90

Indicator	Group	n	M	Me	SD	MIN	MAX
	Control group	30	81.43	82	6,387	65	90
Heart rate, beats/min.	Main group	30	75.44	75	7,120	58	92
	Control group	30	75.67	75	7,248	62	86
t body (°C)	Main group	30	36,56	36.6	0.315	36.0	37.0
	Control group	30	36.60	36.6	0.327	36.0	37.0

Since the SBP, DBP, heart rate, and body temperature data were normally distributed (**Appendix A, table A.3**), the Student's test for independent samples was used to compare groups according to these parameters (**table 14**).

Table 14 - Results of comparison of groups by heart rate using the Student's test for independent samples

Indicator	t-statistics	df	p-value	Difference of mean	Conclusion on homogeneity of groups *
SBR	0.735	58	0.465	-2.41	homogeneous
DBR	0.861	58	0.393	-1.44	homogeneous
Heart rate	0.124	58	0.902	-0.23	homogeneous
t body (°C)	0.483	58	0.631	-0.04	homogeneous
** At a significance level of 0.05.*					

Conclusion. From the results of the analysis presented in **table. 14**, it can be stated that the groups in the initial state did not differ statistically significantly in terms of blood pressure, heart rate and body t.

15.3.4. Analysis of initial homogeneity of groups according to ECG data

According to the protocol, all patients included in the study underwent a standard 12-lead ECG study. All patients in both groups had no clinically significant ECG changes, which suggests that initially the groups did not differ in cardiovascular pathology according to ECG data.

15.3.5. Analysis of initial homogeneity of groups according to laboratory parameters of a general blood test

Before the start of the treatment course, the patients underwent a general blood analysis according to the following indicators: erythrocytes, hemoglobin, hematocrit,

leukocytes, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and ESR. Most of the patients, in both groups, analyzed laboratory indicators were within normal values. In some patients, the laboratory indicators slightly deviated from the norm, but these deviations were determined as clinically insignificant. All deviations of laboratory parameters from normal values did not contradict the requirements of inclusion/exclusion criteria in this study.

The results of the comparative analysis of the general blood analysis data in the groups using the methods of descriptive statistics are shown in **Table 15**.

Table 15 - Results of the comparative analysis of groups in the initial state according to the indicators of the general blood analysis using the methods of descriptive statistics

Parameter	Group	n	M	Me	SD	MIN	MAX
Leukocytes, $x10^9$ cells /l	Main group	30	5.67	5.8	2,641	3,4	7.6
	Control group	30	6.00	6.2	2,409	3.5	7.2
Erythrocytes, $x10^{12}$ /l	Main group	30	4.25	4.5	0.560	3.23	4.68
	Control group	30	4.34	4.3	0.601	3.12	4.85
Hematocrit, %	Main group	30	42,41	43.0	2,755	36.2	46.5
	Control group	30	41.67	42.4	2,612	36.3	45.9
Hemoglobin, g/l	Main group	30	133.55	135	15,309	110	148
	Control group	30	132.10	132	14,881	112	144
Platelets $\times10^9$ cells/l	Main group	30	236.17	240	55,645	195	310
	Control group	30	238.65	242	52,158	198	278
Neutrophils, $x10^9$ cells/l	Main group	30	3.73	3.8	0.548	2.1	5.1
	Control group	30	3.97	4.0	0.531	2.0	5.4
Neutrophils, %	Main group	30	65.83	66.1	8,813	56.2	75.6
	Control group	30	66,17	66.3	8,774	55.7	75.2
Lymphocytes, %	Main group	30	27,22	27.3	2,349	20.5	33.4
	Control group	30	27.35	27.5	2,569	19.8	32.6
Monocytes, %	Main group	30	5.18	5.2	0.955	3.6	7.1
	Control group	30	5.23	5.4	0.897	3,4	6.9
Eosinophils, %	Main group	30	1.78	1.9	0.457	1.1	3.3
	Control group	30	2.03	2.1	0.510	1,2	3.8
Basophils, %	Main group	30	0.50	0.52	0.290	0.1	1.0

Parameter	Group	n	M	Me	SD	MIN	MAX
	Control group	30	0.44	0.40	0.276	0.2	0.8
ESR, mm/h	Main group	30	10.2	10	5,102	4	19
	Control group	30	10.5	11	4,911	3	16

According to the results of checking the normality of the data distribution (**Appendix A, table A.3**), the Student's test for independent samples was used to compare the groups in the initial state according to the parameters of the general blood test (**table 16**).

Table 16 - Results of comparison of groups in the initial state according to indicators of general blood analysis using the Student's test for independent samples

Changeable	Difference of mean	t	df	p-value	Conclusion on homogeneity of groups *
Leukocytes, $x10^9$ cells /l	-0.33	-0.506	58	0.615	homogeneous
Erythrocytes, $x10^{12}$ /l	-0.09	-0.600	58	0.551	homogeneous
Hematocrit, %	0.74	1,068	58	0.290	homogeneous
Hemoglobin, g/l	1.45	0.372	58	0.711	homogeneous
Platelets $\times10^9$ cells/l	-2.48	-0.178	58	0.859	homogeneous
Neutrophils, $x10^9$ cells/l	-0.24	-1.723	58	0.090	homogeneous
Neutrophils, %	-0.34	-0.149	58	0.882	homogeneous
Lymphocytes, %	-0.13	-0.205	58	0.837	homogeneous
Monocytes, %	-0.05	-0.209	58	0.835	homogeneous
Eosinophils, %	-0.25	-1.999	58	0.051	homogeneous
Basophils, %	0.06	0.821	58	0.415	homogeneous
ESR, mm/h	-0.30	-0.232	58	0.817	homogeneous
** The conclusion is made at the significance level of 0.05*.					

Conclusion. According to the data presented in **Table 16** it can be stated that the groups, in the initial state, according to the parameters of the general blood analysis (erythrocytes, hemoglobin, hematocrit, leukocytes, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and ESR), did not differ statistically significantly - they were homogeneous.

15.3.6. Analysis of initial homogeneity of groups according to laboratory indicators of biochemical blood analysis

Before the start of the treatment course, the patients had a biochemical blood analysis based on the following indicators: AST, ALT, total bilirubin, creatinine and glucose. In all patients, in both groups, the analyzed laboratory indicators were within normal values.

The results of a comparative analysis of patients in groups according to indicators of biochemical blood analysis using descriptive statistics are shown in **Table 17**.

Table 17 - Results of comparative analysis of groups in the initial state according to indicators of biochemical blood analysis using methods of descriptive statistics

Parameter	Group	n	M	Me	SD	MIN	MAX
ALT, units/l	Main group	30	35,40	32	4,237	22	40
	Control group	30	34,27	35	4,136	21	39
AST, units/l	Main group	30	32.45	32	4,379	20	38
	Control group	30	32.89	32	4,507	18	38
Total bilirubin, μmol/l	Main group	30	15,24	15.5	2,765	11.2	18.8
	Control group	30	14.73	14.8	2,457	12.4	19.2
Creatinine, μmol/l	Main group	30	75.1	74	11,536	55	84
	Control group	30	73.9	72	10,868	53	90
Glucose, mmol/l	Main group	30	5.25	5.3	0.561	4.2	6.8
	Control group	30	5.42	5.5	0.538	4.5	6.8

According to the results of checking the normality of the data distribution (**Appendix A, table A.3**), the Student's test for independent samples was used to compare the groups in the initial state according to the indicators of biochemical blood analysis (**table 18**).

Table 18 - Results of comparison of groups in the initial state according to indicators of biochemical blood analysis using the Student's test for independent samples

Changeable	Difference of mean	t	df	p-value	Conclusion on homogeneity of groups *
ALT, units/l	1.13	1,045	58	0.300	homogeneous
AST, units/l	-0.44	-0.384	58	0.703	homogeneous
Total bilirubin, μmol/l	0.51	0.755	58	0.453	homogeneous

Changeable	Difference of mean	t	df	p-value	Conclusion on homogeneity of groups *
Creatinine, μmol/l	1.20	0.415	58	0.679	homogeneous
Glucose, mmol/l	-0.17	-1,198	58	0.236	homogeneous
* The conclusion is made at the significance level of 0.05.					

Conclusion. According to the data presented in **table 18**, it can be stated that the groups in the initial state did not differ statistically significantly according to the indicators of biochemical blood analysis (AST, ALT, total bilirubin, creatinine and glucose) - they were homogeneous.

15.3.7. Analysis of the initial homogeneity of the groups according to the laboratory parameters of the general analysis of urine

The results of the analysis of the initial homogeneity of the groups according to the parameters of the general analysis of urine (specific gravity, pH, protein, glucose, epithelial cells, leukocytes, erythrocytes, cylinders and salts) using the methods of descriptive statistics are shown in **Table 19** . In all patients, in both groups, the analyzed laboratory parameters were within normal values.

Table 19 - Results of a comparative analysis of groups by laboratory indicators of the general analysis of urine by methods of descriptive statistics

Parameter	Group	n	M	Me	SD	MIN	MAX
Specific weight	Main group	30	1014.6	1015	3,315	1010	1020
	Control group	30	1015.8	1016	3,217	1010	1019
pH	Main group	30	5.40	5.5	0.163	5.0	5.5
	Control group	30	5.42	5.4	0.168	5.0	5.5
Leukocytes, cl. in sight	Main group	30	4.5	5	1,237	2	8
	Control group	30	4.3	4	1,245	2	8
Erythrocytes, cl. in sight	Main group	30	1.5	2	0.781	0	5
	Control group	30	1,2	1	0.655	0	4
Protein, g/l	Main group	30	0	-	-	0	0
	Control group	30	0	-	-	0	0
Glucose, %	Main group	30	0	-	-	0	0
	Control group	30	0	-	-	0	0
Epithelial cells, cl. in sight	Main group	30	0.5	0	0.247	0	2
	Control group	30	0.4	0	0.210	0	2

Parameter	Group	n	M	Me	SD	MIN	MAX
Cylinders, cl. in sight	Main group	30	0	-	-	0	0
	Control group	30	0	-	-	0	0
Salt	Main group	30	0	-	-	0	0
	Control group	30	0	-	-	0	0

As is obvious from the **table. 19** all patients had no protein, glucose, cylinders and salts in their urine. Therefore, the groups according to the laboratory parameters are homogeneous and further comparison of the groups was not carried out.

Since the data of other laboratory parameters (specific gravity, pH, leukocytes and erythrocytes) in the groups were distributed normally (**Appendix A, table A.3**), the Student's test for independent samples was used to compare the groups according to the parameters of the general urine analysis (**table 20**).

Table 20 - Results of applying the Student's test for independent samples to compare groups according to some laboratory parameters of the general urinalysis

Parameter	t	df	p-value	Difference of mean	Conclusion on homogeneity of groups *
Specific weight	-1.423	58	0.160	-1.20	homogeneous
pH	-0.468	58	0.642	-0.02	homogeneous
Leukocytes	0.626	58	0.534	0.20	homogeneous
Erythrocytes	1,612	58	0.112	0.30	homogeneous
Epithelial cells	1,689	58	0.097	0.10	homogeneous

** The conclusion is made at the significance level of 0.05.*

Conclusion. According to the data presented in the **table. 20**, it can be stated that the groups, in the initial state, according to the parameters of the general analysis of urine (specific gravity, pH, protein, glucose, epithelial cells, leukocytes, erythrocytes, cylinders, salts) did not differ statistically significantly and were homogeneous.

15.4. Analysis of clinical research data in dynamics

15.4.1. Analysis of blood pressure, heart rate and body temperature data in dynamics

During screening (D_{SC}) and then at each visit, the patients' heart rate, blood pressure, and body temperature were measured. Hemodynamic indicators, during treatment, were within normal values or slightly deviated from the norm in both groups. The body temperature mostly did not exceed 37.0°C in almost all patients of both groups during the entire study. An increase in temperature, not related to infection, was observed in 2 (6.7%) patients of the main group and in 3 (10.0%) patients of the control group.

The results of the descriptive analysis of these parameters in the groups are given in the **table. 21** for the main group and **table. 22** for the control group.

Table 21 - Results of the analysis of the dynamics of hemodynamic indicators and body temperature in the main group

Parameter	Time	n	M	Me	SD	Min	Max
SBR, mmHg	Dsc	30	131.24	130	12,336	100	145
	D21	30	130.62	130	12,198	100	145
	D42	30	131.84	132	12,500	100	150
	D63	30	132,43	132	12,403	100	145
	D90	30	132.67	132	12,791	100	145
DBR, mmHg	Dsc	30	79.99	80	6,569	60	90
	D21	30	80.20	80	6,337	65	95
	D42	30	81.25	80	7,445	65	100
	D63	30	82,14	85	7,880	65	100
	D90	30	83.68	85	6,896	65	95
Heart rate, beats/min.	Dsc	30	75.44	75	7,120	58	92
	D21	30	76.83	75	7,463	60	90
	D42	30	77.43	78	7,409	65	92
	D63	30	75.51	75	8,504	62	100
	D90	30	75.16	75	7,265	63	98
Body t °C	Dsc	30	36,56	36.6	0.315	36.0	37.0
	D21	30	36.51	36.6	0.310	36.2	37.2
	D42	30	36.70	36.7	0.397	36.4	37.5
	D63	30	36.65	36.6	0.430	36.2	37.6
	D90	30	36,67	36.7	0.379	36.5	37.2

Table 22 - Results of the analysis of the dynamics of hemodynamic indicators and body temperature in the control group

Parameter	Visit	n	M	Me	SD	Min	Max
SBR, mm Hg	Dsc	30	133.65	135	13,053	95	150
	D21	30	132,43	132	11,869	100	150
	D42	30	133.72	135	10,889	100	150
	D63	30	132.45	132	11,942	100	145

Parameter	Visit	n	M	Me	SD	Min	Max
	D90	30	132.26	132	12,564	100	145
DBR, mmHg	Dsc	30	81.43	82	6,387	65	90
	D21	30	81.50	82	6,771	70	100
	D42	30	82.17	82	6,557	65	95
	D63	30	82,63	80	6,150	65	95
	D90	30	82.45	80	6,538	65	95
Heart rate, beats/min.	Dsc	30	75.67	75	7,248	62	86
	D21	30	74.86	75	7,416	62	98
	D42	30	75.39	75	7,618	62	96
	D63	30	74.95	75	7,202	60	96
	D90	30	75.16	75	7,265	62	96
Body t °C	Dsc	30	36.60	36.6	0.327	36.0	37.0
	D21	30	36.54	36.6	0.376	36.4	37.2
	D42	30	36.62	36.6	0.324	36.5	37.5
	D63	30	36.84	36.8	0.370	36.4	37.5
	D90	30	36.75	36.7	0.420	36.3	37.2

To assess the dynamics of hemodynamic indicators and body temperature, a variance analysis was performed using a mixed two-factor model (the dependent variable is the value of the analyzed indicator, the "time" factor is fixed (Dsc, D14, D28, D42, D56, D70 and D90), the "subjects" factor random). The results of VA are given in **table. 23**.

A comparison of the following levels of the "time" factor with the original data (Dsc) was also made using a contrast analysis (**Table 24-25**). The normality of the distribution of VA residuals was checked using the Shapiro-Wilk test (**table A.5. Appendices A**.

Table 23 - The main results of VA hemodynamic indicators and body temperature

Dependent variable	The factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
Main group						
SBR, mm Hg	Visit	85,533	4	21,383	0.685	0.604
	Patients	18879.733	29	651,025	20,850	0.000
DBR, mmHg	Visit	284,893	4	71,223	2,247	0.075
	Patients	3769,660	29	129,988	5,925	0.000
Heart rate, beats/min.	Visit	117,533	4	29,383	2,117	0.087
	Patients	9213,333	29	317,701	31,540	0.000
Body t °C	Visit	0.738	4	0.185	2,339	0.063
	Patients	12,792	29	0.441	7,983	0.000

Control group						
SBR, mm Hg	Visit	60,173	4	15,043	0.238	0.916
	Patients	12494.673	29	430,851	6,814	0.000
DBR, mmHg	Visit	40,227	4	10,057	0.517	0.723
	Patients	3983.093	29	137,348	7,067	0.000
Heart rate, beats/min.	Visit	12,360	4	3,090	0.528	0.715
	Patients	7660.160	29	264,143	45,137	0.000
Body t °C	Visit	1,811	4	0.453	9,666	0.000
	Patients	10,587	29	0.365	7,794	0.000

Table 24 - Results of contrast analysis of hemodynamic parameters and body temperature in the main group

Dependent variable	Contrasts	Estimated contrast	Stand. error	p-value
SBR, mm Hg	D21 - Dsc	-0.633	1,443	0.662
	D42 - Dsc	0.533		0.712
	D63 - Dsc	1,167		0.420
	D90 - Dsc	1,433		0.323
DBR, mmHg	D21 - Dsc	0.200	1,209	0.869
	D42 - Dsc	1,367		0.261
	D63 - Dsc	2,133		0.090
	D90 - Dsc	2,367		0.058
Heart rate, beats/min.	D21 - Dsc	1,367	0.819	0.098
	D42 - Dsc	2,000		0.056
	D63 - Dsc	0.033		0.968
	D90 - Dsc	-0.233		0.776
Body t °C	D21 - Dsc	-0.050	0.061	0.412
	D42 - Dsc	0.137		0.056
	D63 - Dsc	0.090		0.141
	D90 - Dsc	0.107		0.081

Table 25 - Results of contrast analysis of hemodynamic indicators and body temperature in the control group

Dependent variable	Contrasts	Estimated contrast	Stand. error	p-value
SBR, mm Hg	D21 - Dsc	-1.233	2,053	0.549
	D42 - Dsc	0.033		0.987
	D63 - Dsc	-1.167		0.571
	D90 - Dsc	-1,400		0.497
DBR, mmHg	D21 - Dsc	0.100	1,138	0.930
	D42 - Dsc	0.833		0.466
	D63 - Dsc	1,267		0.268
	D90 - Dsc	1,100		0.336

Heart rate, beats/min.	D21 - Dsc	-0.800	0.625	0.203
	D42 - Dsc	-0.300		0.632
	D63 - Dsc	-0.700		0.265
	D90 - Dsc	-0.500		0.425
Body t °C	D21 - Dsc	-0.053	0.056	0.342
	D42 - Dsc	0.023		0.677
	D63 - Dsc	0.247		0.000*
	D90 - Dsc	0.153		0.007 *
** Statistically significant differences are observed*				

Conclusion: as can be seen from the conducted analysis, hemodynamic parameters mostly did not change significantly during treatment and observation in both studied groups of patients. This indicates the absence of a negative effect of therapy on hemodynamic parameters. Statistically significant changes in body temperature at Visits 5 and 6 in the control group were not clinically significant.

15.4.2. Analysis of the dynamics of indicators of the general blood test

Complete blood count was performed during screening (D_{SC}) and then after each course of chemotherapy.

The results of the analysis of the dynamics of the indicators of the general blood test are given in the **table. 26** for the main group and in **table. 27** comparison groups.

Table 26 - Dynamics of indicators of general blood analysis during the study in patients of the main group

Indicator	Time	n	M	Me	SD	MIN	MAX
Leukocytes, $x10^9$ cells/l	Dsc	30	5.67	5.8	2,641	3,4	7.6
	D21	30	4.41	4.5	2,115	2.6	5.3
	D42	30	4.30	4.4	2,109	2.8	5.2
	D63	30	4.28	4.3	2,226	2.8	5.4
	D90	30	4.26	4.3	2,145	2.8	5.4
	[D21 - Dsc]	30	-1.26	-1.3	1,204	-0.8	-2.3
	[D42 - Dsc]	30	-1.37	-1.4	1,635	-0.6	-2.4
	[D63 - Dsc]	30	-1.39	-1.5	1,603	-0.6	-2.2
	[D90 - Dsc]	30	-1.41	-1.5	1,611	-0.6	-2.2
Erythrocytes, $x10^{12}$ cells/l	Dsc	30	4.25	4.5	0.560	3.23	4.68
	D21	30	4.23	4.3	0.541	3.20	4.55
	D42	30	4.21	4.2	0.537	3.20	4.43
	D63	30	4.18	4.2	0.520	3.21	4.42
	D90	30	4.20	4.2	0.522	3.22	4.45
	[D21 - Dsc]	30	-0.02	-0.2	0.539	-0.03	-0.13
	[D42 - Dsc]	30	-0.04	-0.3	0.321	-0.03	-0.25

Indicator	Time	n	M	Me	SD	MIN	MAX
	[D63 - Dsc]	30	-0.07	-0.3	0.281	-0.02	-0.26
	[D90 - Dsc]	30	-0.05	-0.3	0.349	-0.01	-0.23
Hematocrit, %	Dsc	30	42,41	43.0	2,755	36.2	46.5
	D21	30	40,24	41.2	2,651	34.8	44.5
	D42	30	39,29	40.5	2,558	34.7	44.7
	D63	30	40,45	40.2	2,671	34.5	45.9
	D90	30	40.67	41.1	2,590	35.2	45.7
	[D21 - Dsc]	30	-2.17	-1.8	0.242	-1.4	-2.0
	[D42 - Dsc]	30	-3.12	-2.5	0.256	-1.5	-1.8
	[D63 - Dsc]	30	-1.96	-2.8	0.347	-0.6	-1.6
	[D90 - Dsc]	30	-1.74	-1.9	0.236	-0.8	-1.0
Hemoglobin, g/l	Dsc	30	133.55	135	15,309	110	148
	D21	30	124.75	125	15,335	100	142
	D42	30	121.33	120	15,280	100	142
	D63	30	120.42	120	15,318	98	140
	D90	30	120,31	120	15,227	98	140
	[D21 - Dsc]	30	-8.8	-10	1,156	-6	-10
	[D42 - Dsc]	30	-12.22	-15	1,236	-6	-10
	[D63 - Dsc]	30	-13.13	-15	1,157	-8	-12
	[D90 - Dsc]	30	-13.24	-15	1,295	-8	-12
Platelets×10^9 cells/l	Dsc	30	236.17	240	55,645	195	310
	D21	30	210.55	215	57,347	120	300
	D42	30	206.36	210	56,148	120	290
	D63	30	198.43	196	59,382	110	254
	D90	30	182.36	185	60,150	100	248
	[D21 - Dsc]	30	-25.62	-25	12,457	-10	-75
	[D42 - Dsc]	30	-29.81	-30	9,995	-20	-75
	[D63 - Dsc]	30	-37.74	-44	6,965	-56	-85
	[D90 - Dsc]	30	-53.81	-55	7,226	-62	-95
Neutrophils, x10^9 cells/l	Dsc	30	3.73	3.8	0.548	2.1	5.1
	D21	30	2.82	2.9	0.410	1.4	4.4
	D42	30	2.85	2.8	0.437	1.4	4.6
	D63	30	2.65	2.7	0.459	1,2	4.4
	D90	30	2.72	2.7	0.448	1.4	4.4
	[D21 - Dsc]	30	-0.91	-0.9	0.254	-0.5	-0.7
	[D42 - Dsc]	30	-0.88	-1	0.225	-0.5	-0.7
	[D63 - Dsc]	30	-1.08	-1.1	0.209	-0.7	-0.9
	[D90 - Dsc]	30	-1.01	-1.1	0.243	-0.7	-0.9
Neutrophils, %	Dsc	30	65.83	66.1	8,813	56.2	75.6
	D21	30	64,62	65.2	7,876	55.5	65.3
	D42	30	65.90	65.8	7,650	53.8	65.6
	D63	30	61.91	62.1	7,336	48.4	63.4
	D90	30	62.97	63.3	7,241	54.6	63.9
	[D21 - Dsc]	30	-1.21	-0.9	1,247	-0.7	-10.3
	[D42 - Dsc]	30	0.07	-0.3	1,259	-2.4	-10.0
	[D63 - Dsc]	30	-3.92	-4.0	1,336	-7.8	-12.2

Indicator	Time	n	M	Me	SD	MIN	MAX
	[D90 - Dsc]	30	-2.86	-2.8	1,238	-1.6	-11.7
Lymphocytes, %	Dsc	30	27,22	27.3	2,349	20.5	33.4
	D21	30	28.78	28.8	2,198	21.5	34.6
	D42	30	27.63	27.5	2,226	20.6	35.5
	D63	30	30.86	31.1	2,409	20.4	36.1
	D90	30	30,46	30.8	2,385	20.8	36.5
	[D21 - Dsc]	30	1.56	1.5	0.486	1.0	1,2
	[D42 - Dsc]	30	0.41	0.2	0.873	0.1	2.1
	[D63 - Dsc]	30	3.64	3.8	0.984	-0.1	2.7
	[D90 - Dsc]	30	3.24	3.5	1,247	0.3	3.1
Monocytes, %	Dsc	30	5.18	5.2	0.955	3.6	7.1
	D21	30	5.11	5.2	0.907	3.8	7.5
	D42	30	5.02	5.0	0.961	4.0	7.5
	D63	30	5.57	5.7	0.809	3.8	7.6
	D90	30	4.90	5.0	0.854	3.9	7.2
	[D21 - Dsc]	30	-0.07	0	0.245	0.2	0.4
	[D42 - Dsc]	30	-0.16	-0.2	0.177	0.4	0.5
	[D63 - Dsc]	30	0.39	0.5	0.315	0.2	0.5
	[D90 - Dsc]	30	-0.28	-0.2	0.270	0.1	0.3
Eosinophils, %	Dsc	30	1.78	1.9	0.457	1.1	3.3
	D21	30	1.41	1.5	0.494	1.0	3.2
	D42	30	1.46	1.5	0.526	1.3	3,4
	D63	30	2.44	2.6	0.544	1,2	3.8
	D90	30	1.72	1.8	0.480	1,2	3.5
	[D21 - Dsc]	30	-0.37	-0.4	0.202	-0.1	-0.2
	[D42 - Dsc]	30	-0.32	-0.4	0.231	0.1	0.2
	[D63 - Dsc]	30	0.66	0.7	0.353	0.1	0.5
	[D90 - Dsc]	30	-0.06	-0.1	0.109	0.1	0.2
Basophils, %	Dsc	30	0.50	0.5	0.290	0.1	1.0
	D21	30	0.45	0.5	0.303	0.1	1.5
	D42	30	0.43	0.5	0.384	0.1	1.6
	D63	30	0.39	0.4	0.326	0.1	1.5
	D90	30	0.35	0.4	0.388	0.0	1.7
	[D21 - Dsc]	30	-0.05	0	0.224	0	0.5
	[D42 - Dsc]	30	-0.07	0	0.362	0	0.6
	[D63 - Dsc]	30	-0.11	-0.1	0.379	0	0.5
	[D90 - Dsc]	30	-0.15	-0.1	0.425	-0.1	0.7
ESR, mm/h	Dsc	30	10.2	10	5,102	4	19
	D21	30	12.9	13	4,627	6	23
	D42	30	13.0	13	4,552	6	25
	D63	30	13.6	15	5,632	8	30
	D90	30	12.7	13	5,281	6	25
	[D21 - Dsc]	30	2.7	3	0.775	2	4
	[D42 - Dsc]	30	2.8	3	0.863	2	6
	[D63 - Dsc]	30	3,4	5	2,221	4	11
	[D90 - Dsc]	30	2.5	3	1,409	2	6

Table 27 - Dynamics of indicators of general blood analysis during the study in patients of the control group

Indicator	Time	n	M	Me	SD	MIN	MAX
Leukocytes, x10^9 cells /l	Dsc	30	6.00	6.2	2,409	3.5	7.2
	D21	30	3.88	4.0	2,331	2.4	5.2
	D42	30	3.82	3.9	2,249	2.6	4.8
	D63	30	3.78	3.8	2,109	2.6	4.8
	D90	30	3.79	3.7	2,215	2.6	4.8
	[D21 - Dsc]	30	-2.12	-2.2	0.985	-1.1	-2.0
	[D42 - Dsc]	30	-2.18	-2.3	1,129	-0.9	-2.4
	[D63 - Dsc]	30	-2.22	-2.4	1,062	-0.9	-2.4
	[D90 - Dsc]	30	-2.21	-2.5	1.125	-0.9	-2.4
Erythrocytes, x10^{12} cells/l	Dsc	30	4.34	4.3	0.601	3.12	4.85
	D21	30	4.22	4.2	0.598	3.12	4.45
	D42	30	4.16	4.2	0.514	3.13	4.43
	D63	30	4.15	4.2	0.519	3.15	4.44
	D90	30	4.16	4.1	0.523	3.15	4.45
	[D21 - Dsc]	30	-0.12	-0.1	0.442	0.0	-0.40
	[D42 - Dsc]	30	-0.18	-0.1	0.579	0.01	-0.42
	[D63 - Dsc]	30	-0.19	-0.1	0.664	0.03	-0.41
	[D90 - Dsc]	30	-0.18	-0.2	0.563	0.03	-0.40
Hematocrit, %	Dsc	30	41.67	42.4	2,612	36.3	45.9
	D21	30	40.29	40.9	2,558	35.2	45.3
	D42	30	40,14	40.3	2,741	35.3	44.7
	D63	30	40,28	40.3	2,655	36.1	45.6
	D90	30	40,32	40.5	2,721	35.7	44.2
	[D21 - Dsc]	30	-1.38	-1.5	0.629	-0.6	-1.1
	[D42 - Dsc]	30	-1.53	-2.1	0.599	-1.0	-1.2
	[D63 - Dsc]	30	-1.39	-2.1	0.612	-0.2	-0.3
	[D90 - Dsc]	30	-1.35	-1.9	1.025	-0.6	-1.7
Hemoglobin, g/l	Dsc	30	132.10	132	14,881	112	144
	D21	30	122.44	125	13,971	100	140
	D42	30	118.51	122	13,774	100	140
	D63	30	118.04	120	14,270	94	138
	D90	30	118,11	116	14,571	90	135
	[D21 - Dsc]	30	-9.66	-7	1,138	-4	-12
	[D42 - Dsc]	30	-13.59	-10	1,227	-4	-12
	[D63 - Dsc]	30	-14.06	-12	1,302	-6	-18
	[D90 - Dsc]	30	-13.99	-16	1,726	-9	-22
Platelets×10^9 cells/l	Dsc	30	238.65	242	52,158	198	278
	D21	30	209.29	215	55,117	110	285
	D42	30	200.23	204	59,094	110	285
	D63	30	186.54	195	58,270	100	253
	D90	30	175.71	180	56,960	100	235
	[D21 - Dsc]	30	-29.36	-27	10,126	7	-88
	[D42 - Dsc]	30	-38.42	-38	10,336	7	-88
	[D63 - Dsc]	30	-52.11	-47	9,458	-25	-98

Indicator	Time	n	M	Me	SD	MIN	MAX
	[D90 - Dsc]	30	-62.94	-62	8,259	-43	-98
Neutrophils, $x10^9$ cells/l	Dsc	30	3.97	4.0	0.531	2.0	5.4
	D21	30	2.44	2.6	0.469	1.4	4.0
	D42	30	2.37	2.5	0.439	1,2	4.4
	D63	30	2.33	2.4	0.389	1,2	4.4
	D90	30	2.40	2.5	0.375	1.4	4.4
	[D21 - Dsc]	30	-1.53	-1.4	0.380	-0.6	-1.4
	[D42 - Dsc]	30	-1.6	-1.5	0.368	-0.8	-1.0
	[D63 - Dsc]	30	-1.64	-1.6	0.377	-0.8	-1.0
	[D90 - Dsc]	30	-1.57	-1.5	0.349	-0.6	-1.0
Neutrophils, %	Dsc	30	66,17	66.3	8,774	55.7	75.2
	D21	30	62.36	62.6	7,361	54.3	66.5
	D42	30	62.05	61.8	7,520	54.2	64.9
	D63	30	61.34	61.5	7,740	48.7	62.1
	D90	30	61.91	62.1	7,694	55.9	64.9
	[D21 - Dsc]	30	-3.81	-3.7	1,389	-1.4	-8.7
	[D42 - Dsc]	30	-4.12	-4.5	1,529	-1.5	-10.3
	[D63 - Dsc]	30	-4.83	-4.8	0.874	-7.0	-13.1
	[D90 - Dsc]	30	-4.26	-4.2	1,225	0.2	-10.3
Lymphocytes, %	Dsc	30	27.35	27.5	2,569	19.8	32.6
	D21	30	30.80	31.1	2,846	20.5	35.6
	D42	30	30,30	30.5	2,953	19.6	37.5
	D63	30	30.06	29.8	2,690	21.4	35.1
	D90	30	29.60	29.7	2,748	21.8	35.8
	[D21 - Dsc]	30	3.45	3.6	0.664	0.7	3.0
	[D42 - Dsc]	30	2.95	3.0	0.975	-0.2	4.9
	[D63 - Dsc]	30	2.71	2,3	0.448	1.6	2.5
	[D90 - Dsc]	30	2.25	2,2	0.314	2.0	3.2
Monocytes, %	Dsc	30	5.23	5.4	0.897	3,4	6.9
	D21	30	5.34	5.5	0.709	3,4	7.2
	D42	30	5.64	5.7	0.742	3.8	7.4
	D63	30	5.84	5.9	0.817	3.5	7,8
	D90	30	5.87	5.9	0.844	3.6	7.9
	[D21 - Dsc]	30	0.11	0.1	0.189	0.0	0.3
	[D42 - Dsc]	30	0.41	0.3	0.136	0.4	0.5
	[D63 - Dsc]	30	0.61	0.5	0.268	0.1	0.9
	[D90 - Dsc]	30	0.64	0.5	0.431	0.2	1.0
Eosinophils, %	Dsc	30	2.03	2.1	0.510	1,2	3.8
	D21	30	1.58	1.7	0.542	1.1	3.8
	D42	30	2.03	2.0	0.587	1,2	4.0
	D63	30	2.23	2.4	0.538	1,2	3.8
	D90	30	2.10	2.1	0.570	1.0	4.0
	[D21 - Dsc]	30	-0.45	-0.4	0.101	0.0	-0.1
	[D42 - Dsc]	30	0.0	-0.1	0.124	0.0	0.2
	[D63 - Dsc]	30	0.2	0.3	0.109	0.0	0.1
	[D90 - Dsc]	30	0.07	0	0.203	-0.2	0.2

Indicator	Time	n	M	Me	SD	MIN	MAX
Basophils, %	Dsc	30	0.44	0.4	0.276	0.2	0.8
	D21	30	0.38	0.4	0.305	0.2	1.0
	D42	30	0.45	0.5	0.317	0.1	1.3
	D63	30	0.49	0.5	0.341	0.1	1.4
	D90	30	0.52	0.5	0.356	0.1	1.5
	[D21 - Dsc]	30	-0.06	0	0.166	0.0	0.2
	[D42 - Dsc]	30	0.01	0.1	0.235	-0.1	0.5
	[D63 - Dsc]	30	0.05	0.1	0.260	-0.1	0.6
	[D90 - Dsc]	30	0.08	0.1	0.283	-0.1	0.7
ESR, mm/h	Dsc	30	10.5	11	4,911	3	16
	D21	30	13.4	13	5,289	5	25
	D42	30	14.5	15	5,729	6	28
	D63	30	14.4	15	5,139	6	26
	D90	30	13.3	12	5,226	8	26
	[D21 - Dsc]	30	2.9	2	1,486	2	9
	[D42 - Dsc]	30	4	4	1,690	3	12
	[D63 - Dsc]	30	3.9	4	1,553	3	10
	[D90 - Dsc]	30	2.8	1	1,247	5	10

Graphically, the dynamics of the average values of some indicators of the general blood analysis are shown in **fig. 1-4**.

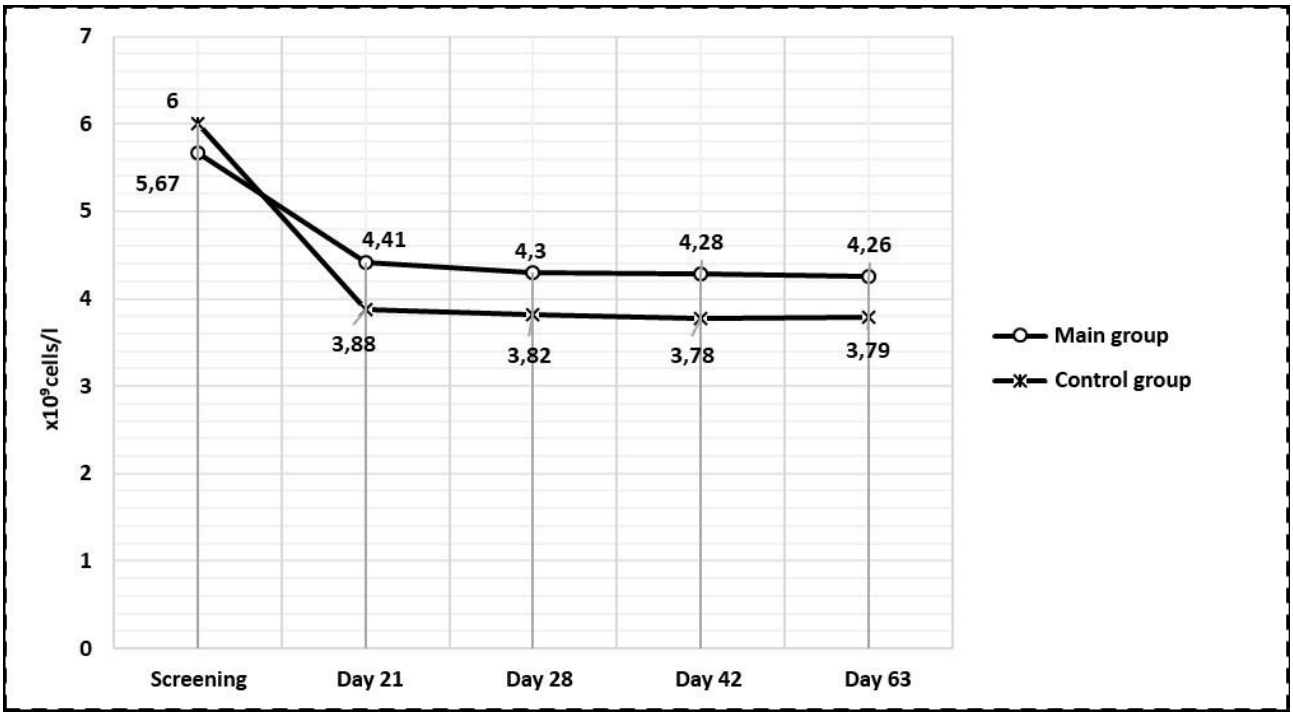

Fig. 1 – Dynamics of the "Leukocytes" indicator in groups

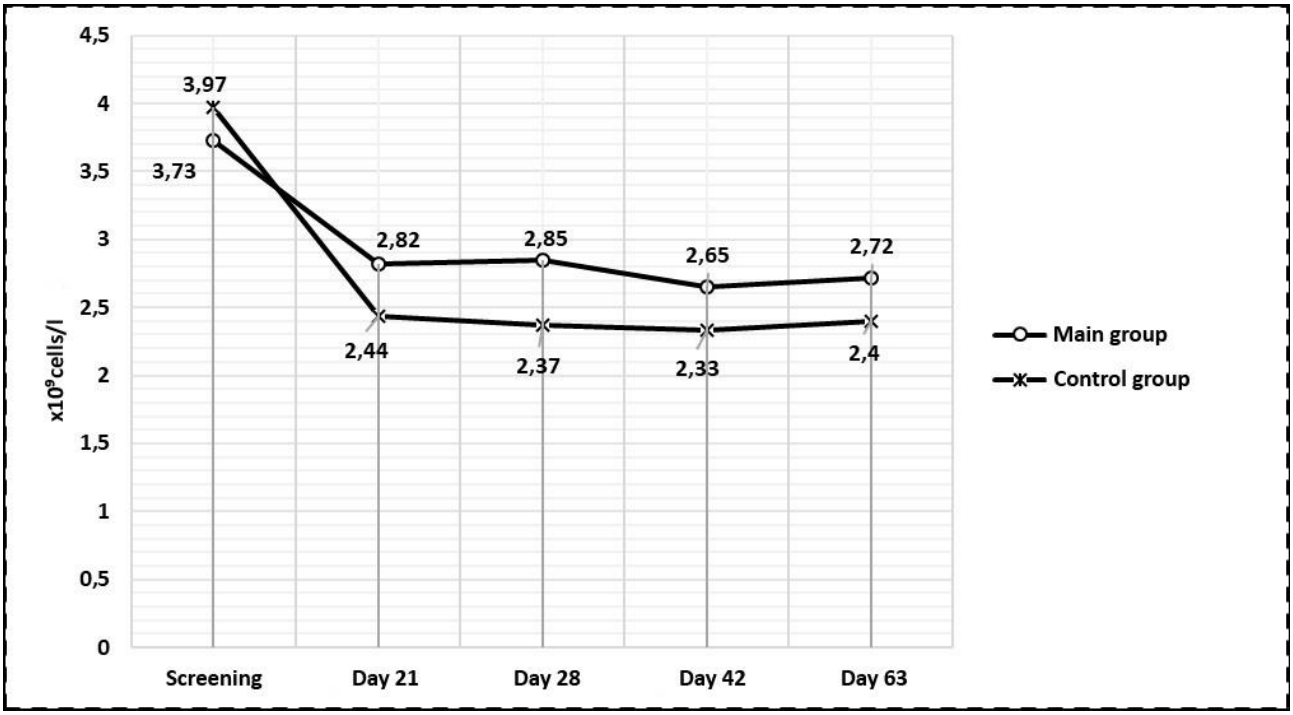

Fig. 2 - Dynamics of the indicator "Neutrophils, abs. number" in groups

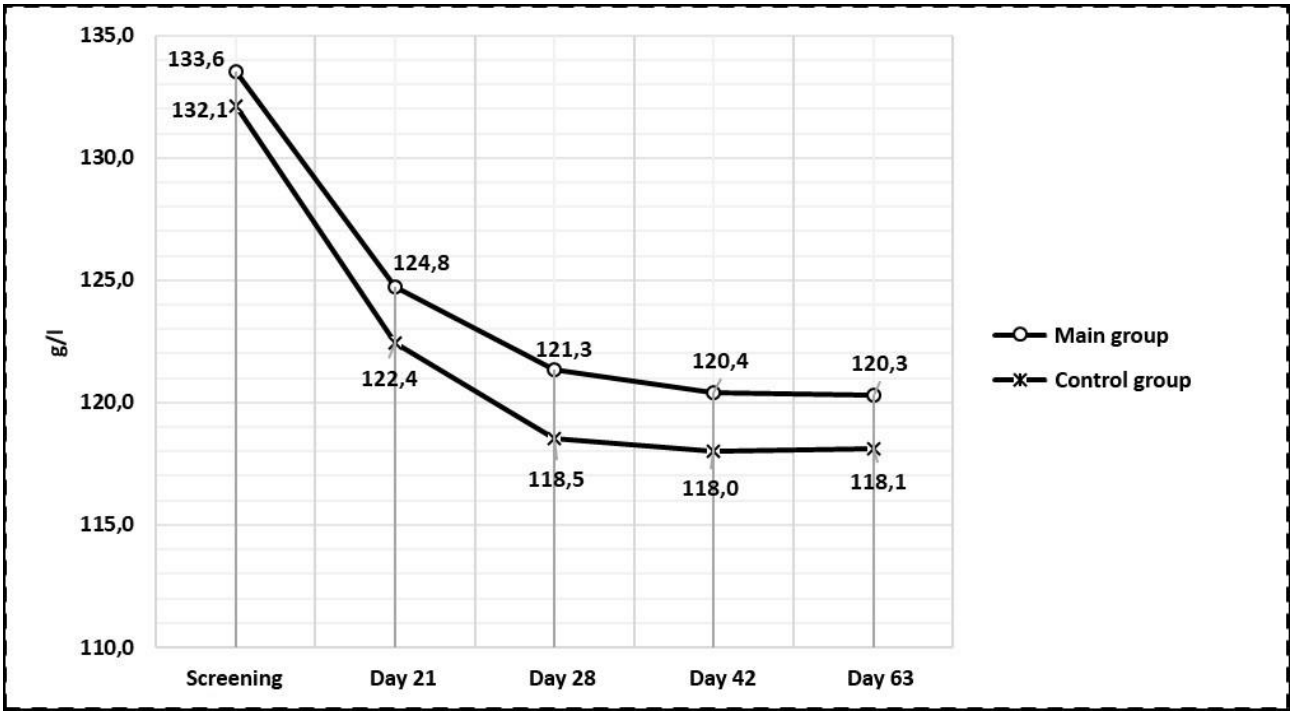

Fig. 3 – Dynamics of the "Hemoglobin" indicator in groups

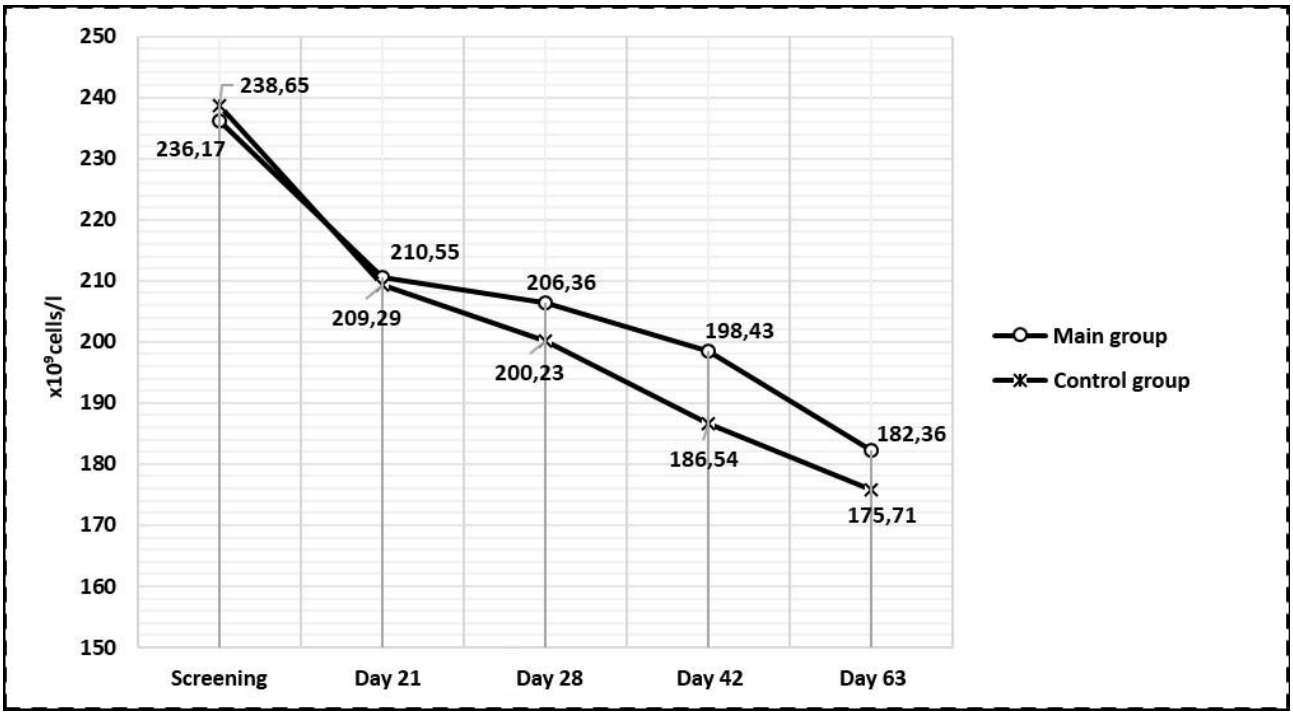

Fig. 4 – Dynamics of the "Platelets" indicator in groups

As can be seen from the graphs, already after the first course of chemotherapy, a decrease in the number of leukocytes, neutrophils, platelets and hemoglobin levels was noted in patients of both groups. These changes corresponded to the toxicity profile of the chemotherapy drugs used and indicated a negative effect of chemotherapy drugs on the hematopoietic system.

To assess the statistical significance of the dynamics of general blood analysis indicators, a variance analysis was performed using a mixed two-factor model (the dependent variable is the value of the analyzed indicator, the "time" factor is fixed (Dscreening, D21, D42, D63, D90), the "subjects" factor is random). The results of VA are given in **table. 28-29** .

A comparison of the following levels of the "visit" factor with the initial data (Dscreening) was also performed using a contrast analysis (**tables 30-31**). The normality of the distribution of VA residuals was checked using the Shapiro-Vilk test (**Table A.6 of Appendix A**).

Table 28 - The main results of the VA indicators of the general blood test in the main group

Dependent variable	The factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
Leukocytes	Visit	48,181	4	12,045	4,670	0.002
	Patients	141,007	29	4,862	1,885	0.010
Erythrocytes	Visit	0.162	4	0.040	0.177	0.950
	Patients	89,327	29	3,080	13,460	0.000
Hematocrit	Visit	155,988	4	38,997	1,273	0.279
	Patients	814,247	29	28,077	6,677	0.000
Hemoglobin	Visit	3771.961	4	942,990	11,858	0.000
	Patients	21248.676	29	732,713	9,213	0.000
Platelets	Visit	46371.707	4	11592.927	9,028	0.000
	Patients	533615.873	29	18400.547	14,330	0.000
Neutrophils, abs.	Visit	23,730	4	5,932	9,034	0.000
	Patients	214,011	29	7,380	11,238	0.000
Neutrophils, %	Visit	371,883	4	92,971	1.001	0.410
	Patients	12490.832	29	430,718	4,639	0.000
Lymphocytes	Visit	321,286	4	80,322	1,483	0.254
	Patients	1518,017	29	52,345	6,180	0.000
Monocytes	Visit	7,615	4	1,904	1,196	0.370
	Patients	74,256	29	2,561	5,643	0.000
Eosinophils	Visit	20,114	4	5,029	1,609	0.096
	Patients	43,222	29	1,490	6,405	0.000
Basophils	Visit	0.402	4	0.100	2,238	0.071
	Patients	6,464	29	0.223	5,411	0.000
ESR	Visit	208,440	4	52,110	1,900	0.095
	Patients	2227,873	29	76,823	13,121	0.000

Table 29 - The main results of the VA indicators of the general blood analysis in the control group

Dependent variable	The factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
Leukocytes	Visit	116,934	4	29,233	17,928	0.000
	Patients	291,664	29	10,057	6,168	0.000
Erythrocytes	Visit	0.802	4	,201	0.900	0.466
	Patients	84,330	29	2,908	13,055	0.000
Hematocrit	Visit	49,193	4	12,298	1,206	0.310
	Patients	938,984	29	32,379	10,546	0.000
Hemoglobin	Visit	4349,512	4	1087,378	17,889	0.000
	Patients	16854.500	29	581,190	9,561	0.000
Platelets	Visit	69899.027	4	17474.757	9,919	0.000
	Patients	551594.860	29	19020,512	10,796	0.000
Neutrophils, abs.	Visit	60,244	4	15,061	20,372	0.000
	Patients	69,096	29	2,383	3,223	0.000

Neutrophils, %	Visit	449,677	4	112,419	1,766	0.140
	Patients	9696.226	29	334,353	5,252	0.000
Lymphocytes	Visit	215,689	4	53,922	1,798	0.125
	Patients	1766,521	29	60,915	7,679	0.000
Monocytes	Visit	10,046	4	2,512	1,546	0.186
	Patients	90,432	29	3,118	8,748	0.000
Eosinophils	Visit	7,138	4	1,785	1,506	0.211
	Patients	29,985	29	1,034	2,611	0.000
Basophils	Visit	,263	4	0.066	1,208	0.311
	Patients	7,299	29	0.252	4,625	0.000
ESR	Visit	311,200	4	77,800	1,867	0.103
	Patients	2430,433	29	83,808	8,474	0.000

Table 30 – Results of contrast analysis of indicators of general blood analysis in the main group

Dependent variable	Contrasts	Estimated contrast	Stand. error	p-value
Leukocytes	D21 - Dsc	-1,313	0.415	0.002
	D42 - Dsc	-1,397		0.001
	D63 - Dsc	-1,430		0.001
	D90 - Dsc	-1,497		0.000
Erythrocytes	D21 - Dsc	-0.033	0.124	0.788
	D42 - Dsc	-0.057		0.647
	D63 - Dsc	-0.097		0.435
	D90 - Dsc	-0.070		0.572
Hematocrit	D21 - Dsc	-1.173	0.529	0.426
	D42 - Dsc	-2.137		0.054
	D63 - Dsc	-0.973		0.557
	D90 - Dsc	-0.740		0.670
Hemoglobin	D21 - Dsc	-8,817	2,303	0.000
	D42 - Dsc	-12,253		0.000
	D63 - Dsc	-13,153		0.000
	D90 - Dsc	-13,253		0.000
Platelets	D21 - Dsc	-25,633	9,252	0.007
	D42 - Dsc	-29,833		0.002
	D63 - Dsc	-37,767		0.000
	D90 - Dsc	-53,833		0.000
Neutrophils, abs.	D21 - Dsc	-0.920	0.209	0.000
	D42 - Dsc	-0.887		0.000
	D63 - Dsc	-1.087		0.000
	D90 - Dsc	-1.020		0.000
Neutrophils, %	D21 - Dsc	-1.177	2,488	0.637
	D42 - Dsc	0.103		0.967

	D63 - Dsc	-3,893		0.120
	D90 - Dsc	-2.827		0.258
Lymphocytes	D21 - Dsc	1,453	0.751	0.256
	D42 - Dsc	0.410		0.786
	D63 - Dsc	2,643		0.055
	D90 - Dsc	2,243		0.087
Monocytes	D21 - Dsc	-0.073	0.174	0.674
	D42 - Dsc	-0.163		0.350
	D63 - Dsc	0.383		0.060
	D90 - Dsc	-0.280		0.110
Eosinophils	D21 - Dsc	-0.277	0.125	0.186
	D42 - Dsc	-0.230		0.210
	D63 - Dsc	0.447		0.085
	D90 - Dsc	-0.070		0.775
Basophils	D21 - Dsc	-0.047	0.052	0.375
	D42 - Dsc	-0.070		0.184
	D63 - Dsc	-0.103		0.078
	D90 - Dsc	-0.143		0.056
ESR	D21 - Dsc	1,700	0.625	0.201
	D42 - Dsc	1,800		0.187
	D63 - Dsc	2,400		0.083
	D90 - Dsc	1,500		0.250
***** The conclusion is made at the significance level of 0.05				

Table 31 - Results of the contrast analysis of indicators of general blood analysis in the control group

Dependent variable	Contrasts	Estimated contrast	Stand. error	p-value
Leukocytes	D21 - Dsc	-2.147	0.330	0.000
	D42 - Dsc	-2,210		0.000
	D63 - Dsc	-2,243		0.000
	D90 - Dsc	-2,223		0.000
Erythrocytes	D21 - Dsc	-0.120	0.122	0.327
	D42 - Dsc	-0.183		0.135
	D63 - Dsc	-0.200		0.103
	D90 - Dsc	-0.177		0.150
Hematocrit	D21 - Dsc	-0.390	0.452	0.602
	D42 - Dsc	-0.530		0.457
	D63 - Dsc	-0.407		0.585
	D90 - Dsc	-0.373		0.633
Hemoglobin	D21 - Dsc	-9,650	2,013	0.000
	D42 - Dsc	-13,587		0.000
	D63 - Dsc	-14,053		0.000
	D90 - Dsc	-13,987		0.000

Platelets	D21 - Dsc	-29,367	10,837	0.008
	D42 - Dsc	-38,433		0.001
	D63 - Dsc	-52,133		0.000
	D90 - Dsc	-62,933		0.000
Neutrophils, abs.	D21 - Dsc	-1.523	0.222	0.000
	D42 - Dsc	-1.597		0.000
	D63 - Dsc	-1.637		0.000
	D90 - Dsc	-1,570		0.000
Neutrophils, %	D21 - Dsc	-3,807	2,060	0.079
	D42 - Dsc	-4,110		0.065
	D63 - Dsc	-4,823		0.053
	D90 - Dsc	-4,257		0.061
Lymphocytes	D21 - Dsc	2,447	0.727	0.075
	D42 - Dsc	1,947		0.105
	D63 - Dsc	1,710		0.156
	D90 - Dsc	1,243		0.348
Monocytes	D21 - Dsc	0.107	0.154	0.690
	D42 - Dsc	0.207		0.457
	D63 - Dsc	0.307		0.198
	D90 - Dsc	0.440		0.092
Eosinophils	D21 - Dsc	-0.343	0.115	0.075
	D42 - Dsc	0.003		0.984
	D63 - Dsc	0.103		0.313
	D90 - Dsc	0.063		0.653
Basophils	D21 - Dsc	-0.060	0.060	0.321
	D42 - Dsc	0.010		0.868
	D63 - Dsc	0.050		0.408
	D90 - Dsc	0.057		0.349
ESR	D21 - Dsc	1,867	0.812	0.167
	D42 - Dsc	2,500		0.063
	D63 - Dsc	1,867		0.167
	D90 - Dsc	1,767		0.211

***** *The conclusion is made at the significance level of 0.05*

Conclusion. Based on the results of the analysis of the significance of the dynamics of hematological indicators, the following conclusions can be drawn.

1. In the main and control groups, a statistically significant decrease in the number of leukocytes, neutrophils, platelets and hemoglobin level was found at all observation points, starting from the 1st course of chemotherapy, compared to the initial data.
2. Changes in other hematological indicators in both groups were statistically and clinically significant throughout the study.

15.4.3. Analysis of the comparison of the dynamics of hematological parameters between groups

Since in the initial state the groups did not differ statistically significantly in terms of hematological parameters, the comparison between the groups was carried out on the differences in dT_i using the Mann-Whitney test (see **Tables A.7-A.8 of Appendix A**).

The results of the analysis of the comparison of the dynamics of hematological indicators between the groups are shown in **Table 32.**

Table 32 - Comparison of groups using the Mann-Whitney test according to the dynamics of hematological indicators

Indicator	dTi	U Mann-Whitney	Wilcoxon W	Z-statistics	p-value (double sided)	Difference between groups*
Leukocytes	dT21	370,500	835,500	-3,185	0.001	Significant
	dT42	334,500	799,500	-3,711	0.001	Significant
	dT63	333,500	798,500	-3.726	0.001	Significant
	dT90	345,500	810,500	-3,549	0.001	Significant
Erythrocytes	dT21	435,000	900,000	-0.279	0.780	Not significant
	dT42	409,000	874,000	-0.735	0.462	Not significant
	dT63	409,500	874,500	-0.788	0.431	Not significant
	dT90	406,000	871,000	-0.903	0.367	Not significant
Hematocrit	dT21	373,000	838,000	-1.275	0.202	Not significant
	dT42	357,500	822,500	-1.632	0.103	Not significant
	dT63	394,500	859,500	-0.917	0.359	Not significant
	dT90	423,000	888,000	-0.442	0.659	Not significant
Hemoglobin	dT21	427,000	892,000	-0.355	0.723	Not significant
	dT42	436,500	901,500	-0.205	0.837	Not significant
	dT63	434,500	899,500	-0.236	0.813	Not significant
	dT90	436,000	901,000	-0.213	0.831	Not significant
Platelets	dT21	446,000	911,000	-0.076	0.939	Not significant
	dT42	439,000	904,000	-0.219	0.826	Not significant
	dT63	411,000	876,000	-3,687	0.001	Significant
	dT90	424,000	889,000	-3,414	0.001	Significant
Neutrophils, abs.	dT21	352,500	817,500	-2,461	0.004	Significant
	dT42	344,000	809,000	-2,584	0.001	Significant
	dT63	367,000	832,000	-2,240	0.009	Significant
	dT90	364,000	829,000	-2,285	0.008	Significant
Neutrophils, %	dT21	348,000	813,000	-1.724	0.085	Not significant
	dT42	373,500	838,500	-1.169	0.242	Not significant
	dT63	433,500	898,500	-0.247	0.805	Not significant
	dT90	397,000	862,000	-0.793	0.428	Not significant
Lymphocytes	dT21	324,500	789,500	-1.121	0.254	Not significant

	dT42	317,500	782,500	-1,212	0.227	Not significant
	dT63	410,000	875,000	-0.648	0.517	Not significant
	dT90	391,000	856,000	-0.947	0.344	Not significant
Monocytes	dT21	382,500	847,500	-1.117	0.264	Not significant
	dT42	372,500	837,500	-1.235	0.217	Not significant
	dT63	395,000	860,000	-0.857	0.391	Not significant
	dT90	337,500	802,500	-1.552	0.126	Not significant
Eosinophils	dT21	421,000	886,000	-0.497	0.619	Not significant
	dT42	374,000	839,000	-1.169	0.243	Not significant
	dT63	334,500	799,500	-1,804	0.071	Not significant
	dT90	386,000	851,000	-0.969	0.333	Not significant
Basophils	dT21	420,500	885,500	-0.574	0.566	Not significant
	dT42	357,000	822,000	-1.908	0.056	Not significant
	dT63	361,000	826,000	-1.443	0.149	Not significant
	dT90	329,500	794,500	-1.831	0.067	Not significant
ESR	dT21	447,500	912,500	-0.038	0.970	Not significant
	dT42	395,500	860,500	-0.836	0.403	Not significant
	dT63	450,000	915,000	0.000	1,000	Not significant
	dT90	443,000	908,000	-0.109	0.914	Not significant
**The conclusion is made at the significance level of 0.05*						

Conclusion.

From the data presented **in the table. 32** we can draw conclusions:

1. A more pronounced decrease in the level of leukocytes was found, starting from the 1st course of chemotherapy in patients of the control group, compared to the main one.
2. A significantly more pronounced decrease in the level of neutrophils (abs.) was found starting from the 1st course of chemotherapy in patients of the control group compared to the main group.
3. A more pronounced decrease in the level of platelets was found starting from the 3rd course of chemotherapy in patients of the control group compared to the main group.
4. The groups did not differ significantly according to the rest of the hematological parameters.

For statistical analysis, the indicators of the general blood test were transformed into categorical variables with the following categories: "Normal", "Beyond the norm".

Further analysis of indicators was carried out with the construction of a frequency table. χ^2 Pearson tests (or Fisher's exact test) were used to compare frequencies . The results of this analysis are shown in **table. 33**.

Table 33 - Results of general blood analysis in groups

Indicator	Time	Category	Main group (n=30)		Control group (n=30)		p-value*
			n	%	n	%	
Leukocytes	Dsc	It's normal	28	93.3	29	96.7	1,000
		Outside the norm	2	6,7	1	3.3	
	D21	It's normal	17	56.7	7	23.3	0.018 *
		Outside the norm	13	43.3	23	76.7	
	D42	Norm	17	56.7	8	26.7	0.036 *
		Outside the norm	13	43.3	22	73.3	
	D63	Norm	18	60.0	9	30.0	0.038 *
		Outside the norm	12	40.0	21	70.0	
	D90	Norm	18	60.0	9	30.0	0.038 *
		Outside the norm	12	40.0	21	70.0	
Hemoglobin	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0.0	
	D21	It's normal	28	93.3	27	90.0	1,000
		Outside the norm	2	6,7	3	10.0	
	D42	Norm	26	86.7	25	83.3	1,000
		Outside the norm	4	13.3	5	16.7	
	D63	Norm	25	83.3	24	80.0	1,000
		Outside the norm	5	16.7	6	20.0	
	D90	Norm	25	83.3	22	73.3	0.531
		Outside the norm	5	16.7	8	26.7	
Platelets	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	29	96.7	28	93.3	1,000
		Outside the norm	1	3.3	2	6,7	
	D42	Norm	28	93.3	28	93.3	1,000
		Outside the norm	2	6,7	2	6,7	
	D63	Norm	28	93.3	26	86.7	0.671
		Outside the norm	2	6,7	4	13.3	
	D90	Norm	29	96.7	27	90.0	0.612
		Outside the norm	1	3.3	3	10.0	
Neutrophils	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	22	73.3	12	40.0	0.019 *
		Outside the norm	8	27.7	18	60.0	
	D42	Norm	21	70.0	12	40.0	0.038 *
		Outside the norm	9	30.0	18	60.0	

Indicator	Time	Category	Main group (n=30)		Control group (n=30)		p-value*
			n	%	n	%	
	D63	Norm	22	73.3	15	50.0	0.111
		Outside the norm	8	27.7	15	50.0	
	D90	Norm	23	76.7	17	56.7	0.171
		Outside the norm	7	23.3	13	43.3	
Erythrocytes	Dsc	It's normal	29	96.7	29	96.7	1,000
		Outside the norm	1	3.3	1	3.3	
	D21	It's normal	28	93.3	28	93.3	1,000
		Outside the norm	2	6,7	2	6,7	
	D42	Norm	28	93.3	28	93.3	1,000
		Outside the norm	2	6,7	2	6,7	
	D63	Norm	28	93.3	27	90.0	1,000
		Outside the norm	2	6,7	3	10.0	
	D90	Norm	28	93.3	28	93.3	1,000
		Outside the norm	2	6,7	2	6,7	
Hematocrit	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D42	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D63	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D90	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
Lymphocytes	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D42	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D63	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D90	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
Monocytes	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	30	100.0	29	96.7	1,000
		Outside the norm	0	0	1	3.3	
	D42	Norm	29	96.7	29	96.7	1,000
		Outside the norm	1	3.3	1	3.3	
	D63	Norm	30	100.0	30	100.0	1,000

Indicator	Time	Category	Main group (n=30)		Control group (n=30)		p-value*
			n	%	n	%	
		Outside the norm	0	0	0	0	
	D90	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
Eosinophils	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D42	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D63	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D90	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
Basophils	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D42	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D63	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D90	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
ESR	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	29	96.7	28	93.3	1,000
		Outside the norm	1	3.3	2	6,7	
	D42	Norm	28	93.3	29	96.7	1,000
		Outside the norm	2	6,7	1	3.3	
	D63	Norm	29	96.7	29	96.7	1,000
		Outside the norm	1	3.3	1	3.3	
	D90	Norm	29	96.7	28	93.3	1,000
		Outside the norm	1	3.3	2	6,7	

Estimated using Fisher's exact test in combination with Pearson's chi-square test at a significance level of 0.05 and df=1
**There are significant differences between groups*

As can be seen from **Table 33**, the most frequent side effect from the hematopoietic system was leukopenia (leukocytes <4.0x10^9 cells/l), which was observed in 13 (43.3%) patients of the main group and in 23 (76.3%) of the control group, and neutropenia, which was observed in 9 (30.0%) patients of the main group and in 18 (60.0%) patients of the control group. A decrease in the level of

hemoglobin (<110 g/l) was observed in 5 (16.7%) patients of the main group and in 8 (26.7%) patients of the control group. And a decrease in the number of platelets (<150x10^9 cells/l) was observed in 2 (6.7%) patients of the main group and in 4 (13.3%) patients of the control group.

Conclusion. From the data presented in the **table. 33**, it can be concluded that in the control group there was a significantly higher number of patients in whom deviations from the norm of such indicators as the number of leukocytes and the number of neutrophils were observed, compared to the main group.

According to other indicators, the difference between the groups is not reliable.

In **fig. 5-8** presents the frequency of development of leukopenia, neutropenia, anemia and thrombocytopenia in patients of the main and control groups during the study.

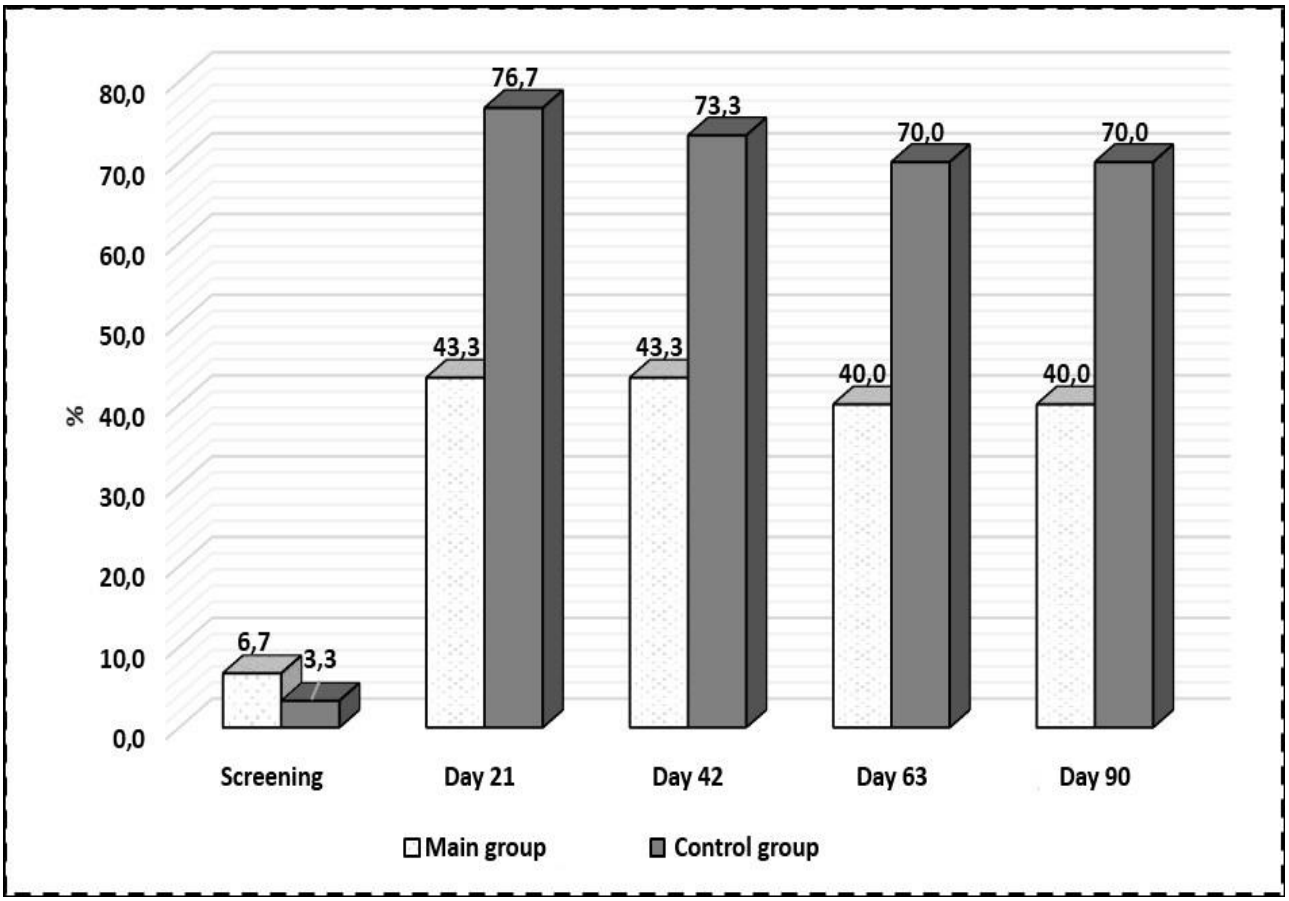

Fig. 5 - Frequency of development of leukopenia

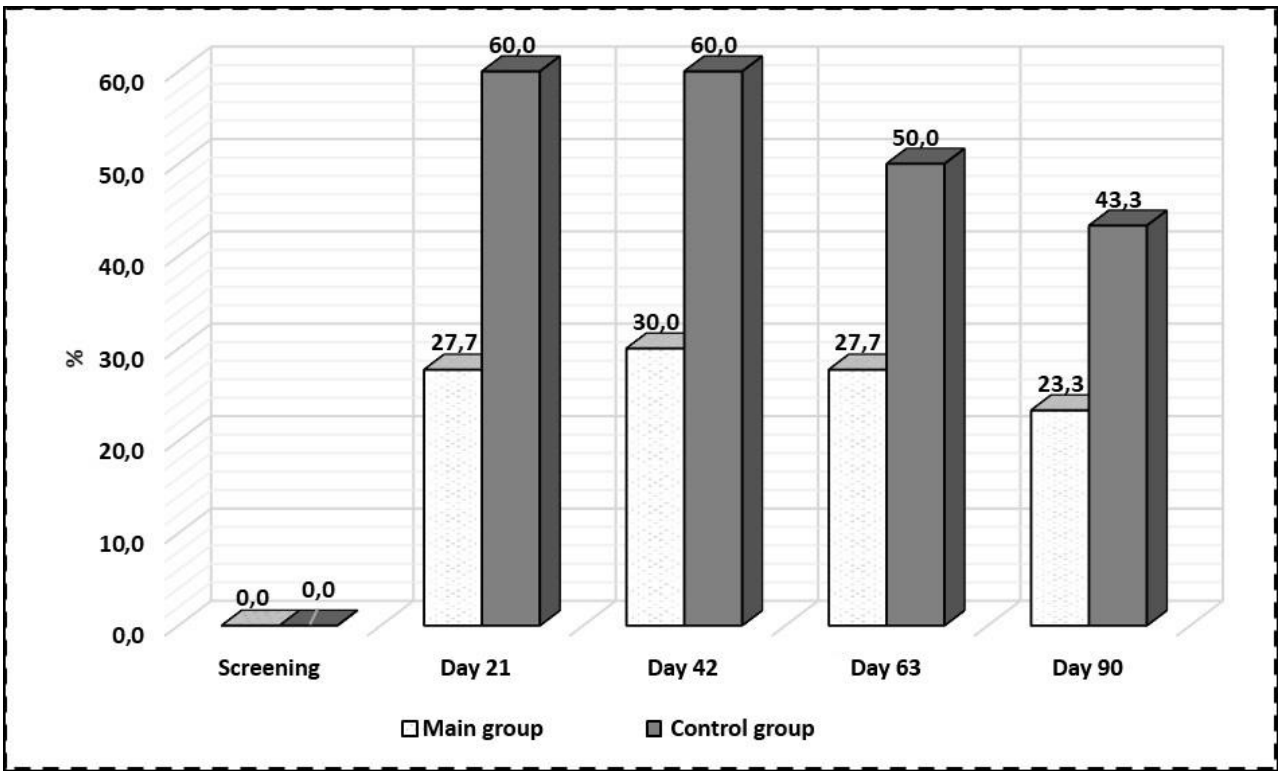

Fig. 6 – Frequency of neutropenia (absence of neutrophils)

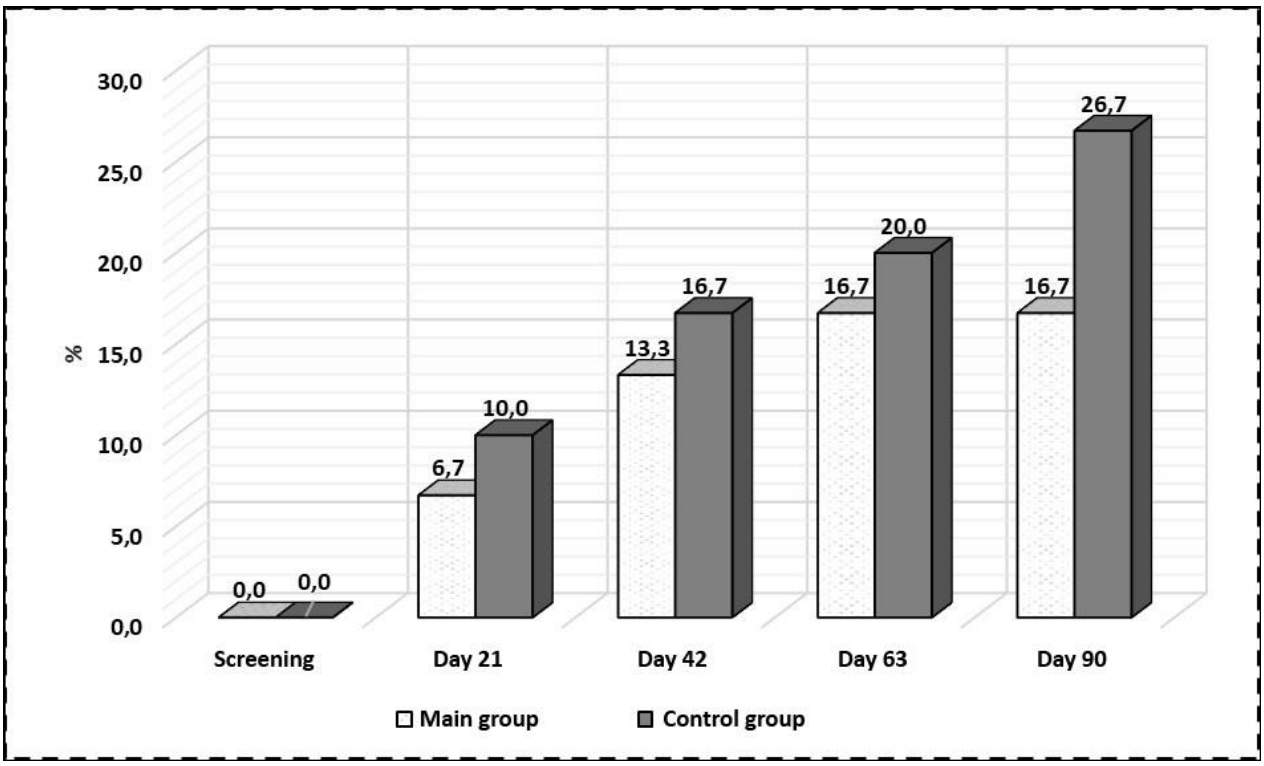

Fig. 7 – Frequency of development of anemia (hemoglobin)

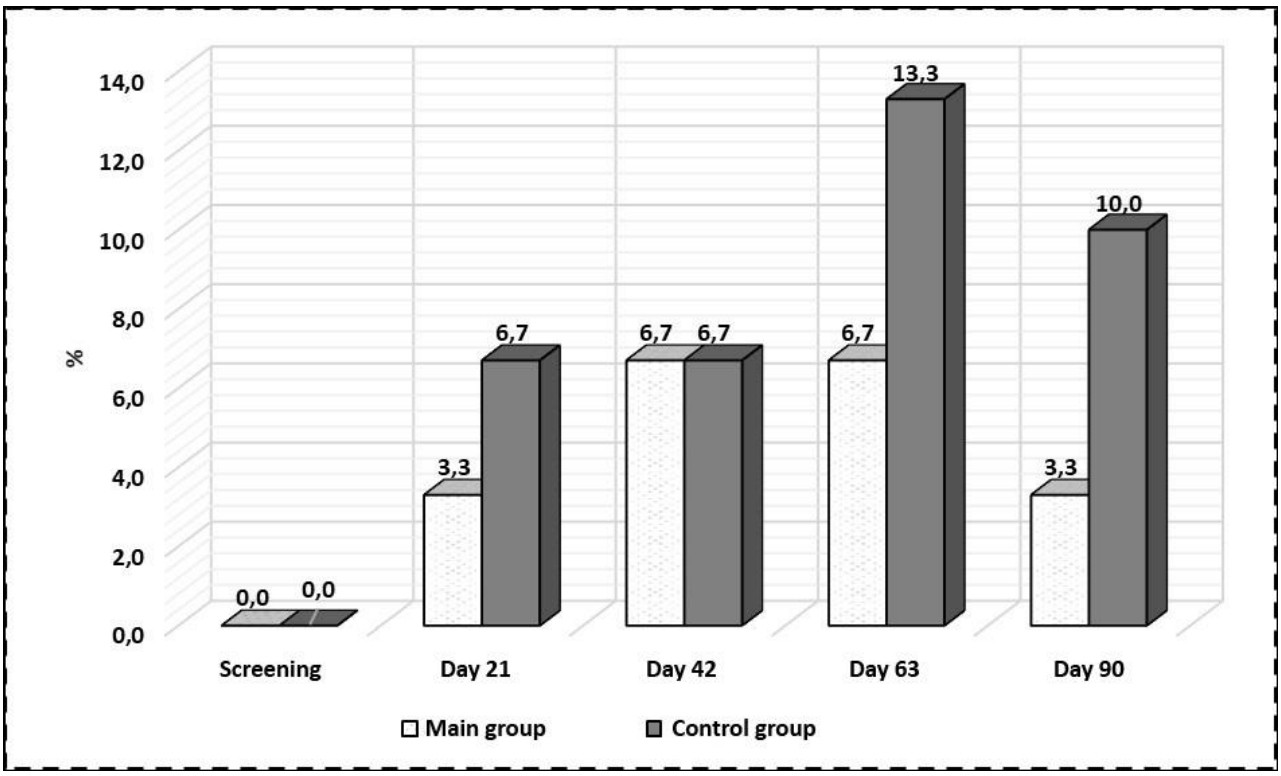

Fig. 8 – Frequency of development of thrombocytopenia

15.4.4. Analysis of dynamics of biochemical blood analysis parameters

Biochemical blood analysis (ALT, AST, total bilirubin, creatinine, glucose) was performed during screening (D_{SC}) and then after each course of chemotherapy.

The results of the analysis of the dynamics of the indicators of the biochemical analysis of blood by the method of descriptive statistics are shown in the **table. 34** for the main group and in **table. 35** comparison groups.

Table 34 - Dynamics of indicators of biochemical blood analysis during the study in patients of the main group

Parameter	Time	n	M	Me	SD	MIN	MAX
ALT, units/l	Dsc	30	35,40	32	4,237	22	40
	D21	30	38.82	35	4,232	25	44
	D42	30	41.29	40	5,466	27	59
	D63	30	43.57	42	6,457	30	63
	D90	30	44.92	45	6,895	32	61
	[D21 - Dsc]	30	3.42	3	0.335	3	4
	[D42 - Dsc]	30	5.89	8	2,555	5	19
	[D63 - Dsc]	30	8,17	10	2,568	8	23
	[D90 - Dsc]	30	9.52	13	3,127	10	21

AST, units/l	Dsc	30	32.45	32	4,379	20	38
	D21	30	36.85	35	4,636	23	42
	D42	30	39.45	40	5,221	25	53
	D63	30	41.63	42	5,774	31	59
	D90	30	42.82	42	5,790	30	58
	[D21 - Dsc]	30	4.4	3	0.224	3	4
	[D42 - Dsc]	30	7	8	2,680	5	15
	[D63 - Dsc]	30	9,18	10	2,701	11	21
	[D90 - Dsc]	30	10.37	10	2,226	10	20
Total bilirubin, μmol/l	Dsc	30	15,24	15.5	2,765	11.2	18.8
	D21	30	15.49	15.7	2,547	13.8	19.4
	D42	30	15.85	15.9	2,769	13.2	20.8
	D63	30	16.38	16.3	2,912	14.2	21.0
	D90	30	16.43	16.7	2,772	13.9	20.6
	[D21 - Dsc]	30	0.25	0.2	1,116	0.6	2.6
	[D42 - Dsc]	30	0.61	0.4	0.894	1.5	2.0
	[D63 - Dsc]	30	1.14	0.8	0.778	2,2	3.0
	[D90 - Dsc]	30	1.19	1,2	1,180	1.8	2.7
Creatinine, μmol/l	Dsc	30	75.1	74	11,536	55	84
	D21	30	72.9	72	10,037	62	81
	D42	30	73.6	72	9,275	61	82
	D63	30	74.4	75	10,611	62	80
	D90	30	74.3	75	9,613	64	81
	[D21 - Dsc]	30	-2.2	-2	3,124	-3	7
	[D42 - Dsc]	30	-1.5	-2	2,783	-2	6
	[D63 - Dsc]	30	-0.7	1	2,225	-4	7
	[D90 - Dsc]	30	-0.8	1	3,457	-3	9
Glucose, μmol/l	Dsc	30	5.25	5.3	0.561	4.2	6.8
	D21	30	5.22	5.2	0.548	4.0	6.3
	D42	30	5.18	5.2	0.517	4.2	6.5
	D63	30	5.15	5.1	0.494	4.2	6,7
	D90	30	5.33	4.9	0.652	4.0	6.2
	[D21 - Dsc]	30	-0.03	-0.1	0.361	-0.2	-0.5
	[D42 - Dsc]	30	-0.07	-0.1	0.250	0	-0.3
	[D63 - Dsc]	30	-0.1	-0.2	0.148	0	-0.1
	[D90 - Dsc]	30	0.08	-0.4	0.223	-0.2	-0.6

Table 35 - Dynamics of indicators of biochemical blood analysis during the study in patients of the control group

Parameter	Time	n	M	Me	SD	MIN	MAX
ALT, units/l	Dsc	30	34,27	35	4,136	21	39
	D21	30	38,59	40	4,313	26	47
	D42	30	43,18	45	5,225	26	58
	D63	30	44,41	45	5,673	32	62
	D90	30	46.23	45	6,114	33	62

Parameter	Time	n	M	Me	SD	MIN	MAX
	[D21 - Dsc]	30	4.32	5	1,678	5	8
	[D42 - Dsc]	30	8.91	10	3,221	5	19
	[D63 - Dsc]	30	10,14	10	3,260	11	23
	[D90 - Dsc]	30	11.96	10	2,997	12	23
AST, units/l	Dsc	30	32.89	32	4,507	18	38
	D21	30	36,29	35	5,332	22	44
	D42	30	40.64	40	6,268	24	56
	D63	30	42.92	42	5,889	30	55
	D90	30	43.32	42	6,148	30	60
	[D21 - Dsc]	30	3,4	3	0.863	4	6
	[D42 - Dsc]	30	7.75	8	2,225	6	18
	[D63 - Dsc]	30	10.03	10	1,468	12	17
	[D90 - Dsc]	30	10.43	10	2,447	12	22
Total bilirubin, µmol/l	Dsc	30	14.73	14.8	2,457	12.4	19.2
	D21	30	15,27	15.1	2,106	13.6	20.5
	D42	30	15.43	15.5	2,684	13.5	21.3
	D63	30	15.86	15.7	2,930	14.2	21.2
	D90	30	16,20	16.3	3,294	13.8	21.0
	[D21 - Dsc]	30	0.54	0.3	0.215	1,2	1.3
	[D42 - Dsc]	30	0.7	0.7	0.331	1.1	2.1
	[D63 - Dsc]	30	1.13	0.9	0.248	1.8	2.0
	[D90 - Dsc]	30	1.47	1.5	0.279	1.4	1.8
Creatinine, µmol/l	Dsc	30	73.9	72	10,868	53	90
	D21	30	73.5	75	10,181	58	81
	D42	30	74.6	75	9,746	60	80
	D63	30	74.8	75	10,566	64	80
	D90	30	75.3	75	9,897	63	81
	[D21 - Dsc]	30	-0.4	3	5.1137	5	-9
	[D42 - Dsc]	30	0.7	3	6,093	7	-10
	[D63 - Dsc]	30	0.9	3	8,445	11	-10
	[D90 - Dsc]	30	1.4	3	9,116	10	-9
Glucose, µmol/l	Dsc	30	5.42	5.5	0.538	4.5	6.8
	D21	30	5.52	5,6	0.872	4.0	6.5
	D42	30	5.58	5.7	0.924	4.0	6.8
	D63	30	5.46	5.4	0.641	3.9	6,7
	D90	30	5.39	5.4	0.732	4.0	6.6
	[D21 - Dsc]	30	0.1	0.1	0.146	-0.3	-0.5
	[D42 - Dsc]	30	0.16	0.2	0.329	0	-0.5
	[D63 - Dsc]	30	0.04	-0.1	0.371	-0.1	-0.6
	[D90 - Dsc]	30	-0.03	-0.1	0.273	-0.2	-0.5

Graphically, the dynamics of the average values of some indicators are shown in **fig. 9-12** .

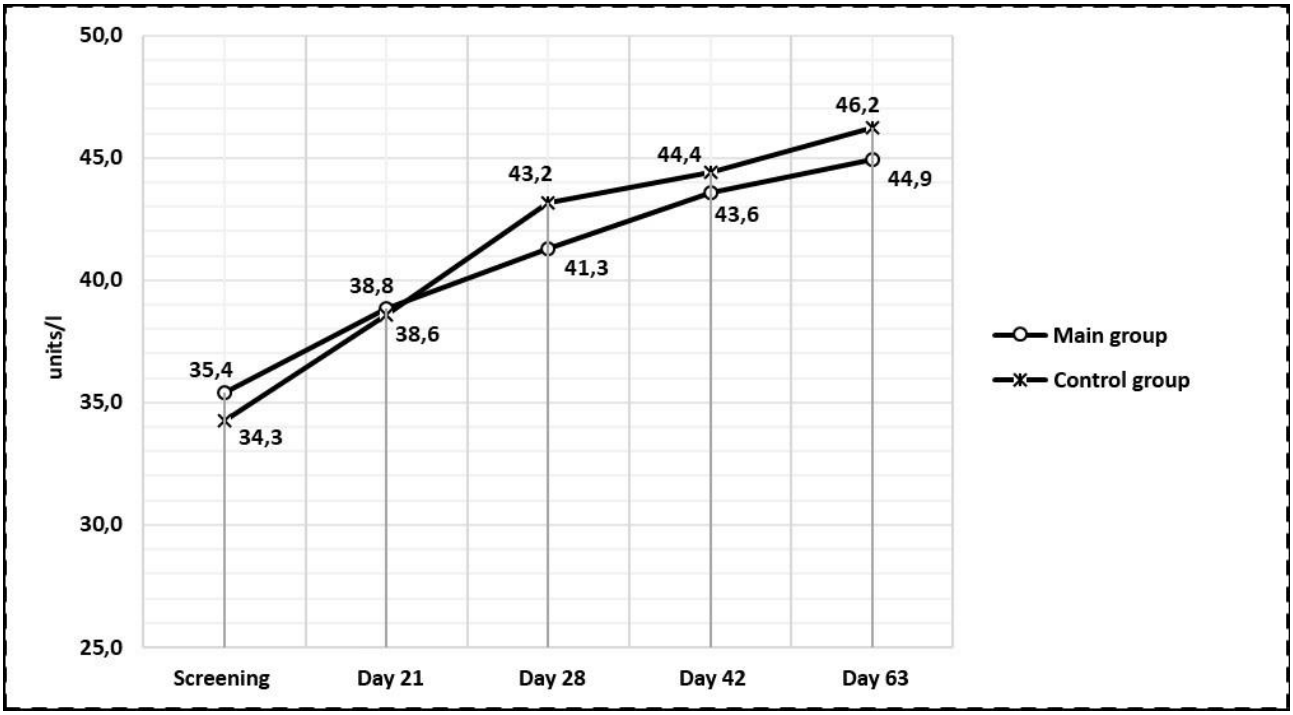

Fig. 9 – Dynamics of average ALT values in groups

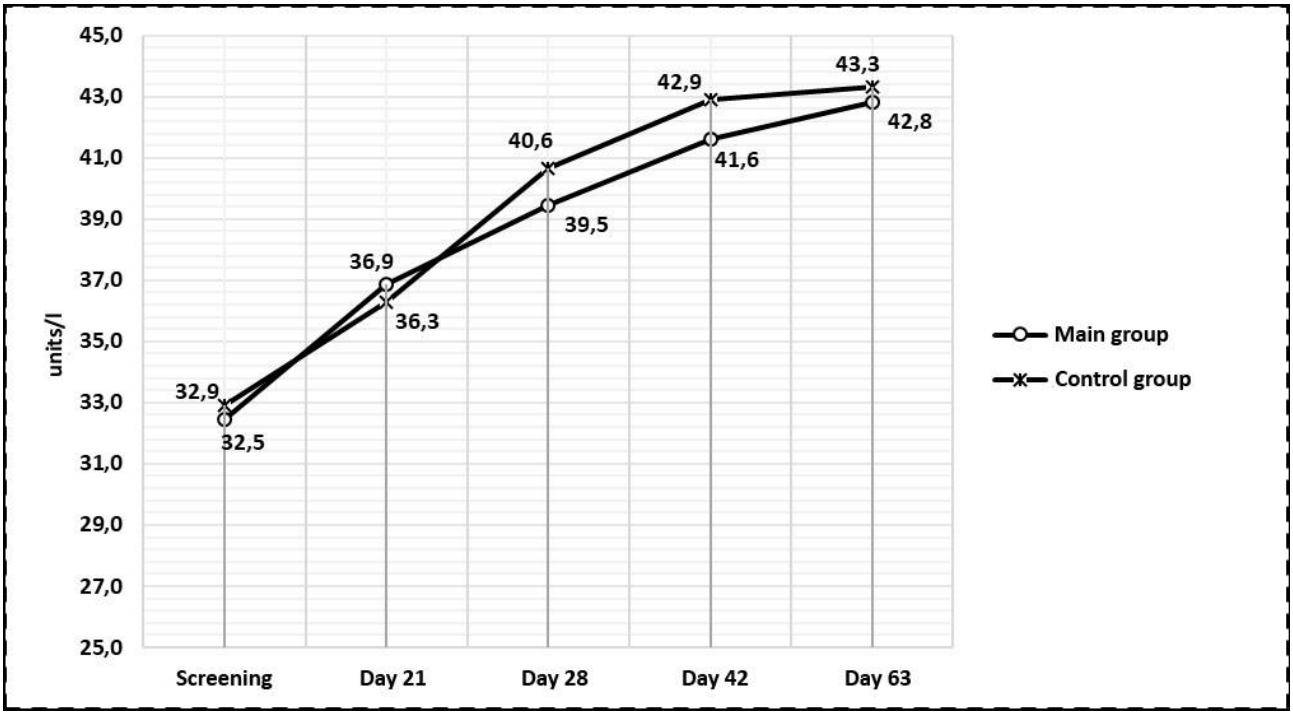

Fig. 10 – Dynamics of average AST values in groups

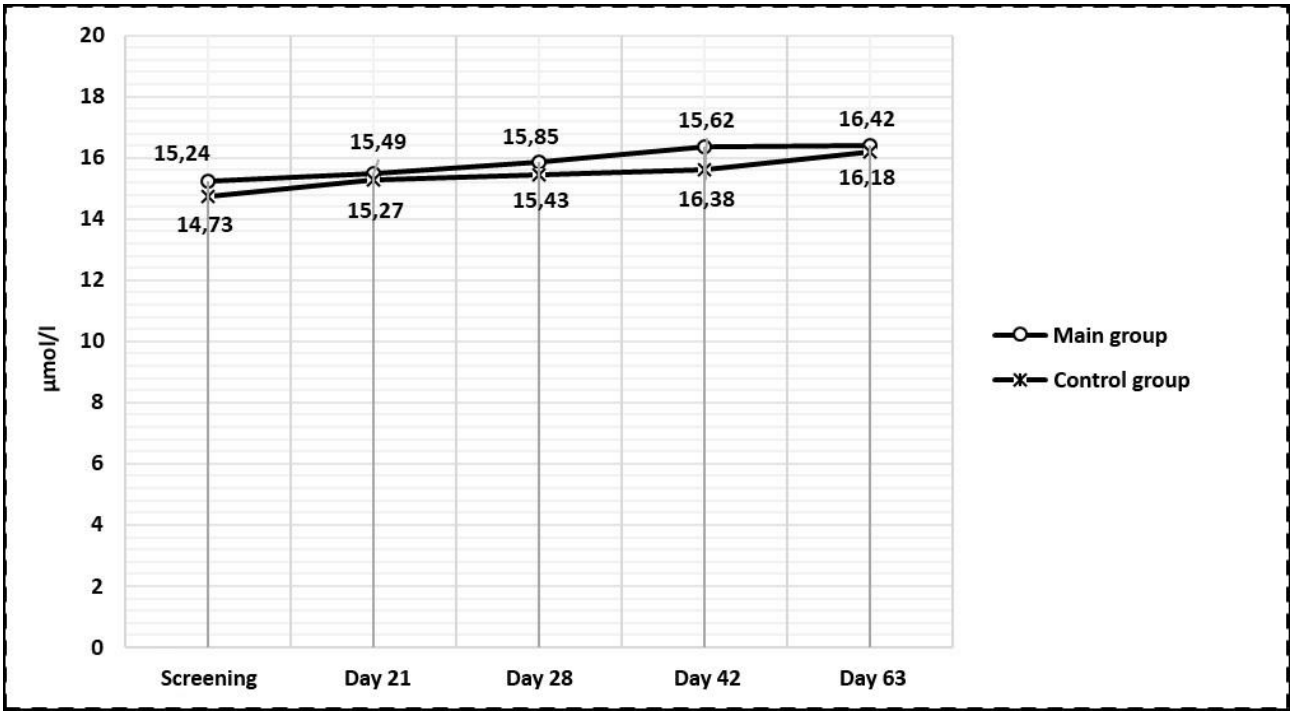

Fig. 11 - Dynamics of average values of total bilirubin in groups

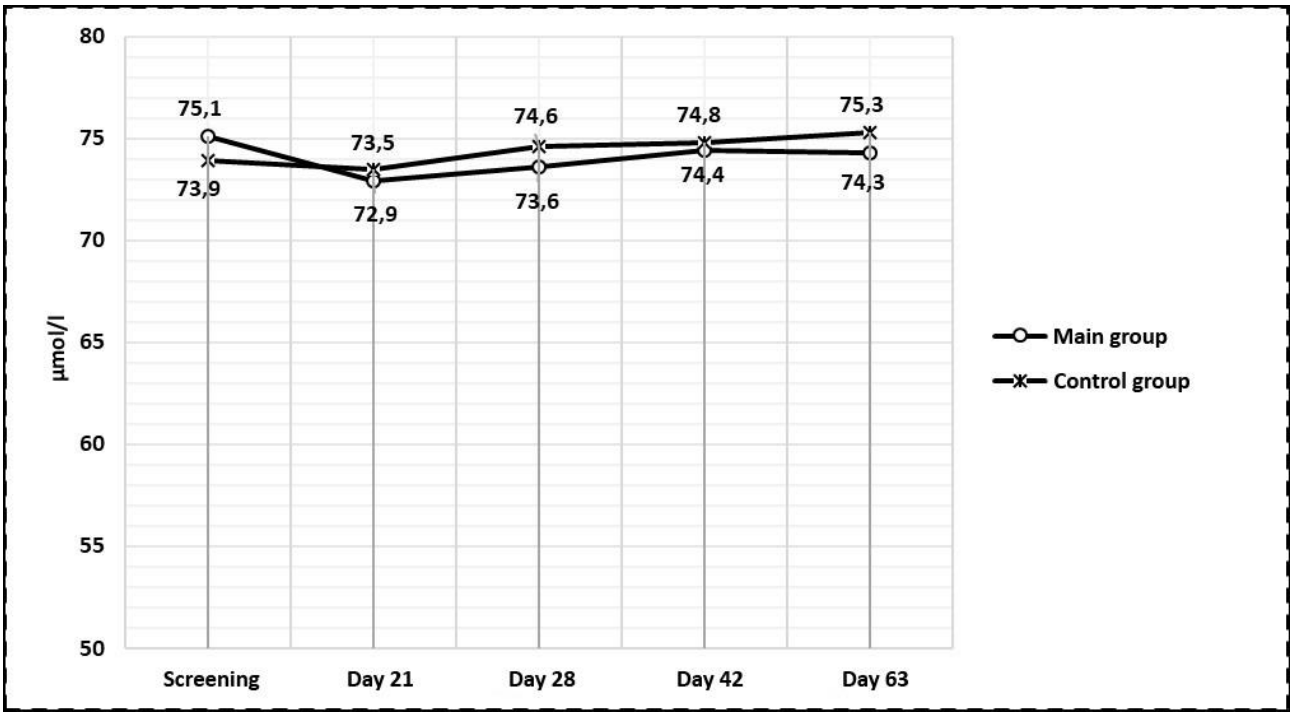

Fig. 12 – Dynamics of average values of creatinine in groups

As can be seen from the graphs, the patients of the main and control groups had an increase in the level of ALT and AST during treatment. These changes indicated a negative effect of chemotherapy drugs on the hepatobiliary system.

To assess the significance of the dynamics of biochemical blood analysis indicators, a variance analysis was performed using a mixed two-factor model (the dependent variable is the value of the analyzed indicator, the "time" factor is fixed (Dsc, D21, D42, D63, D90), the "subjects" factor is random). The results of VA are given in **table. 36-37**.

A comparison of the following levels of the "visit" factor with the initial data (Dsc) was also performed using the contrast analysis of **tables 38-39**. The normality of the distribution of VA residuals was checked using the Shapiro-Wilk test (**Table A.9 of Appendix A**).

Table 36 - The main results of VA indicators of biochemical blood analysis in the main group

Dependent variable	The factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
ALT	Visit	1641,854	4	410,464	4,200	0.003
	Patients	16151.849	29	556,960	5,699	0.000
AST	Visit	2057,324	4	514,331	16,649	0.000
	Patients	6384.592	29	220,158	7,126	0.000
Total bilirubin	Visit	32,972	4	8,243	2,094	0.086
	Patients	687,144	29	23,695	6,020	0.000
Creatinine	Visit	86,191	4	21,548	1,079	0.370
	Patients	12244.532	29	422,225	21,134	0.000
Glucose	Visit	0.549	4	0.137	1,658	0.114
	Patients	41,889	29	1,444	38,478	0.000

Table 37 – The main results of VA indicators of biochemical blood analysis in the control group

Dependent variable	The factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
ALT	Visit	2826,674	4	706,668	6,906	0.000
	Patients	14073.756	29	485,302	4,743	0.000
AST	Visit	2434,379	4	608,595	16,986	0.000
	Patients	6602,940	29	227,688	6,355	0.000
Total bilirubin	Visit	38,105	4	9,526	2,088	0.094
	Patients	594,019	29	20,483	5,564	0.000
Creatinine	Visit	63,779	4	15,945	0.792	0.533
	Patients	11217.540	29	386,812	19,218	0.000

Glucose	Visit	0.739	4	0.185	1,350	0.256
	Patients	73,362	29	2,530	18,487	0.000

Table 38 – Results of contrast analysis of biochemical blood analysis indicators in the main group

Dependent variable	Contrasts	Estimated contrast	Stand. error	p-value
ALT	D21 - Dsc	4,430	2,552	0.085
	D42 - Dsc	5,870		0.023 *
	D63 - Dsc	8,197		0.002*
	D90 - Dsc	9,497		0.000*
AST	D21 - Dsc	2,907	1,435	0.057
	D42 - Dsc	6,990		0.000*
	D63 - Dsc	9,157		0.000*
	D90 - Dsc	10,390		0.000*
Total bilirubin	D21 - Dsc	0.260	0.512	0.613
	D42 - Dsc	0.593		0.249
	D63 - Dsc	1.027		0.080
	D90 - Dsc	1,093		0.059
Creatinine	D21 - Dsc	-2,223	1,154	0.056
	D42 - Dsc	-1.517		0.191
	D63 - Dsc	-0.723		0.532
	D90 - Dsc	-0.787		0.497
Glucose	D21 - Dsc	-0.027	0.050	0.595
	D42 - Dsc	-0.067		0.185
	D63 - Dsc	-0.100		0.058
	D90 - Dsc	0.077		0.128

** Statistically significant differences are observed*
The conclusion is made at the significance level of 0.05

Table 39 - Results of contrast analysis of biochemical blood analysis indicators in the control group

Dependent variable	Contrasts	Estimated contrast	Stand. error	p-value
ALT	D21 - Dsc	4,297	2,612	0.103
	D42 - Dsc	8,897		0.001 *
	D63 - Dsc	10,130		0.000*
	D90 - Dsc	11,953		0.000*
AST	D21 - Dsc	3,173	1,546	0.052
	D42 - Dsc	7,723		0.000*
	D63 - Dsc	10,023		0.000*
	D90 - Dsc	10,423		0.000*

Total bilirubin	D21 - Dsc	0.557	0.495	0.263
	D42 - Dsc	0.740		0.138
	D63 - Dsc	1,040		0.093
	D90 - Dsc	1,177		0.057
Creatinine	D21 - Dsc	-0.393	1,158	0.735
	D42 - Dsc	0.733		0.538
	D63 - Dsc	0.937		0.420
	D90 - Dsc	1,417		0.224
Glucose	D21 - Dsc	0.103	0.096	0.282
	D42 - Dsc	0.160		0.097
	D63 - Dsc	0.033		0.728
	D90 - Dsc	-0.033		0.728
** Statistically significant differences are observed* *The conclusion is made at the significance level of 0.05*				

Conclusion. Based on the results of the analysis of the significance of the dynamics of the parameters of the biochemical blood analysis, the following conclusions can be drawn.

1. In the main and control groups, a statistically significant increase in the level of ALT and AST was found, starting from the 2nd course of CT compared to the initial data.
2. Changes in other biochemical parameters in both groups were statistically and clinically significant.

15.4.5. Analysis of the comparison of the dynamics of biochemical blood test parameters between groups

Since in the initial state the groups did not differ statistically significantly according to the indicators of the biochemical analysis of blood, the comparison between the groups was performed on the differences in dT_i using the Mann-Whitney test, because individual differences dT_i are not normally distributed in both groups **(see Tables A.10-A.11 of Appendix A).** The results of this comparison are shown in **Table 40.**

Table 40 - Comparison of groups using the Mann-Whitney test according to the dynamics of biochemical blood analysis indicators

Indicator	dTi	U Mann-Whitney	Wilcoxon W	Z-statistics	p-value (double sided)	Difference between groups*
ALT	dT21	448,000	913,000	-0.030	0.976	Not significant
	dT42	397,000	862,000	-0.792	0.428	Not significant
	dT63	424,000	889,000	-0.386	0.700	Not significant
	dT90	416,500	881,500	-0.497	0.619	Not significant

AST	dT21	390,500	855,500	-0.973	0.331	Not significant
	dT42	431,000	896,000	-0.303	0.762	Not significant
	dT63	428,500	893,500	-0.332	0.740	Not significant
	dT90	442,000	907,000	-0.121	0.903	Not significant
Total bilirubin	dT21	366,000	831,000	-1.913	0.058	Not significant
	dT42	411,000	876,000	-0.854	0.393	Not significant
	dT63	390,000	855,000	-1.027	0.304	Not significant
	dT90	384,000	849,000	-1.079	0.280	Not significant
Creatinine	dT21	380,000	845,000	-1.534	0.125	Not significant
	dT42	349,500	814,500	-1.909	0.066	Not significant
	dT63	391,500	856,500	-1.016	0.310	Not significant
	dT90	345,500	810,500	-1,960	0.053	Not significant
Glucose	dT21	377,500	842,500	-1.923	0.059	Not significant
	dT42	351,000	816,000	-1.956	0.055	Not significant
	dT63	411,000	876,000	-0.800	0.424	Not significant
	dT90	388,000	853,000	-1.207	0.227	Not significant
	dT21	448,000	913,000	-0.030	0.976	Not significant

Conclusion: based on the results of the analysis given in the **table. 40**, it can be stated that the groups did not differ statistically significantly in the dynamics of biochemical blood analysis indicators.

For statistical analysis, indicators of biochemical blood analysis were transformed into categorical variables with categories: "Normal", "Outside the norm".

Further analysis of indicators was carried out with the construction of a frequency table. Fisher's exact test was used to compare frequencies. The results of this analysis are shown in **table. 41**.

Table 41 - Results of analysis of indicators of biochemical blood analysis

Indicator	Time	Category	Main group (n=30)		Control group (n=30)		p-value*
			n	%	n	%	
ALT	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	25	83.3	26	86.7	1,000
		Outside the norm	5	16.7	4	13.3	
	D42	Norm	25	83.3	26	86.7	1,000
		Outside the norm	5	16.7	4	13.3	
	D63	Norm	21	70.0	18	60.0	0.588
		Outside the norm	9	30.0	12	40.0	

Indicator	Time	Category	Main group (n=30)		Control group (n=30)		p-value*
			n	%	n	%	
	D90	Norm	20	66.7	18	60.0	0.789
		Outside the norm	10	33.3	12	40.0	
AST	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	25	83.3	26	86.7	1,000
		Outside the norm	5	16.7	4	13.3	
	D42	Norm	25	83.3	26	86.7	1,000
		Outside the norm	5	16.7	4	13.3	
	D63	Norm	21	70.0	20	60.0	1,000
		Outside the norm	9	30.0	10	40.0	
	D90	Norm	21	70.0	20	60.0	1,000
		Outside the norm	9	40.0	10	40.0	
Total bilirubin	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D42	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D63	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D90	Norm	30	100.0	30	100.0	1,000
		Outside the norm	30	100.0	30	100.0	
Creatinine	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D21	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D42	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D63	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D90	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
Glucose	Dsc	It's normal	26	93.3	25	83.3	1,000
		Outside the norm	4	6,7	5	16.7	
	D21	It's normal	26	93.3	25	83.3	1,000
		Outside the norm	4	6,7	5	16.7	
	D42	Norm	25	86.7	25	83.3	1,000
		Outside the norm	5	13.3	5	16.7	
	D63	Norm	26	86.7	23	76.7	0.506
		Outside the norm	4	13.3	7	23.3	
	D90	Norm	26	86.7	25	83.3	1,000
		Outside the norm	4	13.3	5	16.7	

** Estimated using Fisher's exact test.*

As can be seen from **table 41**, most of the patients, indicators of biochemical blood analysis, during the entire study, were within the physiological norm. The toxic effect of the applied chemotherapy was manifested, mainly, in an increase in the level of such indicators as ALT and AST. Thus, an increase in the level of ALT was observed in 10 (33.3%) patients of the main group and in 12 (40.0%) patients of the control group. An increase in the level of AST was observed in 9 (30.0%) patients of the main group and in 10 (33.3%) patients of the control group.

Conclusion. Based on the analysis, no significant difference was found regarding the frequency of increase in biochemical indicators between the groups during the study.

15.4.6. Analysis of the dynamics of parameters of the general analysis of urine.

General analysis of urine (specific gravity, pH, protein, glucose, leukocytes, erythrocytes, cylinders, epithelial cells, salts). performed at screening and then after each course of chemotherapy.

The results of the analysis of the dynamics of indicators of the general analysis of urine by the method of descriptive statistics are shown in the **table. 42** for the main group and in **table. 43** for the control group.

Table 42 - Dynamics of indicators of the general analysis of urine during the study in patients of the main group

Parameter	Time	n	M	Me	SD	MIN	MAX
Specific weight	Dsc	30	1014.6	1015	3,315	1010	1020
	D21	30	1015.2	1015	3,341	1012	1020
	D42	30	1015.3	1015	3,327	1012	1020
	D63	30	1014.9	1015	3,209	1012	1020
	D90	30	1015.6	1015	3,502	1012	1021
	[D21 - Dsc]	30	0.6	0	0.234	0	2
	[D42 - Dsc]	30	0.7	0	0.213	0	2
	[D63 - Dsc]	30	0.3	0	0.256	0	2
	[D90 - Dsc]	30	1.0	0	0.175	1	2
pH	Dsc	30	5.40	5.5	0.163	5.0	5.5
	D21	30	5.46	5.5	0.288	4.9	5,6
	D42	30	5.47	5.5	0.315	5.0	5.8
	D63	30	5.46	5.5	0.341	4.9	5.8
	D90	30	5.42	5.5	0.342	5.0	5.8
	[D21 - Dsc]	30	0.06	0	0.125	-0.1	0.1
	[D42 - Dsc]	30	0.07	0	0.217	0	0.3
	[D63 - Dsc]	30	0.06	0	0.277	-0.1	0.3

Parameter	Time	n	M	Me	SD	MIN	MAX
	[D90 - Dsc]	30	0.02	0	0.215	0	0.3
Leukocytes, cl. in sight	Dsc	30	4.5	5	1,237	2	8
	D21	30	4.6	5	1,242	2	8
	D42	30	4.4	4	1,131	2	7
	D63	30	4.3	4	1,099	2	7
	D90	30	3.2	3	1,215	2	8
	[D21 - Dsc]	30	0.1	0	0.135	0	-1
	[D42 - Dsc]	30	-0.1	-1	0.129	0	-1
	[D63 - Dsc]	30	-0.2	-1	0.136	0	-1
	[D90 - Dsc]	30	-1.3	-2	0.153	0	1
Erythrocytes, cl. in sight	Dsc	30	1.5	2	0.781	0	5
	D21	30	1.9	2	0.724	0	5
	D42	30	2.0	2	0.825	0	6
	D63	30	1.8	2	0.766	0	5
	D90	30	1.8	2	0.740	0	5
	[D21 - Dsc]	30	0.4	0	0.167	0	1
	[D42 - Dsc]	30	0.5	0	0.231	0	2
	[D63 - Dsc]	30	0.3	0	0.180	0	-1
	[D90 - Dsc]	30	0.3	0	0.174	0	-1
Epithelial cells, cl. in sight	Dsc	30	0.5	0	0.247	0	2
	D21	30	0.6	1	0.235	0	2
	D42	30	0.6	1	0.253	0	2
	D63	30	0.5	0	0.215	0	2
	D90	30	0.7	1	0.318	0	3
	[D21 - Dsc]	30	0.1	1	0.120	0	1
	[D42 - Dsc]	30	0.1	1	0.127	0	1
	[D63 - Dsc]	30	0	0	0.126	0	1
	[D90 - Dsc]	30	0.2	1	0.159	0	2

Table 43 - Dynamics of indicators of the general analysis of urine during the study in patients of the control group

Parameter	Time	n	M	Me	SD	MIN	MAX
Specific weight	Dsc	30	1015.8	1016	3,217	1010	1019
	D21	30	1015.6	1015	3,125	1011	1018
	D42	30	1015.9	1015	3,190	1010	1018
	D63	30	1016.1	1016	3,458	1012	1020
	D90	30	1016.3	1016	3,449	1013	1020
	[D21 - Dsc]	30	-0.2	-1	0.215	-1	1
	[D42 - Dsc]	30	0.1	-1	0.157	0	-1
	[D63 - Dsc]	30	0.3	0	0.169	1	2
	[D90 - Dsc]	30	0.5	0	0.210	1	3
pH	Dsc	30	5.42	5.4	0.168	5.0	5.5
	D21	30	5.37	5.5	0.247	5.0	5,6

Parameter	Time	n	M	Me	SD	MIN	MAX
	D42	30	5.50	5.5	0.317	4.8	5.8
	D63	30	5.56	5.5	0.337	4.8	5,6
	D90	30	5.52	5.5	0.350	5.0	5.8
	[D21 - Dsc]	30	-0.05	0.1	0.102	0	0.1
	[D42 - Dsc]	30	0.08	0.1	0.208	-0.2	0.3
	[D63 - Dsc]	30	0.14	0.1	0.221	-0.2	0.1
	[D90 - Dsc]	30	0.10	0.1	0.191	0	0.3
Leukocytes, cl. in sight	Dsc	30	4.3	4	1,245	2	8
	D21	30	4.4	5	1,304	2	8
	D42	30	4.8	5	1,231	2	7
	D63	30	4.5	5	1,206	2	7
	D90	30	4.2	4	1,355	2	8
	[D21 - Dsc]	30	0.1	1	0.201	0	2
	[D42 - Dsc]	30	0.5	1	0.154	0	-1
	[D63 - Dsc]	30	0.2	1	0.143	0	-1
	[D90 - Dsc]	30	-0.1	0	0.148	0	1
Erythrocytes, cl. in sight	Dsc	30	1,2	1	0.655	0	4
	D21	30	1.5	2	0.765	0	5
	D42	30	1.3	1	0.733	0	5
	D63	30	1.8	2	0.702	0	6
	D90	30	2.0	2	0.712	0	6
	[D21 - Dsc]	30	0.3	1	0.111	0	1
	[D42 - Dsc]	30	0.1	0	0.115	0	1
	[D63 - Dsc]	30	0.6	1	0.173	0	2
	[D90 - Dsc]	30	0.8	1	0.181	0	2
Epithelial cells, cl. in sight	Dsc	30	0.4	0	0.210	0	2
	D21	30	0.4	0	0.215	0	2
	D42	30	0.5	0	0.224	0	2
	D63	30	0.5	1	0.231	0	2
	D90	30	0.5	1	0.368	0	3
	[D21 - Dsc]	30	0	0	0.098	0	1
	[D42 - Dsc]	30	0.1	0	0.102	0	1
	[D63 - Dsc]	30	0.1	1	0.099	0	1
	[D90 - Dsc]	30	0.1	1	0.082	0	1

Since protein, glucose, cylinders and salts were absent in the urine of all patients, both the main group and the control group, during the entire study, the analysis of the dynamics of these parameters was not carried out.

For other properties, an analysis of the significance of changes during the study period was performed.

To evaluate the dynamics of general urinalysis indicators, a variance analysis of a mixed two-factor model was performed (the dependent variable is the value of

the analyzed indicator, the "time" factor is fixed (Dsc, D21, D42, D63, D90), the "subjects" factor is random). The results of VA are given in **table. 44-45**.

A comparison of the following levels of the "visit" factor with the initial data (Dsc) was also performed using the contrast analysis of **tables 46-47**. The normality of the distribution of VA residuals was checked using the Shapiro-Wilk test (**Table A.12 of Appendix A**).

Table 44 - The main results of the VA indicators of the general analysis of urine in the main group

Dependent variable	The factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning
Specific weight	Visit	16,560	4	4,140	1,348	0.212
	Patients	1292,060	29	44,554	36,031	0.000
pH	Visit	0.097	4	0.024	0.404	0.806
	Patients	5,741	29	0.198	3,293	0.000
Leukocytes, cl. in sight	Visit	39,120	4	9,780	1,741	0.094
	Patients	378,691	29	13,058	11,670	0.000
Erythrocytes, cl. in sight	Visit	3,467	4	0.867	1,293	0.277
	Patients	137,633	29	4,746	7,082	0.000
Epithelial cells, cl. in sight	Visit	0.840	4	0.210	1,526	0.199
	Patients	73,740	29	2,543	18,481	0.000

Table 45 - The main results of the VA indicators of the general analysis of urine in the control group

Dependent variable	The factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning
Specific weight	Visit	7,733	4	1,933	0.905	0.464
	Patients	1140,400	29	39,324	18,403	0.000
pH	Visit	0.794	4	0.198	1,973	0.072
	Patients	4,803	29	0.166	2,481	0.000
Leukocytes, cl. in sight	Visit	6,473	4	1,618	1,765	0.141
	Patients	466,822	29	16,097	17,557	0.000
Erythrocytes, cl. in sight	Visit	12,573	4	3,143	1,648	0.101
	Patients	59,573	29	2,054	3,299	0.000
Epithelial cells, cl. in sight	Visit	0.360	4	0.090	1,851	0.124
	Patients	57,260	29	1,974	40,61	0.000

Table 46 – Results of the contrast analysis of indicators of the general analysis of urine in the main group

Dependent variable	Contrasts	Estimated contrast	Stand. error	p-value
Specific weight	D21 - Dsc	0.567	0.287	0.225
	D42 - Dsc	0.700		0.154
	D63 - Dsc	0.300		0.398
	D90 - Dsc	0.767		0.112
pH	D21 - Dsc	0.057	0.063	0.373
	D42 - Dsc	0.063		0.319
	D63 - Dsc	0.063		0.319
	D90 - Dsc	0.023		0.713
Leukocytes, cl. in sight	D21 - Dsc	0.103	0.273	0.706
	D42 - Dsc	-0.097		0.724
	D63 - Dsc	-0.200		0.465
	D90 - Dsc	-1,100		0.078
Erythrocytes, cl. in sight	D21 - Dsc	0.333	0.211	0.218
	D42 - Dsc	0.467		0.069
	D63 - Dsc	0.267		0.210
	D90 - Dsc	0.267		0.210
Epithelial cells, cl. in sight	D21 - Dsc	0.100	0.096	0.299
	D42 - Dsc	0.100		0.299
	D63 - Dsc	0.000		1,000
	D90 - Dsc	0.200		0.069

***** *The conclusion is made at the significance level of 0.05*

Table 47 - Results of the contrast analysis of indicators of the general analysis of urine in the control group

Dependent variable	Contrasts	Estimated contrast	Stand. error	p-value
Specific weight	D21 - Dsc	-0.200	0.377	0.597
	D42 - Dsc	0.133		0.725
	D63 - Dsc	0.267		0.481
	D90 - Dsc	0.467		0.219
pH	D21 - Dsc	-0.053	0.067	0.426
	D42 - Dsc	0.080		0.233
	D63 - Dsc	0.147		0.059
	D90 - Dsc	0.107		0.080
Leukocytes, cl. in sight	D21 - Dsc	0.103	0.247	0.677
	D42 - Dsc	0.503		0.064
	D63 - Dsc	0.200		0.420
	D90 - Dsc	-0.103		0.677
Erythrocytes, cl. in sight	D21 - Dsc	0.267	0.204	0.293
	D42 - Dsc	0.033		0.870
	D63 - Dsc	0.567		0.086

	D90 - Dsc	0.633		0.055
Epithelial cells, cl. in sight.	D21 - Dsc	0.000	0.057	1,000
	D42 - Dsc	0.100		0.082
	D63 - Dsc	0.100		0.082
	D90 - Dsc	0.100		0.082
***** *The conclusion is made at the significance level of 0.05*				

Conclusion. On the basis of the conducted analysis, it can be concluded that no statistically significant changes in the parameters of the general urine analysis were observed during the treatment.

15.4.7. Analysis of ECG data dynamics.

ECG studies were performed at the beginning of CT, then after each course of CT. During the analysis of ECG data in dynamics, during treatment, non-specific pathological changes were detected in 5 patients (16.7%) of the main group and in 6 (20.0%) patients of the control group. Among them: in 2 primary patients and in 3 control patients, a pronounced decrease in the amplitude of QRS complexes was observed; ST segment depression of 1 mm or more was observed in 1 patient of the main group and 1 patient of the control group; in 2 patients of each group, the phenomenon of blockade of the legs of the bundle of His was observed. It should be noted that nonspecific pathological changes on the ECG in patients from both groups were registered after the 3rd and 4th courses of CT. In no case did these changes require cancellation of CT or postponement of the next course.

The distribution of female patients in groups based on the presence of cardiovascular pathology according to ECG data during treatment is presented in **Table 48.**

Table 48 - Distribution of female patients in groups in the presence of cardiovascular pathology according to ECG data during treatment

ECG results	Main group n=30		Control group n=30		p-value *
	n	%	n	%	
A decrease in the amplitude of QRS complexes	2	6,7	3	10.0	1,000
Depression of the ST segment by 1 mm or more	1	3.3	1	3.3	1,000
Blockade of the legs of the bundle of His	2	6,7	2	6,7	1,000

Conclusion. From the data given in **table. 48,** it can be concluded that there was no significant difference in the frequency of pathological changes, according to ECG data, between the groups.

15.5. Evaluation of efficiency by the main variable

15.5.1. Analysis of the toxicity of chemotherapy

The main variable in this study was the degree of chemotherapy toxicity during treatment. It was assumed that the use of the study drug Donovit-VS® against the background of chemotherapy will reduce the frequency and severity of toxic reactions caused by the use of chemotherapeutic drugs.

In this study, toxic reactions to chemotherapy were assessed after each course of chemotherapy using the CTC *NCIC* toxicity scale.

Of 60 patients who received neoadjuvant polychemotherapy according to the AS scheme (doxorubicin 60 mg/m^2 plus cyclophosphamide at a dose of 600 mg/m^2), complications developed in 100% of patients. The toxic reactions of the applied chemotherapy regimen were predictable and corresponded mainly to grade 1-2 toxicity according to the CTC *NCIC scale.* The 3rd degree of toxicity was observed only according to the "alopecia" indicator. None of the patients, with any of the indicators, did not experience grade 4 toxicity during the entire study. In no case, in this study, was there a postponement or cancellation of the course of chemotherapy due to the development of toxic reactions.

Hematological toxicity was found in 36 (60.0%) patients. The most frequent complication of chemotherapy from the blood system was the development of 1-2 degree leukopenia, which was observed in 34 (56.7%) patients. Neutropenia of the 1st-2nd degree was observed in 25 (40.7%) patients. Moreover, febrile neutropenia was not registered in any case. Grade 1 anemia was observed in 12 (20.0%) patients and grade 2 anemia in 1 patient (1.7%). A decrease in the number of platelets <100x10^9 cells /l was not observed in any case.

From non-hematological toxicity, the following were most often observed: nausea/vomiting of the 1st-2nd degree - in 39 (65.0%) patients, alopecia from minimal, at the beginning of treatment, to complete, before the end of the 4th course of CT - in 100% of patients, stomatitis 1st degree - in 12 patients (20.0%), 2nd degree

- in 1 (1.7%) patient, sleep disorders - in 40 (66.7%) patients, peripheral neuropathies of the 1st degree - in 13 (21.7%) patients, stool disorders (constipation) - in 16 (26.7%). Hepatotoxicity of the 1st degree developed in 22 patients (367%). Heart rhythm disturbances (tachycardia) – in 8 (13.3%) patients, cardiotoxicity of the 1st degree – in 11 patients (18.3%), 2nd degree – in 2 patients.

15.5.2. Analysis of hematological toxicity in groups

In the main group, grade 1 leukopenia was found in 10 (33.3%) patients and grade 2 - in 3 (10.0%) patients. In the control group, grade 1 leukopenia was detected in 15 (50.0%) patients and grade 2 - in 7 (23.3%) patients. In the main group, 1st degree neutropenia was observed in 5 (16.7%) patients, 2nd degree - in 4 (13.3%) patients. In the control group: 1st degree - in 10 (33.3%) patients, 2nd degree - in 8 (26.7%) patients. Anemia of the 1st degree was observed in 5 (16.7%) patients of the main group and in 7 (23.3%) patients of the control group, of the 2nd degree - in 1 patient of the control group.

The birth rate and the percentage ratio of hematological toxicity of chemotherapy in the groups are presented in the **table. 49.**

Table 49 - Analysis of hematological toxicity of chemotherapy in groups

Parameter	Degree toxicity	Main group n=30		Control group n=30		P-value *
		n	%	n	%	
Leukopenia	1	10	33.3	15	50.0	0.036 *
	2	3	10.0	7	23.3	
	3	0	0	0	0	
	4	0	0	0	0	
Neutropenia	1	5	16.7	10	33.3	0.038 *
	2	4	13.3	8	26.7	
	3	0	0	0	0	
	4	0	0	0	0	
Anemia	1	5	16.7	7	23.3	0.411
	2	0	0	1	3.3	
	3	0	0	0	0	
	4	0	0	0	0	

** Statistically significant differences are observed*
The conclusion is made at the significance level of 0.05

Conclusion. A significantly higher frequency of leukopenia and neutropenia was found in patients of the control group compared to the main group.

15.5.3. Analysis of non-hematological toxicity

During the entire treatment, 15 (50.0%) primary patients and 24 (80.0%) control patients complained of nausea and vomiting of varying intensity. The severity of nausea/vomiting corresponded to the 1st degree of toxicity in 9 (30.0%) patients of the main group and in 12 (40.0%) of the control patients, to the 2nd degree of toxicity - in 6 (20.0%) of the patients of the main group . and in 12 (40.0%) control patients.

Stomatitis of the 1st degree was observed in 5 (16.7%) patients of the main group and in 7 (23.3%) patients of the control group, 2nd degree – in 1 (3.3%) patient of the control group.

Hepatotoxicity of the 1st degree was observed in 10 (33.3%) patients of the main group and in 12 (40.0%) patients of the control group,

Neurotoxicity of the 1st degree (sleep disturbance) - in 18 (60.0%) primary patients and in 22 (73.3%) control patients, peripheral neuropathy of the 1st degree - in 6 (20.0%) primary patients and in 7 (23.3%) control patients, defecation disorders (constipation) – in 10 (33.3%) primary patients and in 6 (20.0%) control patients. Alopecia, from minimal, at the beginning of treatment, to complete, before the end of the 4th course of CT - in 100% of patients of both groups.

Heart rhythm disturbances (tachycardia) were observed in 4 (6.7%) patients of the main group and in 4 (6.7%) patients of the control group. Cardiotoxicity of the 1st degree (according to ECG data) - in 4 patients (13.3%) of the main group and in 5 (16.7%) patients of the control group, of the 2nd degree - in 1 patient (3.3%) in to each of the groups.

The birth rate and the percentage ratio of non-hematological toxicity of chemotherapy in the groups are presented in the **table. 50.**

Table 50 - Analysis of non-hematological toxicity in groups

Parameter	Degree toxicity	Main group n=30		Control group n=30		P-value *
		n	%	n	%	
Nausea /vomiting	1	9	30.0	12	40.0	0.030*
	2	6	20.0	12	40.0	
	3	0	0	0	0	
Stomatitis	1	5	16.7	7	23.3	0.531

	2	0	0	1	3.3	
	3	0	0	0	0	
Hepatotoxicity	1	10	33.3	12	40.0	0.789
	2	0	10.0	0	13.3	
	3	0	0	0	0	
Sleep disturbance	1	18	60.0	22	73.3	0.411
	2	0	0	0	0	
	3	0	0	0	0	
Peripheral neuropathies	1	6	20.0	7	23.3	0.754
	2	0	0	0	0	
	3	0	0	0	0	
Constipation	1	10	33.3	6	20.0	0.778
	2	0	0	2	6,7	
	3	0	0	0	0	
Alopecia	1	0	0	0	0	0.796
	2	14	46.7	15	50.0	
	3	16	53.3	15	50.0	
Violation of heart rhythm	1	4	6,7	4	6,7	1,000
	2	0	0	0	0	
	3	0	0	0	0	
Cardiotoxicity	1	4	13.3	5	16.7	0.739
	2	1	3.3	1	3.3	
	3	0	0	0	0	

** Statistically significant differences are observed*
The conclusion is made at the significance level of 0.05

Conclusion. Analyzing the results presented in **Table 50,** we can come to the conclusion that there were statistically significantly more patients in the control group who had nausea/vomiting as a result of chemotherapy.

According to other indicators, the difference between the groups was unreliable.

In summary, it can be stated that the overall toxicity profile for the group of patients who received the study drug Donovit-VS® on the background of chemotherapy was less pronounced than in the group that received only chemotherapy. This testifies to the positive effect of the drug Donovit-VS® the patient's body, in terms of preventing toxic reactions of chemotherapy or reducing their severity.

Graphically, the analysis of the toxicity of chemotherapy is presented in **fig. 13-14.**

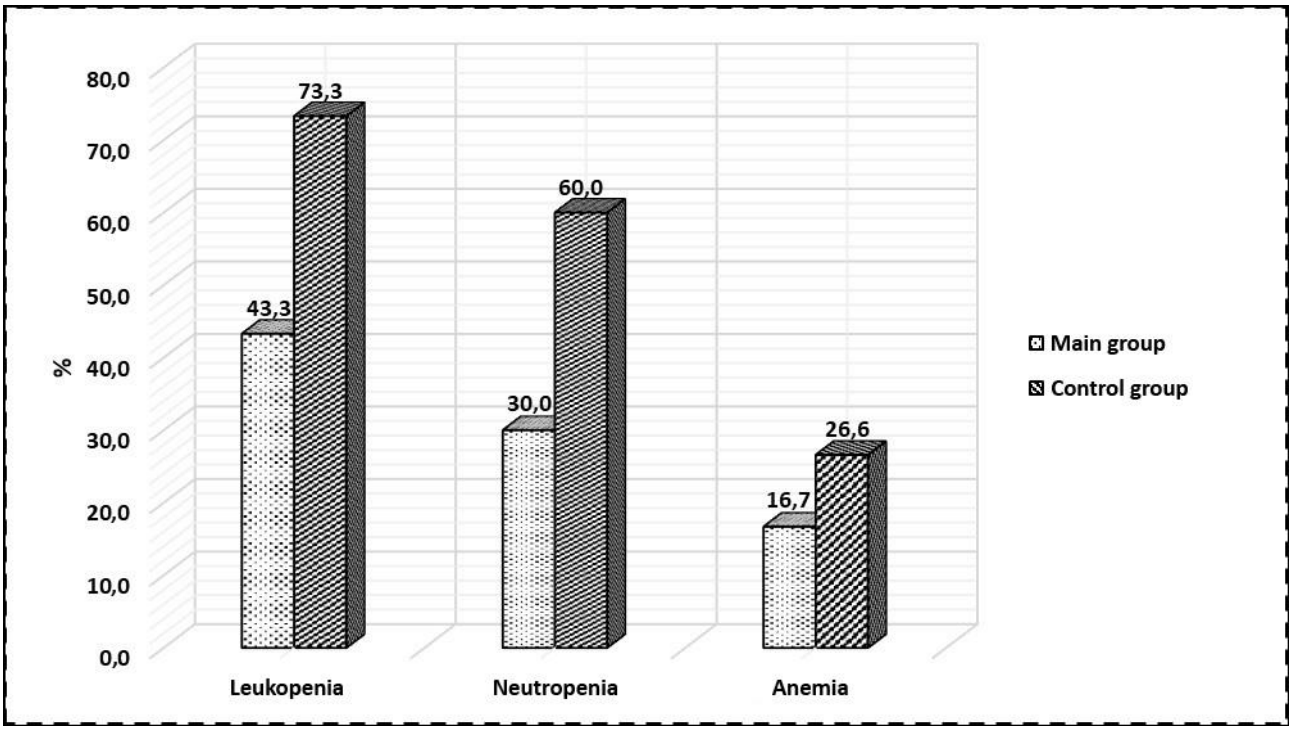

Fig. 13 - Analysis of hematological toxicity of chemotherapy in groups

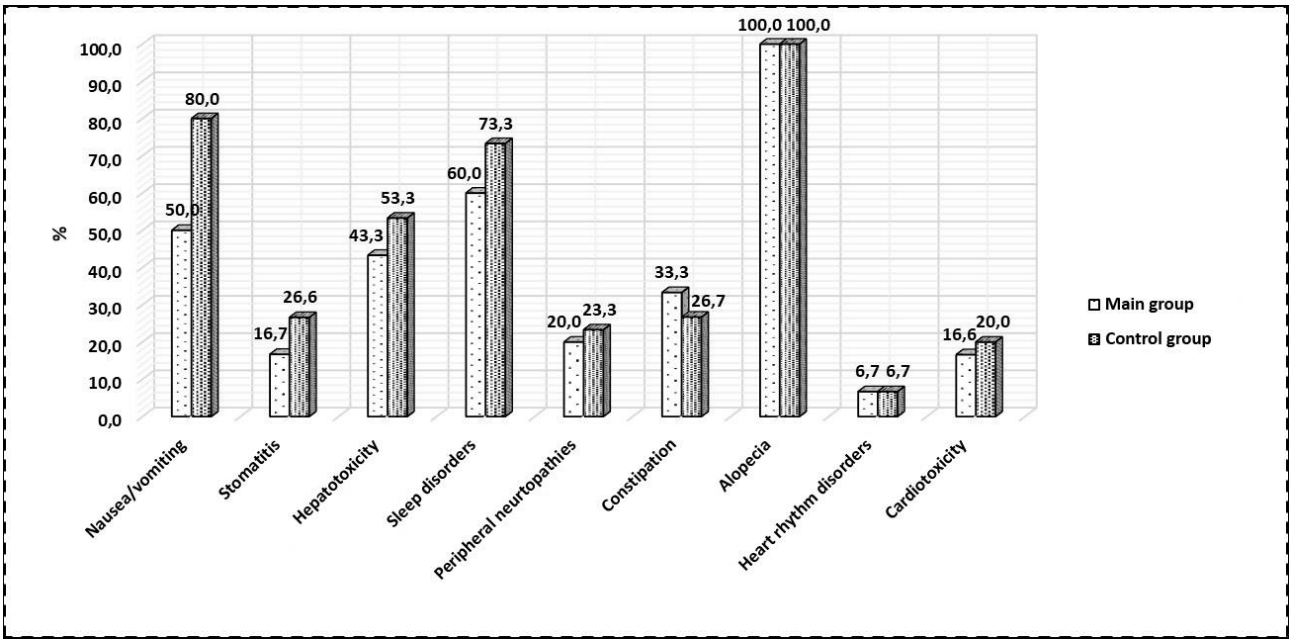

Fig. 14 - Analysis of non-hematological toxicity of chemotherapy in groups

15.6. Assessment of quality of life

Determining quality of life in research is one of the important criteria for evaluating the effectiveness of treatment in oncology. In this study, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used for assessment (Appendix B).

The level of quality of life was assessed in all patients before the start of chemotherapy, then after the 2nd and 4th courses of CT.

The analysis of the data obtained during the treatment showed a progressive decrease in the quality of life in both groups. Changes related to the clinical picture (symptoms) prevailed, which is a consequence of general CT on the body. Patients were concerned about such asthenic manifestations as malaise, general weakness, increased fatigue, and reduced work capacity. The "nausea/vomiting" indicator had high values. It should be noted that in the group of patients receiving chemotherapy + Donovit-VS®, the decrease in quality of life was less pronounced according to most indicators.

We analyzed 2 integral scales of the EORTC QLQ-C30 Questionnaire: the "quality of life" scale and the "general health status" scale. The maximum possible amount of points that can be scored on each of the scales is 7 points, which was 100%. The total score for each of the scales was calculated according to the following formula:

$$S_y = \frac{S_x - S_{min}}{S_{max} - S_{min}} \cdot 100$$

During the statistical analysis of the data obtained before the treatment, no significant differences in the above indicators were found in the patients of the main and control groups (see **Tables 53-54**).

The average score on the "quality of life" scale before the start of chemotherapy was 86.65 (SD = 10.25) in the main group and 84.93 (SD = 10.64) in the control group. In the course of treatment, a progressive decrease of this indicator was noted in both groups. Thus, after the 4th course of chemotherapy, the average score in the main group was 62.46 (SD = 8.34) points, and in the control group - 54.40 (SD = 8.45).

According to the scale of "general state of health", the situation was similar. The average score before the start of chemotherapy was 77.25 (SD = 9.43) in the

main group and 78.33 (SD = 9.062) in the control group. In the course of treatment, a progressive decrease of this indicator was noted, and after the 4th course of chemotherapy, the average score of the general state of health in the main group was 60.35 (SD = 10.83), and in the control group – 51.74 (SD = 18,86).

Descriptive statistics data are presented in **tables 51-52.**

Table 51 - Dynamics of quality of life assessment in groups according to the EORTC QLQ-C30 questionnaire

Time	Group	n	M	Me	SD	MIN	MAX
D0	Main group	30	86.65	88	10,250	66.6	100.0
	Control group	30	84.93	85	10,636	66.6	100.0
D42	Main group	30	67.54	65	7,941	50.0	83.3
	Control group	30	61,21	62	10,242	33.3	66.6
D90	Main group	30	62.46	64	8,341	33.3	66.6
	Control group	30	54.40	55	8,455	33.3	66.6

Table 52 - Dynamics of the assessment of "general health" in groups according to the data of the EORTC QLQ-C30 questionnaire

Time	Group	n	M	Me	SD	MIN	MAX
D0	Main group	30	77.25	80	9,437	66.6	100.0
	Control group	30	78.33	80	9,062	66.6	100.0
D42	Main group	30	64,68	62	10,205	33.3	66.6
	Control group	30	59,24	60	13,382	33.3	66.6
D90	Main group	30	60.35	60	10,828	33.3	66.6
	Control group	30	51.74	50	18,868	16.6	66.6

To compare the groups for the assessment of "quality of life" and assessment of "general state of health" according to the data of the EORTC QLQ - C30 questionnaire, the Student's test for independent samples was applied (**tables 53-54**), since the data were distributed normally in both groups (**Appendix A, Tables A.13-14**).

Table 53 — Results of the comparison of groups on the assessment of quality of life according to the data of the EORTC QLQ-C30 questionnaire using the Student's test for independent samples

Day	t-statistics	df	p-value	Difference of mean	Differences *
D0	0.640	58	0.525	1.72	Not significant
D42	2,677	58	0.010	6.33	Significant

D90	2,646	58	0.010	8.06	Significant
** At a significance level of 0.05.*					

Table 54 - Results of the comparison of groups for the assessment of "general health" according to the data of the EORTC QLQ-C30 questionnaire using the Student's test for independent samples

Day	t-statistics	df	p-value	Difference of mean	Differences *
D0	-0.452	58	0.653	1.08	Not significant
D42	2,098	58	0.040	5.44	Significant
D90	2,155	58	0.032	8.61	Significant
** At a significance level of 0.05.*					

Graphically, the dynamics of the assessment of "quality of life" and the assessment of "general health" during the treatment process are presented in **fig. 15-16.**

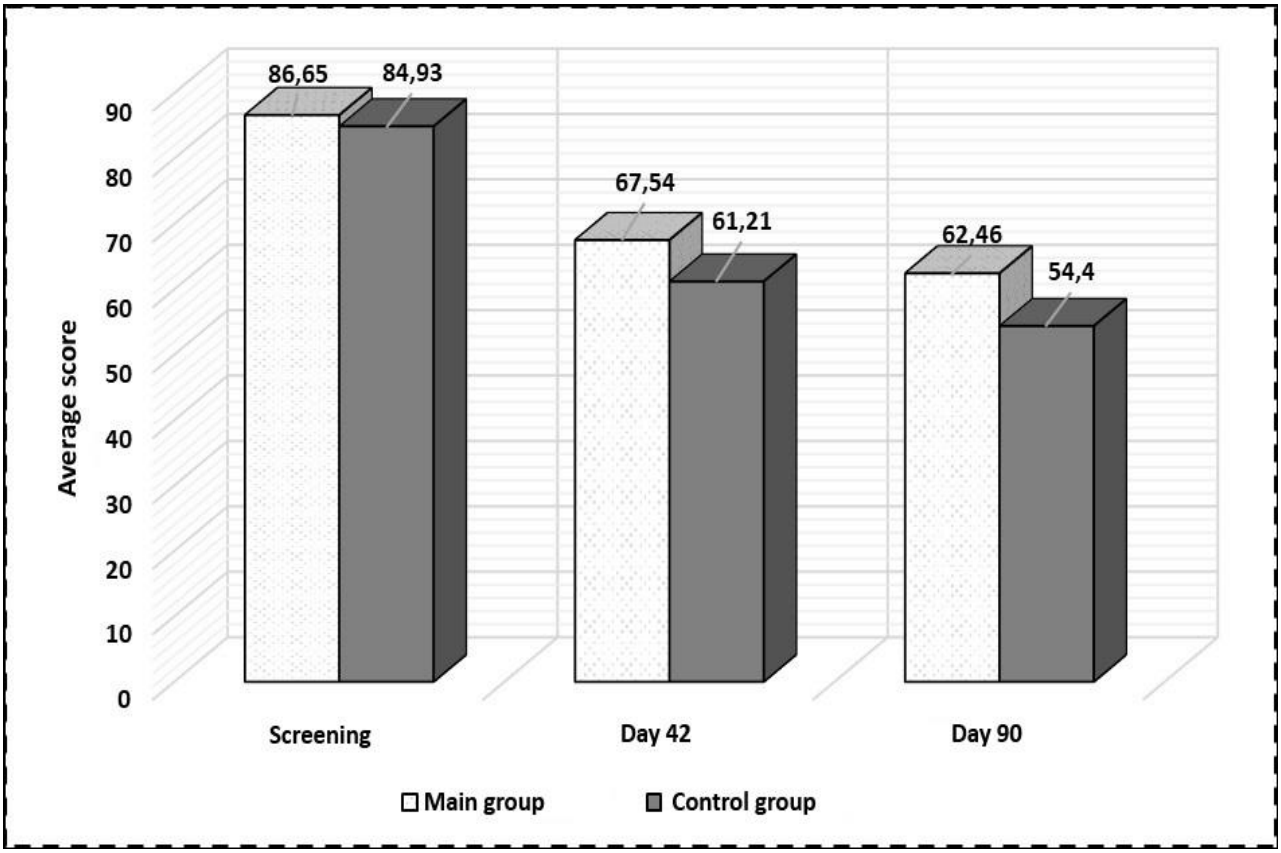

Fig. 15 - Dynamics of assessment of "quality of life" in groups

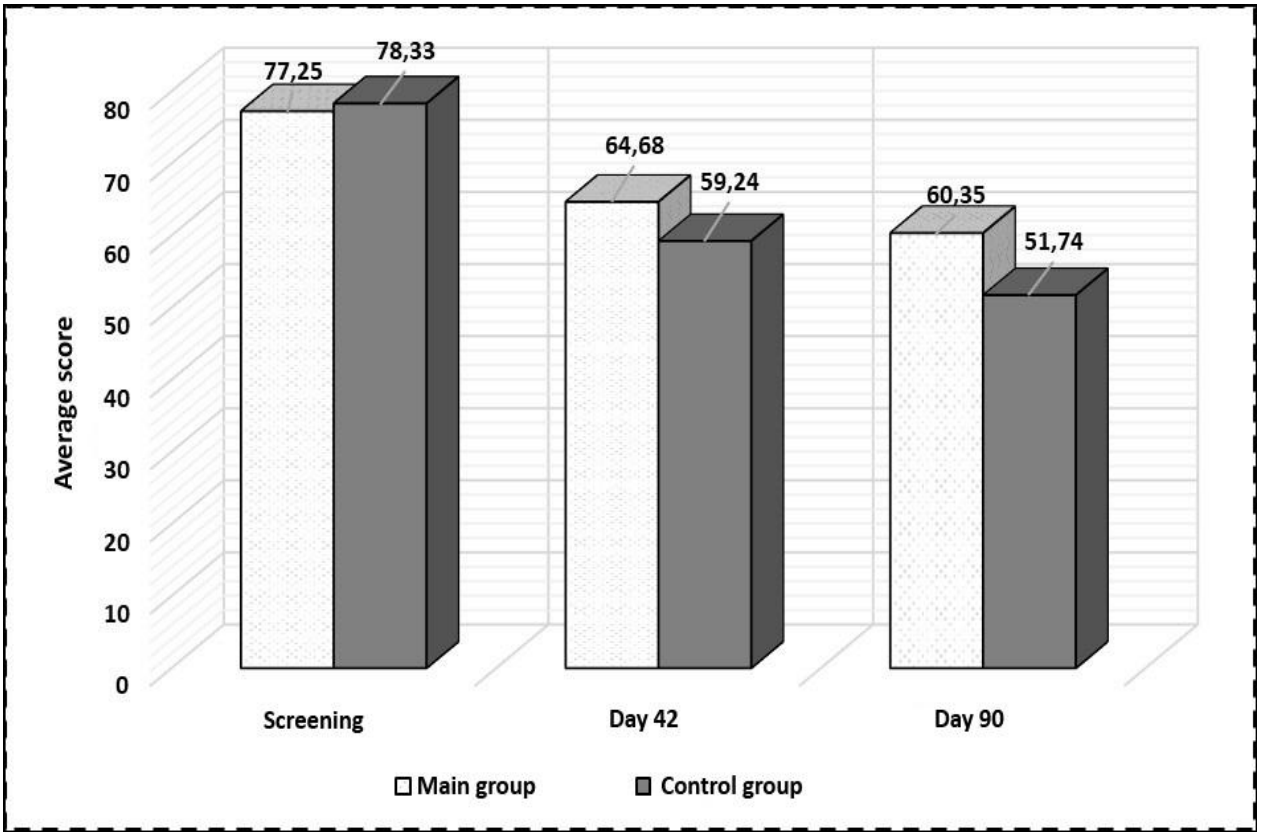

Fig. 16 - Dynamics of assessment of "general state of health" in groups

Since in the initial state the groups did not differ statistically significantly in quality of life indicators, the comparison between the groups was carried out on the differences in dTi using the Mann-Whitney test, because individual differences in dT_i were not normally distributed in both groups.

The results of the analysis comparing the dynamics of quality of life indicators between groups are shown in **Table 55.**

Table 55 - Comparison of groups using the Mann-Whitney test according to the dynamics of quality of life indicators

Indicator	dTi	U Mann-Whitney	Wilcoxon W	Z-statistics	p-value (double sided)	Difference between groups*
Assessment of "quality of life"	D42	580,000	845,000	-2,241	0.021	Significantly
	D90	590,000	885,000	-2.446	0.006	Significantly
Assessment of "general state of health"	D42	628,000	793,000	-2.126	0.038	Significantly
	D90	667,000	832,000	-2,238	0.024	Significantly

Conclusion.

1). In both groups, a statistically significant decrease in the quality of life was established according to the "general health" scale and the "quality of life" assessment.

2). Patients of the control group had a significantly more significant decrease in quality of life on the scale of "assessment of the general state of health" and the scale of assessment of "quality of life" compared to patients of the main group at all stages of treatment.

15.7. Evaluation of the general condition of patients according to the ECOG scale

When assessing the general condition of the patients according to the ECOG scale, it was found that the general condition of the patients during treatment corresponded to 1-2 points and was stable throughout the study.

Characteristics of the general condition of patients during treatment according to the ECOG scale are presented in **Table 56** .

Table 56 - Characteristics of the general condition of patients according to the ECOG scale during treatment (abs. in, %)

General condition (Points)	Main group n = 30	Control group n = 30	p-value *
0	-	-	0.048 *
1	13 (43.3%)	5 (16.7%)	
2	17 (56.7%)	25 (83.3%)	
3	-	-	
4	-	-	
*Statistically significant differences are observed Conclusion at the significance level of 0.05			

Conclusion. According to the results of the data analysis shown in **table 56**, it can be stated that the groups in the treatment process differed statistically significantly in the evaluation of the general condition according to the ECOG scale in favor of the patients of the main group.

15.8. Evaluation of the effectiveness of neoadjuvant chemotherapy

The assessment of the direct therapeutic effect of neoadjuvant chemotherapy was carried out in accordance with the standard criteria for the effectiveness of the therapy of solid tumors according to the RECIST 1.1 scale, based on the data of mammography performed 3 months after the start of CT.

When interpreting mammological images, the following tumor criteria for treatment were used:

The complete answer is the disappearance of all cells, in the absence of the appearance of new ones.

A partial response is a reduction of 30% or more in measurable tumor formations, provided there are no signs of the appearance of new metastases or the progression of old ones.

Stabilization of the process - there is no decrease sufficient to be evaluated as partial regression, or an increase that can be evaluated as progression.

Progression of the process involves an increase in the smallest number of lesions registered during observation by 20% or the appearance of new foci.

Analyzing the results of the distribution of patients, according to the reaction of the tumor to the treatment, it should be noted that **complete regression** of the tumor was observed in 4 patients of the main group and in 3 patients of the control group; **partial regression** - in 22 primary patients and 21 control patients, **stabilization of the process** - in 4 primary patients and 6 control patients, and no **progression of the process** was observed in any of the patients of both groups.

The results of evaluating the effectiveness of neoadjuvant chemotherapy in groups, depending on the objective response of the tumor to treatment, are presented in **table. 57.**

Table 57 - Results of evaluating the effectiveness of neoadjuvant chemotherapy in groups depending on the objective response of the tumor to treatment

Effect of neoadjuvant chemotherapy	Main group n = 30		Control group n = 30		p-value *
	n	%	n	%	
Full answer	4	13.3	3	10.0	1,000
A partial answer	22	73.3	21	70.0	1,000
Process stabilization	4	13.3	6	20.0	0.731
Progression of the process	0	0	0	0	1,000
**The conclusion is made at a significance level of 0.05*					

Conclusion. Analysis of the frequency of tumor responses to chemotherapy treatment showed no statistically significant differences between the groups.

15.9. Conclusion of exceeding efficiency.

A conclusion about the superior effectiveness of therapy including the study drug (main group) compared to therapy without the study drug (control group) should be made on the basis of statistically significant differences when comparing groups according to the main variables assessing the degree of toxicity. Any reduction in toxicity for any of the variables was assumed to be clinically relevant.

Based on the results of the analysis, it can be concluded that there are statistically significant differences between the groups, proving a positive effect in preventing toxic reactions of chemotherapy and reducing their severity, as well as in assessing the quality of life in patients who received antitumor chemotherapy. The study drug Donovit-VS® compared to a group of patients who received only chemotherapy.

1) A more pronounced decrease in the level of leukocytes and neutrophils (abs.q) was revealed, starting from the 1st course of chemotherapy in patients of the control group, compared to the main one.
2) A more pronounced decrease in the level of platelets was found starting from the 3rd course of chemotherapy in patients of the control group compared to the main group.
3) A significantly higher frequency of leukopenia and neutropenia was found in patients of the control group compared to the main group.
4) A statistically significantly higher number of patients in the control group compared to the main group experienced chemotherapy-induced nausea/vomiting.
5) A significantly more significant decrease in the quality of life according to the "general health assessment" scale and the "quality of life assessment" scale according to the data of the EORTC QLQ - C30 questionnaire was established in patients of the control group compared to the main group at all stages of treatment.

6) It can also be stated that the groups in the course of treatment differed statistically significantly in the evaluation of the general condition on the ECOG scale in favor of the patients of the main group.

The above confirms the conclusion about the superior effectiveness of the treatment in the group of patients who received, against the background of antitumor chemotherapy, the researched drug Donovit-VS® comparison with the group of patients who received only chemotherapy.

15.10. Tolerability analysis

In the course of the study, AE/AR were registered in 100% of the main and control groups. None of the reported AE/AR were classified as serious. All AE/AR were directly related to chemotherapy and matched the toxicity profile of chemotherapy drugs. In no case did the researcher establish a connection between the observed AE/AR and the study drug. It should also be taken into account that in the group of patients taking the study drug Donovit-VS®, the number of AE/AR was significantly lower than in the group of patients not taking Donovit-VS® (the number of AE/AE: 132 in the main group and 173 - in the control room).

In the course of the study, no allergic and anaphylactic reactions, significant fluctuations in hemodynamic parameters were recorded in the group of patients taking the study drug. No serious AE/AR were reported in any of the study drug patients, and none of the patients dropped out of the study due to AE/AR.

Based on the above, it can be assumed that the tolerability of the study drug Donovit-VS® was good in all 100% of patients.

The list of registered AE/AR is given in **table. 58,** final statistics of AE/AR - in **table. 59.**

Table 58 - List of registered AE/AR

Parameter	Main group n=30		Control group n=30	
	n	%	n	%
Nausea vomiting	15	50.0	24	80.0
Alopecia	30	100.0	30	100.0
Stomatitis	5	16.7	8	26.7
Sleep disorders (insomnia)	18	60.0	22	73.3

Peripheral neuropathy	6	20.0	7	23.3
Stool disturbance (constipation)	3	10.0	5	16.7
Leukopenia	13	43.3	21	70.0
Neutropenia	9	30.0	16	53.3
Anemia	5	16.7	8	26.7
Increase in ALT	10	33.3	12	40.0
Increase in AST	9	30.0	10	33.3
Heart rhythm disturbances (tachycardia)	4	6,7	4	6,7
A decrease in the amplitude of QRS complexes	2	6,7	3	10.0
Depression of the ST segment by 1 mm or more	1	3.3	1	3.3
Blockade of the legs of the bundle of His	2	6,7	2	6,7

Table 59 - Summary statistics of AE/AR

Analyzed indicators	**Main group**		**Control group**	
	n	**%**	**n**	**%**
Subjects evaluated for AE/AR	30	100.0	30	100.0
The number of AE/AR	132	-	173	-
Patients with AE/AR	30	100.0	30	100.0
Number of serious AE/AR	0	0	0	0
Patients with severe AE/AR	0	0	0	0
Patients who dropped out as a result of AE/AR	0	0	0	0
Patients with a reduced dose or temporary discontinuation due to AE/AR	0	0	0	0

15.11. Discussion of research results

This research was conducted in accordance with the ethical principles of the Declaration of Helsinki, current regulatory documents and legislation of Ukraine, as well as in accordance with the clinical research protocol.

The main goal of the study was to evaluate the effectiveness and tolerability of the drug Donovit-VS®, a tablet produced by Astrapharm LLC, used in patients with breast cancer on the background of chemotherapy compared to a group of patients receiving only chemotherapy.

The task of the study was to study the effect of the drug under study on the degree of toxicity of chemotherapy and on the quality of life of patients taking chemotherapy drugs. Then, the comparison of the treatment results obtained in the main and control groups in order to establish the superior efficiency in the group of patients receiving chemotherapy + Donovit-VS® comparison with the group of patients receiving only chemotherapy. It was assumed that the use of the study drug Donovit-VS® would reduce the degree of toxicity of the applied chemotherapy and improve the quality of life of patients.

All potential study participants provided written informed consent prior to initiation of any study procedures.

60 patients were randomized to the study, of which: 30 patients - to the main group (patients receiving chemotherapy + Donovit-VS®) and 30 patients - to the control group (patients receiving only chemotherapy). The studied groups were comparable in terms of gender and age, nosology, hemodynamic index, laboratory and ECG data.

The patients included in the study were diagnosed with breast cancer ($T_1N_{1-3}M_0$, $T_2N_{0-3}M_0$, $T_3N_{0-3}M_0$), confirmed by the data of a histological or cytological examination. All patients were prescribed neoadjuvant polychemotherapy according to the AS scheme (doxorubicin 60 mg/m^2 plus cyclophosphamide at a dose of 600 mg/m^2) in the form of 4 courses with an interval of 3 weeks. In addition, patients of the main group, simultaneously with CT, received the study drug Donovit-VS®, tablets produced by Astrapharm LLC, 1 tablet 3 times a day for 3 months.

All patients of the main and control groups received the planned course of chemotherapy. The average number of courses received by patients in the course of this study was 4 in the main and control groups. The average cumulative dose of doxorubicin was 393.3 mg/m^2 in the main group and 389.3 mg/m^2 in the control group.

In no case was there a reduction in the dose of chemotherapy drugs, nor a delay in the course of chemotherapy.

In the course of the study, there were no cases of early withdrawal of patients from the study due to a serious adverse reaction or for any other reason. All randomized patients completed the protocol study. All 60 patients were included in the analysis of efficacy and tolerability.

The main variable in this study was the degree of toxicity of chemotherapy during treatment according to the CTC *NCIC* scale.

The secondary variable is the level of the patient's quality of life during treatment according to the EORTC QLQ - C 30 questionnaire and the response of the tumor to treatment according to mammography data 3 months after the start of CT.

When assessing tolerability, the following were taken into account: the presence and nature of adverse events, their relationship with the drug under study; dynamics of vital indicators (BP, heart rate, body t); dynamics of ECG data; dynamics of laboratory indicators

Chemotherapy toxicities were assessed after each course of chemotherapy using the CTC NCIC toxicity scale.

Based on the analysis of the research results, the following conclusions were made:

1) According to the results of the analysis of the dynamics of hematological indicators:

- in the main and control groups, a statistically significant decrease in the level of leukocytes, neutrophils, hemoglobin and platelets was found at all observation points, starting from the 1st course of chemotherapy, compared to the initial data;
- changes in other hematological parameters in both groups were not statistically and clinically significant throughout the study;
- a more pronounced decrease in the level of leukocytes and neutrophils (absolute quantity) was detected, starting from the 1st course of chemotherapy in patients of the control group, compared to the main one;

- a more pronounced decrease in the level of platelets was found, starting from the 3rd course of chemotherapy in patients of the control group, compared to the main one;
- according to the dynamics of other hematological indicators, the groups did not differ significantly.
- a significantly higher frequency of leukopenia and neutropenia was found in patients of the control group compared to the main group.

2). *According to the results of the analysis of the dynamics of parameters of the biochemical blood test:*

- in the main and control groups, a statistically significant increase in the level of ALT and AST was found, starting from the 2nd course of CT compared to the initial data;
- groups did not differ statistically significantly in the dynamics of biochemical blood analysis indicators.
- there was also no significant difference in the frequency of increase in biochemical indicators between groups during the entire study.

3). *According to the results of the analysis of the degree of CT toxicity according to the CTC NCIC toxicity scale :*

- a significantly higher frequency of leukopenia and neutropenia was found in patients of the control group compared to the main group;
- in the control group, there were statistically significantly more patients who experienced nausea/vomiting as a result of chemotherapy;
- according to other indicators, the difference between the groups was unreliable.

4). *According to the results of the quality of life analysis, according to the EORTC QLQ-C30 questionnaire:*

- in both groups, a statistically significant decrease in the quality of life was established according to the "general health" scale and the "quality of life" assessment scale;
- the patients of the control group had a significantly more significant decrease in the quality of life according to the scale of "assessment of the general state of health" and the scale of assessment of "quality of life" compared to the patients of the main group at all stages of treatment.

5). It can also be stated that the groups in the course of treatment differed statistically significantly in the evaluation of the general condition on the ECOG scale in favor of the patients of the main group.

6). Analysis of the frequency of tumor responses to chemotherapy treatment showed no statistically significant differences between the groups.

The above testifies to the benefit of the greater effectiveness of therapy in the group of patients who took the study drug Donovit-VS® against the background of antitumor chemotherapy compared to the group of patients who only received chemotherapy.

In summary, it can be stated that the overall toxicity profile for the group of patients who received the study drug Donovit-VS® on the background of chemotherapy was less pronounced than in the group that received only chemotherapy. This testifies to the positive effect of the drug Donovit-VS® the patient's body, in terms of preventing toxic reactions of chemotherapy or reducing their severity.

The data obtained during the research also allow us to conclude about the good tolerability of the studied drug. In the course of the study, no allergic and anaphylactic reactions, significant fluctuations in hemodynamic parameters were recorded in the group of patients taking the study drug. No serious AE/AR were reported in any of the study drug patients, and none of the patients dropped out of the study due to AE/AR.

All AE/AR registered during the study were directly related to chemotherapy and corresponded to the toxicity profile of the chemotherapy drugs used. In no case did the researcher establish a connection between the observed AE/ADR and the study drug. It should also be taken into account that in the group of patients taking the study drug Donovit-VS® ’ the number of AE/AR was significantly lower than in the group of patients not taking Donovit-VS® (the number of AE/AR: 132 in the main group and 173 - in the control room).

Based on the above, it can be assumed that the tolerability of the studied drug Donovit-VS® was good in all 100% of patients.

16. CONCLUSIONS AND RECOMMENDATIONS

1. On the basis of the analysis of the data of the clinical study, it was proven that the treatment of patients with breast cancer was more effective in terms of the main variable in the group of patients who took, against the background of neoadjuvant antitumor chemotherapy, the study drug Donovit-VS®, tablets produced by Astrapharm LLC, compared to the group of patients receiving only chemotherapy. This was manifested in a decrease in the severity and frequency of such chemotherapy complications as: leukopenia, neutropenia, as well as in a decrease in the severity and frequency of nausea and vomiting.

2. It was established that in patients who took the study drug Donovit-VS®, a higher quality of life was observed in the process of treatment with chemotherapy drugs, according to the EORTC QLQ-C30 questionnaire, compared to patients who did not take Donovit-VS®.

3. The study drug Donovit-VS®, tablets produced by Astrapharm LLC, was well tolerated by all 100% of patients. In the course of the study, no allergic and anaphylactic reactions, significant fluctuations in hemodynamic indicators were recorded in the group of patients taking the drug Donovit-VS®. None of the patients taking the study drug had serious AE/AR and none of the patients dropped out of the study due to AE/AR. It should be noted that in the group of patients who took the study drug Donovit-VS® , the number of AE/AR was significantly lower than in the group of patients who did not take Donovit-VS® (number of AE/AR: 132– in the main group and 173 - in the control room).

4. Based on the data obtained during the clinical study, the researched drug Donovit-VS®, tablets produced by Astrapharm LLC, can be recommended for medical use in patients with breast cancer as an accompanying drug during a course of chemotherapy, in order to prevent and reduce the degree of severity of toxic reactions and improvement of the quality of life of patients. Recommended regimen: 1 tablet 2-3 times a day for 3 months.

17. LIST OF REFERENCES

1. Amosova E.M., Zuyeva E.P., Homan A.V., Dementyeva L.A. The effect of extracts of Pallas's milk, Baikal's milkweed, poisonous aconite and golden root on the development of some animal tumors in an experiment. // Actual problems of modern oncology, No. 2, 1983, p. 22-24, Siberian branch of the All-Union Oncology Center of the USSR Academy of Medical Sciences.
2. Volosyanka M.I., state Traditional methods of cancer prevention and treatment. - Moscow: Aquarium, 1994.
3. Gonikman E.I., edited by Ways of treatment. The world of medicinal plants. - Minsk: Santana, 1994, pp. 66-67, 81-83.
4. Garbukov O.Yu., Slonimska O.M., Krasulina N.A., Doroshenko O.V., Kokorina Yu.L. Neoadjuvant therapy for breast cancer// Siberian Oncological Journal. - 2005. - Vol. 2, No. 14. - P. 63-72.
5. Danikov N.I. Treatment is possible. - M.: Ripod Classic, 1997, p. 274-275.
6. Danikov N.I. Healing forces of nature. - M.: Ripod Classic, 1997.
7. Denisov L.E. Mammography in the treatment of diseases of the mammary gland // Vestn. Roentgenol. and radio – 1987. – N 1. – C. 50–54.
8. Zaitsev O.M. Ultrasound and mammography in the diagnosis of breast cancer: Autoref. thesis Ph.D. honey. Sciences: 14.00.19/O.M. Zaitsev // Research Institute of Oncology named after N.M. Petrova - St. Petersburg, 1995. - 24 p.
9. Ionova TI, Novik AA, Sukhonis YA. The concept of the quality of life of patients with an oncological profile // Oncology 2000; 2 (1–2): 25–7.
10. Clinical trials of drugs/Ed. Maltseva V.I., Yefimtseva T.K., Bilousova Yu.B., Kovalenko V.M. - 2nd ed., revision. and add. - K.: MORION, 2006. - 456 p.
11. Lapach S.M., Chubenko O.V., Babich P.M. Basic principles of application of statistical methods in clinical trials. - K.: MORION, 2002. - 160 p.
12. Lapach S.M., Chubenko O.V., Babich P.M. Statistical methods in medical and biological research using Excel. - Kyiv, 2000. - 320 p.
13. Maksimova E.V., Klyaritska I.L. Assessment of quality of life and frequency of side effects during chemotherapy in patients with breast cancer and ovarian cancer // Molodiy ucheniy. - 2012. - No. 12. - P. 551-555.

14. Drug treatment of malignant neoplasms // Solid neoplasms / ed. member-cor. NAS of Ukraine V.F. Chekhuna // Handbook "VADAMECUM Doctor Oncologist". - K: LLC "VIRA "Health of Ukraine", 2007. - 456 p.
15. Methodological recommendations for clinical trials of medicinal products in Ukraine. - Kyiv, 2005
16. Novyk A.A., Ionova T.I., Guide to the study of the quality of life in medicine. Study guide for higher educational institutions/ ed. Acad. RAMS Shevchenko Yu.L. Moscow: CJSC "OLMA Media Group", 2007. P. 204-206.
17. Perevodchikova N.I., Portniy S.M., Stenina M.B. Medical therapy of breast cancer // M.: Practice, 2014. - P. 284.
18. Semiglazov V.F., Paltuev R.M., Semiglazova T.Yu., Semiglazov V.V., Dashyan G.A., Manikhas A.G. Clinical recommendations for diagnosis and treatment of breast cancer. St. Petersburg: ABS-press, 2013, 234 c.
19. Semiglazov V.F. Manikhas A.G., Semiglazova T.Yu., Bessonov A.A., Semiglazov V.V. Neoadjuvant systemic therapy for breast cancer: A guide for physicians. - St. Petersburg: Azzaf, 2012. - 112 p.
20. Semiglazov V.F. Neoadjuvant and adjuvant treatment of breast cancer: study guide / V.F. Semiglazov, V.V.
21. Sobetsky V.V. Non-traditional methods of cancer treatment. - Kyiv: Zdorovya, 1999. - 56 p.
22. Chubenko O.V., Babich P.M., Lapach S.M., Yefimtseva T.K., Maltsev V.I. etc. - Principles of application of statistical methods in conducting clinical trials of medicinal products: Methodological recommendations. - K.: "Avicenna" Publishing House, 2003. - 60 p.
23. Conover, WJ, Iman, RL (1981). The transformation level is a bridge between parametric and non-parametric statistics. American Statistician, 35, 124-129.
24. Conover WJ, Iman RL: Analysis of covariance using rank transformation. *Biometrics* 1982, 38:715-724.
25. Cortazar P., Lang Zhang, Untch M., et al. Meta-analysis of results from commercial trials in unresectable breast cancer (CTNeoBC) // Presented at the San Antonio Breast Cancer Symposium Conference. - 2012; San Antonio, TX. Abstract S 1-11.
26. Early Breast Cancer Trialists' Collaborative Group. Associations between different polychemotherapy regimens for early breast cancer: long-term meta-

analyses of 100,000 women in 123 randomized trials. *Lancet* , 2012, 379 (9814): 432-444.

27. Guideline on choosing a non-inferiority margin. London: Committee For Proprietary Medicinal Products, 2005. (Accessed July 27, 2005 at http://www.emea.europa.eu/pdfs/human/ewp/215899en.pdf).
28. Fleiss, JL (1981). Statistical methods for rates and proportions (2nd ed.). New York: John Wiley. ISBN 0-471-26370-2.
29. Glantz, Primer of Biostatistics (6 ed), McGraw-Hill, 2005

Appendix A
Randomization scheme and additional results of statistical data processing

Table A.1 - Scheme of randomization for 60 patients in a ratio of 1:1

No. of the subject	Random numbers	Group
001	0.840088	The main one
002	0.493878	The main one
003	0.418434	The main one
004	0.174489	Control
005	0.75465	Control
006	0.156684	The main one
007	0.460531	The main one
008	0.206645	The main one
009	0.432843	Control
010	0.048133	Control
011	0.25811	Control
012	0.648136	The main one
013	0.855683	The main one
014	0.787668	The main one
015	0.265334	The main one
016	0.198976	Control
017	0.735635	Control
018	0.800401	The main one
019	0.519372	Control
020	0.810152	Control
021	0.032232	Control
022	0.77023	Control
023	0.281028	Control
024	0.761756	The main one
025	0.717702	Control
026	0.342968	Control

No. of the subject	Random numbers	Group
027	0.925363	The main one
028	0.991105	The main one
029	0.792597	Control
030	0.079467	The main one
031	0.082321	Control
032	0.670866	Control
033	0.551409	The main one
034	0.658743	Control
035	0.027353	The main one
036	0.037185	The main one
037	0.098204	The main one
038	0.331102	The main one
039	0.322044	The main one
040	0.467808	Control
041	0.112242	Control
042	0.621262	Control
043	0.704737	The main one
044	0.810209	The main one
045	0.863604	The main one
046	0.281483	The main one
047	0.231156	Control
048	0.959712	The main one
049	0.478816	Control
050	0.494685	Control
051	0.665034	The main one
052	0.687619	Control
053	0.456474	Control
054	0.327582	Control
055	0.118737	The main one
056	0.719331	The main one
057	0.432868	The main one
058	0.433798	Control

No. of the subject	Random numbers	Group
059	0.943889	Control
060	0.06248	Control

Table A.2 — Results of testing the normality of data distribution for the indicator "Age" and "Body weight" in groups

Group	Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
The main one	Age, years	0.962	30	0.342	Normal
Control		0.961	30	0.321	Normal
The main one	Body weight, kg	0.955	30	0.279	Normal
Control		0.933	30	0.058	Normal
* *The conclusion is made at the significance level of 0.01*					

Table A.3 - Results of checking the normality of data distribution for hemodynamic indicators in groups

Group	Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
The main one	heart rate	0.959	30	0.292	Normal
Control		0.975	30	0.686	Normal
The main one	SBR	0.968	30	0.474	Normal
Control		0.942	30	0.104	Normal
The main one	DBR	0.975	30	0.675	Normal
Control		0.988	30	0.981	Normal
The main one	t body	0.932	30	0.054	Normal
Control		0.978	30	0.784	Normal
**At a significance level of 0.01*					

Table A.4 - Results of testing the normality of data distribution for laboratory indicators in groups

Group	Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
The main one	Leukocytes, $x10^9$ cells/l	0.963	30	0.375	Normal
Control		0.961	30	0.320	Normal
The main one	Erythrocytes, $x10^{12}$/l	0.965	30	0.417	Normal
Control		0.974	30	0.660	Normal

The main one	Hematocrit, %	0.972	30	0.597	Normal
Control		0.978	30	0.775	Normal
The main one	Hemoglobin, g/l	0.976	30	0.710	Normal
Control		0.967	30	0.460	Normal
The main one	Platelets $\times 10^9$ cells/l	0.945	30	0.121	Normal
Control		0.962	30	0.346	Normal
The main one	Neutrophils, $x10^9$ cells/l	0.938	30	0.083	Normal
Control		0.963	30	0.368	Normal
The main one	Neutrophils, %	0.974	30	0.643	Normal
Control		0.974	30	0.643	Normal
The main one	Lymphocytes, %	0.980	30	0.829	Normal
Control		0.988	30	0.976	Normal
The main one	Monocytes, %	0.960	30	0.315	Normal
Control		0.963	30	0.336	Normal
The main one	Eosinophils, %	0.970	30	0.552	Normal
Control		0.975	30	0.689	Normal
The main one	Basophils, %	0.957	30	0.252	Normal
Control		0.983	30	0.902	Normal
The main one	ESR, mm/h	0.965	30	0.413	Normal
Control		0.967	30	0.455	Normal
The main one	ALT, units/l	0.971	30	0.546	Normal
Control		0.970	30	0.527	Normal
The main one	AST, units/l	0.963	30	0.377	Normal
Control		0.965	30	0.404	Normal
The main one	Total bilirubin, μmol/l	0.934	30	0.063	Normal
Control		0.982	30	0.876	Normal
The main one	Creatinine, μmol/l	0.976	30	0.704	Normal
Control		0.975	30	0.670	Normal
The main one	Glucose, mmol/l	0.953	30	0.204	Normal
Control		0.977	30	0.756	Normal
The main one	Specific weight	,953	30	0.209	Normal
Control		0.983	30	0.897	Normal
The main one	pH	0.944	30	0.120	Normal
Control		0.971	30	0.566	Normal
The main one	Leukocytes, cl. in sight	0.963	30	0.372	Normal
Control		0.948	30	0.149	Normal
The main one	Erythrocytes, cl. in sight	0.982	30	0.870	Normal
Control		0.983	30	0.909	Normal

Table A.5 - Results of checking the normality of the distribution of variance analysis residuals for hemodynamic indicators and body temperature

Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
Main group				
SBR	0.983	150	0.058	Normal
DBR	0.987	150	0.148	Normal
heart rate	0.981	150	0.038	Normal
Body t	0.985	150	0.096	Normal
Control group				
SBR	0.988	150	0.170	Normal
DBR	0.982	150	0.043	Normal
heart rate	0.984	150	0.091	Normal
Body t	0.986	150	0.126	Normal
**The conclusion is made at a significance level of 0.01*				

Table A.6 – Results of checking the normality of the distribution of variance analysis residuals for general blood analysis indicators

Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
Main group				
Leukocytes	0.985	150	0.105	Normal
Erythrocytes	0.992	150	0.582	Normal
Hematocrit	0.980	150	0.028	Normal
Hemoglobin	0.890	150	0.499	Normal
Platelets	0.987	150	0.127	Normal
Neutrophils	0.983	150	0.034	Normal
Neutrophils, %	0.985	150	0.100	Normal
Lymphocytes	0.985	150	0.101	Normal
Monocytes	0.995	150	0.892	Normal
Eosinophils	0.991	150	0.471	Normal
Basophils	0.986	150	0.119	Normal
ESR	0.988	150	0.224	Normal
Control group				
Leukocytes	0.995	150	0.900	Normal
Erythrocytes	0.993	150	0.696	Normal
Hematocrit	0.980	150	0.026	Normal
Hemoglobin	0.996	150	0.937	Normal
Platelets	0.982	150	0.045	Normal
Neutrophils	0.996	150	0.962	Normal

Neutrophils, %	0.995	150	0.904	Normal
Lymphocytes	0.993	150	0.668	Normal
Monocytes	0.978	150	0.015	Normal
Eosinophils	0.995	150	0.911	Normal
Basophils	0.995	150	0.898	Normal
ESR	0.979	150	0.020	Normal
**The conclusion is made at a significance level of 0.01*				

Table A.7 - Results of checking the normality of the distribution of individual differences in hematological indicators in the main group

Indicator	dTi	Statistics	Number of degrees of freedom	p-value	Conclusion*
Leukocytes	dT21	0.809	30	0.000	Not normal
	dT42	0.834	30	0.000	Not normal
	dT63	0.789	30	0.000	Not normal
	dT90	0.791	30	0.000	Not normal
Erythrocytes	dT21	0.815	30	0.000	Not normal
	dT42	0.776	30	0.000	Not normal
	dT63	0.784	30	0.000	Not normal
	dT90	0.734	30	0.000	Not normal
Hematocrit	dT21	0.780	30	0.000	Not normal
	dT42	0.745	30	0.000	Not normal
	dT63	0.784	30	0.000	Not normal
	dT90	0.774	30	0.000	Not normal
Hemoglobin	dT21	0.811	30	0.000	Not normal
	dT42	0.803	30	0.000	Not normal
	dT63	0.698	30	0.000	Not normal
	dT90	0.674	30	0.000	Not normal
Platelets	dT21	0.590	30	0.000	Not normal
	dT42	0.781	30	0.000	Not normal
	dT63	0.753	30	0.000	Not normal
	dT90	0.779	30	0.000	Not normal
Neutrophils	dT21	0.804	30	0.000	Not normal
	dT42	0.762	30	0.000	Not normal
	dT63	0.805	30	0.000	Not normal
	dT90	0.834	30	0.000	Not normal
Lymphocytes	dT21	0.784	30	0.000	Not normal
	dT42	0.742	30	0.000	Not normal
	dT63	0.765	30	0.000	Not normal
	dT90	0.794	30	0.000	Not normal

Monocytes	dT21	0.755	30	0.000	Not normal
	dT42	0.735	30	0.000	Not normal
	dT63	0.678	30	0.000	Not normal
	dT90	0.749	30	0.000	Not normal
Eosinophils	dT21	0.762	30	0.000	Not normal
	dT42	0.756	30	0.000	Not normal
	dT63	0.760	30	0.000	Not normal
	dT90	0.730	30	0.000	Not normal
Basophils	dT21	0.788	30	0.000	Not normal
	dT42	0.791	30	0.000	Not normal
	dT63	0.665	30	0.000	Not normal
	dT90	0.751	30	0.000	Not normal
ESR	dT21	0.763	30	0.000	Not normal
	dT42	0.816	30	0.000	Not normal
	dT63	0.724	30	0.000	Not normal
	dT90	0.736	30	0.000	Not normal

Table A.8 - Results of checking the normality of the distribution of individual differences in hematological indicators in the control group

Indicator	dTi	Statistics	Number of degrees of freedom	p-value	Conclusion*
Leukocytes	dT21	0.770	30	0.000	Not normal
	dT42	0.780	30	0.000	Not normal
	dT63	0.765	30	0.000	Not normal
	dT90	0.738	30	0.000	Not normal
Erythrocytes	dT21	0.752	30	0.000	Not normal
	dT42	0.763	30	0.000	Not normal
	dT63	0.740	30	0.000	Not normal
	dT90	0.789	30	0.000	Not normal
Hematocrit	dT21	0.679	30	0.000	Not normal
	dT42	0.674	30	0.000	Not normal
	dT63	0.800	30	0.000	Not normal
	dT90	0.803	30	0.000	Not normal
Hemoglobin	dT21	0.784	30	0.000	Not normal
	dT42	0.694	30	0.000	Not normal
	dT63	0.677	30	0.000	Not normal
	dT90	0.793	30	0.000	Not normal
Platelets	dT21	0.768	30	0.000	Not normal
	dT42	0.740	30	0.000	Not normal
	dT63	0.774	30	0.000	Not normal
	dT90	0.781	30	0.000	Not normal

Neutrophils	dT21	0.709	30	0.000	Not normal
	dT42	0.931	30	0.000	Not normal
	dT63	0.750	30	0.000	Not normal
	dT90	0.774	30	0.000	Not normal
Lymphocytes	dT63	0.795	30	0.000	Not normal
	dT90	0.811	30	0.000	Not normal
	dT21	0.805	30	0.000	Not normal
	dT42	0.787	30	0.000	Not normal
Monocytes	dT21	0.821	30	0.000	Not normal
	dT42	0.730	30	0.000	Not normal
	dT63	0.678	30	0.000	Not normal
	dT90	0.774	30	0.000	Not normal
Eosinophils	dT21	0.763	30	0.000	Not normal
	dT42	0.772	30	0.000	Not normal
	dT63	0.785	30	0.000	Not normal
	dT90	0.809	30	0.000	Not normal
Basophils	dT21	0.767	30	0.000	Not normal
	dT42	0.765	30	0.000	Not normal
	dT63	0.820	30	0.000	Not normal
	dT90	0.762	30	0.000	Not normal
ESR	dT21	0.560	30	0.000	Not normal
	dT42	0.609	30	0.000	Not normal
	dT63	0.761	30	0.000	Not normal
	dT90	0.801	30	0.000	Not normal

Table A.9 – Results of checking the normality of the distribution of variance analysis residuals for indicators of biochemical blood analysis

Difference of means	Difference of means	Difference of means	Difference of means	Difference of means
Difference of means				
Difference of means	Difference of means	Difference of means	Difference of means	Difference of means
Difference of means	Difference of means	Difference of means	Difference of means	Difference of means
Difference of means	Difference of means	Difference of means	Difference of means	Difference of means
Difference of means	Difference of means	Difference of means	Difference of means	Difference of means
Difference of means	Difference of means	Difference of means	Difference of means	Difference of means
Difference of means				
Difference of	Difference of	Difference of means	Difference	Difference of means

means	means		of means	
Difference of means	Difference of means	Difference of means	Difference of means	Difference of means
Difference of means	Difference of means	Difference of means	Difference of means	Difference of means
Difference of means	Difference of means	Difference of means	Difference of means	Difference of means
Difference of means	Difference of means	Difference of means	Difference of means	Difference of means
Difference of means				

Table A.10 - Results of checking the normality of the distribution of individual differences in biochemical blood analysis indicators in the main group

Indicator	dTi	Statistics	Number of degrees of freedom	p-value	Conclusion*
ALT	dT21	0.765	30	0.000	Not normal
	dT42	0.664	30	0.000	Not normal
	dT63	0.593	30	0.000	Not normal
	dT90	0.811	30	0.000	Not normal
AST	dT21	0.783	30	0.000	Not normal
	dT42	0.791	30	0.000	Not normal
	dT63	0.664	30	0.000	Not normal
	dT90	0.693	30	0.000	Not normal
Total bilirubin	dT21	0.784	30	0.000	Not normal
	dT42	0.762	30	0.000	Not normal
	dT63	0.506	30	0.000	Not normal
	dT90	0.777	30	0.000	Not normal
Creatinine	dT21	0.801	30	0.000	Not normal
	dT42	0.786	30	0.000	Not normal
	dT63	0.790	30	0.000	Not normal
	dT90	0.742	30	0.000	Not normal
Glucose	dT21	0.791	30	0.000	Not normal
	dT42	0.754	30	0.000	Not normal
	dT63	0.659	30	0.000	Not normal
	dT90	0.678	30	0.000	Not normal

Table A.11 - Results of checking the normality of the distribution of individual differences in biochemical blood analysis indicators in the control group

Indicator	dTi	Statistics	Number of degrees of freedom	p-value	Conclusion*
ALT	dT21	0.798	30	0.000	Not normal
	dT42	0.719	30	0.000	Not normal
	dT63	0.785	30	0.000	Not normal
	dT90	0.734	30	0.000	Not normal
AST	dT21	0.805	30	0.000	Not normal
	dT42	0.736	30	0.000	Not normal
	dT63	0.683	30	0.000	Not normal
	dT90	0.681	30	0.000	Not normal
Total bilirubin	dT21	0.781	30	0.000	Not normal
	dT42	0.673	30	0.000	Not normal
	dT63	0.694	30	0.000	Not normal
	dT90	0.780	30	0.000	Not normal
Creatinine	dT21	0.776	30	0.000	Not normal
	dT42	0.750	30	0.000	Not normal
	dT63	0.748	30	0.000	Not normal
	dT90	0.760	30	0.000	Not normal
Glucose	dT21	0.771	30	0.000	Not normal
	dT42	0.725	30	0.000	Not normal
	dT63	0.746	30	0.000	Not normal
	dT90	0.784	30	0.000	Not normal

Table A.12 – Results of checking the normality of the distribution of variance analysis residuals for indicators of general urine analysis

Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
Main group				
Specific weight	0.990	150	0.343	Normal
pH	0.985	150	0.129	Normal
Leukocytes, cl. in sight	0.991	150	0.418	Normal
Erythrocytes, cl. in sight	0.991	150	0.416	Normal
Epithelial cells, cl. in sight.	0.986	150	0.151	Normal
Control group				
Specific weight	0.985	150	0.133	Normal
pH	0.989	150	0.278	Normal
Leukocytes, cl. in sight	0.987	150	0.221	Normal
Erythrocytes, cells in sight	0.989	150	0.307	Normal

Epithelial cells, cl. in sight.	0.985	150	0.116	Normal
**The conclusion is made at a significance level of 0.01*				

Table A.13 - Results of testing the normality of the data distribution of the quality of life assessment index according to the EORTC QLQ-C30 scale

Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
Main group				
EORTC QLQ-C30 (D0)	0.967	30	0.462	Normal
EORTC QLQ-C30 (D42)	0.979	30	0.791	Normal
EORTC QLQ-C30 (D90)	0.965	30	0.411	Normal
Control group				
EORTC QLQ-C30 (D0)	0.908	30	0.013	Normal
EORTC QLQ-C30 (D42)	0.975	30	0.696	Normal
EORTC QLQ-C30 (D90)	0.964	30	0.389	Normal
**The conclusion is made at a significance level of 0.01*				

Table A.14 – Results of testing the normality of the data distribution of the EORTC QLQ-C30 general health assessment index

Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
Main group				
EORTC QLQ-C30 (D0)	0.930	30	0.049	Normal
EORTC QLQ-C30 (D42)	0.974	30	0.675	Normal
EORTC QLQ-C30 (D90)	0.967	30	0.471	Normal
Control group				
EORTC QLQ-C30 (D0)	0.931	30	0.053	Normal
EORTC QLQ-C30 (D42)	0.953	30	0.350	Normal
EORTC QLQ-C30 (D90)	0.956	30	0.241	Normal
**The conclusion is made at a significance level of 0.01*				

Appendix B

European Organization for Research and Treatment of Cancer Quality of Life Assessment Questionnaire
EORTC QLQ-C30 (version 3.0)

We would like to ask you several questions concerning you and your health. Please answer all questions yourself by circling the answer number that most accurately reflects your situation. There are no "right" or "wrong" answers here. All information provided by you will be kept confidential.

Please specify:

Your initials (first letters of Surname, name, patronymic):_____

Date of birth (day, month, year): _____

Today's date (day, month, year): _____

		No	Rather no than yes	More likely than not	Yes
1.	Do you experience any difficulties when performing work that requires significant physical effort, for example, when carrying a heavy business bag or suitcase?	1	2	3	
2.	Do you experience any difficulties while taking a long walk?	1	2	3	4
3.	Do you experience any difficulties while taking a short walk outside?	1	2	3	4
4.	Should you spend most of the day in bed or in a chair?	1	2	3	4

5.	Do you need help eating, dressing, washing or using the toilet?	1	2	3	4

During the last week:

		No	Rather no than yes	More likely than not	Yes
6	Did something limit you in one way or another when you performed your work or other daily tasks?	1	2	3	4
7.	Did something limit you in one way or another during your favorite activity or other leisure activity?	1	2	3	4
8.	Have you had shortness of breath?	1	2	3	4
9.	Did you have pain?	1	2	3	4
10.	Did you need a rest?	1	2	3	4
11.	Did you have a disturbed sleep?	1	2	3	4
12.	Did you feel weak?	1	2	3	4
13.	Did you have a decrease in appetite?	1	2	3	4
14.	Did you feel nauseous?	1	2	3	4
15.	Did you vomit?	1	2	3	4
16,	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Did you feel tired?	1	2	3	4
19.	Has the pain prevented you from doing your daily activities?	1	2	3	4
20.	Did you find it difficult to concentrate on something, such as reading a newspaper or watching TV?	1	2	3	4
21.	Did you feel a sense of tension?	1	2	3	4
22.	Did you feel a sense of anxiety?	1	2	3	4
23.	Did you feel a sense of irritation?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Was it difficult for you to remember something?	1	2	3	4
26.	Has your physical condition or treatment interfered with your family life?	1	2	3	4
27.	Did your physical condition or treatment prevent you from appearing in public (visiting, going to the movies, etc.)?	1	2	3	4
28.	Has your physical condition or treatment caused you financial difficulties?	1	2	3	4

When answering the following questions, please circle the answer number in the interval from 1 to 7 that most accurately reflects your situation.

29. How would you rate your overall health over the last week?

1	2	3	4	5	6	7
Very bad						**Excellent**

30. How would you rate your overall quality of life over the last week?

1	2	3	4	5	6	7
Very bad						**Excellent**