"APPROVE"
Chief physician of KU "Rivne regional oncological dispensary"
(*signature, seal***) Maksimyak G.I.**
"____" _____2018

«УТВЕРЖДАЮ»
Главный врач КУ «Ровенский областной онкологический диспансер»
_____ Максимяк Г.И.
«____» _____ 2018 г.

REPORT
about the clinical trial

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

Research phase - II

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

Sponsor of the study - LLC NPF "Aksomed LTD"

Location of the study - KU "Rivne Regional oncology dispensary", proctology department
33013, Rivne, st. Alexandra Olesya, 12. Tel. (036) 268-36-69

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Head department,
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(подпись)

CONTENT

1. SUMMARY OF THE REPORT (SUMMARY)

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

Research phase - II.

Study code - AF-DN-2 / f .2 / 10.14

Protocol version - No. 1 dated March 14, 2015.

Start of the study: 06.10.2015

End of the study: 04.09.2017

Purpose of the study. Evaluation of the efficacy and tolerability of Donovit-VS®, a tablet manufactured by Astrapharm LLC, used in patients with colorectal cancer on the background of chemotherapy in comparison with a group of patients receiving only chemotherapy.

Research objectives:

- study the effect of the study drug on the degree of toxicity of chemotherapy;
- study the effect of the investigational drug on the quality of life;
- 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® in comparison with the group of patients receiving only chemotherapy.

Study design: open, comparative, randomized, parallel

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

The group of test subjects. Patients of both sexes aged 18 to 70 years with a diagnosis of colorectal cancer (rectal cancer $T_{2-4}N_{0-2}M_0$, colon cancer $T_{3-4}N_{1-2}M_0$) after radical surgical treatment.

Number of patients:

Planned number of patients: 60 patients (30 patients in the main group and 30 patients in 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 was 60.

Inclusion Criteria:

- men and women aged 18 to 70;
- diagnosis: colorectal cancer (rectal cancer $T_{2-4}N_0$-$2M_0$, colon cancer $T_{2-4}N_{1-2}M_0$);
- patients after surgical resection of the tumor who were prescribed adjuvant chemotherapy according to the FOLFOX-4 scheme;
- histological confirmation of colorectal cancer;
- life expectancy of at least 12 weeks (3 months);
- the functional state of the patient before surgery 0-2 points on the ECOG scale;
- for women of reproductive age - a negative pregnancy test result, as well as the use of reliable contraceptives during the study period;
- informed written consent of the patient to participate in the study.

Criteria for non-inclusion:

- known hypersensitivity to the components of the study drug;
- pregnancy, lactation;
- number of leukocytes < 2.0×10^9 cells/l;
- number of neutrophils < 1.5×10^9 cells/l;
- platelet count < 100×10^9 cells/l;
- hemoglobin level < 100 g/l;
- creatinine exceeds the upper limit of normal by more than 1.25 times;
- transaminases (AST, ALT) exceed the upper limit of the norm by more than 2.5 times; total bilirubin exceeds the upper limit of normal by more than 1.5 times;
- any unstable medical or psychiatric condition that, in the opinion of the investigator, may impair the patient's ability to complete the study or preclude participation in the study;
- the need to take non-recommended drugs (see section 8.2);
- participation in any other clinical trial.

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

Patients **of the main and control groups** received polychemotherapy in accordance with international standards for the treatment of colorectal cancer according to the FOLFOX-4 regimen: Oxaliplatin 85 mg/m^2 IV (day 1) + Leucovorin 200 mg/m^2/day IV (days 1-2) + 5-fluorouracil 400 mg/m^2/day IV (days 1-2) and 5-fluorouracil 600 mg/m^2/day IV for 22 hours. (1st 2nd days). Therapy was started on the 14th day after the operation. The planned number of courses is 6, with an interval of 14 days.

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

Efficiency evaluation criteria:

Main variable:

- the degree of manifestation of toxicity of chemotherapy during treatment (assessment is carried out according to the toxicity scale Common Toxicity Criteria NCIC (CTC NCIC).

Secondary variable:

- the level of quality of life of the patient in the course of treatment (assessment is carried out according to the questionnaire of the European Organization for Research and Treatment of Cancer EORTC - QLQ - C 30)

Tolerability score:

- the presence and nature of adverse events, their relationship with the study drug;
- dynamics of vital signs (BP, heart rate, body t);
- ECG data dynamics;
- dynamics of laboratory parameters (general blood count, general urinalysis, 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. Mann criterion - Whitney 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, Wilcoxon's signed-rank test or Student's t-test for related samples was used to compare the values of indicators before and after treatment. When performing comparisons, the significance level 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.

Software.

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

Efficiency Evaluation Results.

1). In the main and control groups, a statistically significant decrease in the level of leukocytes after the first course of chemotherapy, erythrocytes and platelets, after the third course of chemotherapy, hemoglobin, after the fourth course of chemotherapy compared with the baseline was revealed.

Changes in other hematological parameters in both groups were not statistically and clinically significant throughout the study.

2). A significantly more pronounced decrease was found:

- the level of leukocytes, after the first course of chemotherapy, in patients of the control group, compared with the main one;
- hemoglobin level, after the fourth course of chemotherapy, in patients of the control group, compared with the main one;
- the level of platelets after the third course of chemotherapy in patients of the control group, compared with the main one.

The groups did not differ significantly in other hematological parameters.

3). A significantly higher incidence of leukopenia was revealed in patients of the control group compared to the main group ($p = 0.015$). A decrease in the number of leukocytes ($< 4.0x10^9$ cells/l) was observed in 6 (20.0%) patients of the main group and in 16 (53.3%) patients of the control group.

4). A higher incidence of anemia and thrombocytopenia was noted in patients in the control group compared to the main group. Yes, the decline

hemoglobin level (<110 g/l) was observed in 2 (6.7%) patients of the main group and in 7 (23.3%) patients of the control group. A decrease in the number of platelets (<100 $x10^9$ cells/l) was observed in 3 (10.0%) patients of the main group and in 10 (33.3%) patients of the control group. However, the difference between the groups in these parameters was not significant.

5). In the main and control groups, a statistically significant increase in the level of ALT, AST was revealed starting from the 42nd day of therapy (after the third course).

Changes in other biochemical parameters in both groups were within the physiological norm and were not statistically or clinically significant.

6). A higher number of patients with elevated levels of ALT, AST and bilirubin was noted in the control group compared to the main one. However, the difference between the groups in these indicators is not significant.

7). A significantly larger number of patients with nausea/vomiting was found in the control group compared to the main group ($p = 0.0003$).

8). A significantly more significant decrease in the quality of life according to the EORTC QLQ-C30 scale was found in patients in the control group, compared with patients in the main group, according to the following scales:

- on a scale of general health;
- on a scale for assessing the quality of life;
- on a scale of physical function;
- on the scale of social function;
- on symptomatic scales: fatigue, nausea/vomiting.

The above evidences in favor of the superior efficacy in the group of patients who received, against the background of antitumor chemotherapy, the study drug Donovit-VS® compared with the group of patients who received only chemotherapy.

The results of the tolerance assessment.

The data obtained during the study also allow us to conclude that the study drug is well tolerated. During the study, in the group of patients taking the study drug, there were no allergic and anaphylactic reactions, significant fluctuations in hemodynamic parameters. None of the patients taking the study drug had serious AE/AR and none of the patients withdrew from 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 was an association of the observed AE/AR with the study drug established by the investigator. 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® (number of AE/AR: 93 in the main group and 156 in in the control).

Based on the above, it can be considered that the tolerance 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 colorectal cancer was more effective in the group of patients who received, against the background of antitumor chemotherapy, the study drug Donovit-VS®, tablets manufactured by Astrapharm LLC, in comparison with the group of patients receiving only chemotherapy on the main variable. This was manifested in a decrease in the severity and frequency of such complications of chemotherapy as: leukopenia, anemia and thrombocytopenia, as well as in a decrease in the severity and frequency of nausea and vomiting.

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

3. The study drug Donovit-VS®, tablets manufactured by Astrapharm LLC, was well tolerated by all 100% of patients. During the study, in the group of patients taking the drug Donovit-VS®, there were no allergic and anaphylactic reactions, significant fluctuations in hemodynamic parameters. None of the patients taking study medication had a serious AE/AR and none of the patients withdrew from the study due to AE/AR. It should be noted 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® (number of AE/AR: 93 in the main group and 156 in control).

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

The report contains: pages - 153, tables - 79, figures - 18,
bibliography - 25 sources.

2. LIST OF ABBREVIATIONS AND TERMS

BP - blood pressure
ALT - alanine aminotransferase
AST - aspartate aminotransferase
ASA - acetylsalicylic acid
ULN - upper limit of normal
WHO - World Health Organization
SEC MZU - State Expert Center of the Ministry healthcare of Ukraine
DBP - diastolic blood pressure
IRF - individual registration form
VA - variance analysis
MTD - maximum tolerated dose
NSAIDs - non-steroidal anti-inflammatory drugs
AO - abdominal organs
CO - chest organs
AR - adverse reaction
AE - adverse effect
PCT - poly chemotherapy
CRC - colorectal cancer
RN - randomization number
SBP - systolic blood pressure
DBR - diastolic blood pressure
HF - heart failure
SND - standard normal distribution
ESR - erythrocyte sedimentation rate
Ultrasound - ultrasonography
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^o - body temperature
EORTC QLQ C-30 - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
CTC NCIC - Common Toxicity Criteria National Cancer Institute

3. ETHICAL AND LEGAL ASPECTS OF RESEARCH

3.1. Approval of the protocol by official bodies

Prior to the start of the study, the Sponsor of the study submitted the clinical study protocol, the IRF sample, written information for the patient and the informed consent form to the Central Executive Authority (CBEP) and the Commission on Ethics at the Rivne Regional Oncology Dispensary. This study was started only after receiving the decision of the Center for Clinical Research and the approval of the protocol by the Ethics Commission.

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 (WMA), Fortaleza, Brazil, October 2013, international principles of clinical trials (ICH GCP), current regulatory documents and legislation of Ukraine.

3.3. Procedure for obtaining informed consent

Written informed consent was obtained from each applicant for participation in the study prior to any screening procedures.

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

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

Patients were informed that they could refuse to participate in the trial 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 it by authorized persons (in case of audit, inspection, etc.).

Each patient was given a sufficient amount of time to consider the possibility of his participation in the study and to ask the researcher questions that interested him. The researcher did not put pressure on the patient in order to influence his decision.

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

3.4. Confidentiality

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

3.5. Insurance

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

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

4. RESEARCHERS AND ADMINISTRATIVE STRUCTURE OF THE RESEARCH

Research sponsor LLC NPF "Aksomed LTD" 04210, Kyiv, prospect Heroev Stalingrada 6, building 4. tel. (044) 537-78-41

Director	Aksenov G.N.
Scientific consultant	Doctor of Medicine Sobetsky V.V.

Place of research	
CU "Rovno regional oncological dispensary", proctology department 33013, Rivne, st. Aleksandra Olesya, 12 (036) 268-36-69	
Responsible executor	Chief department, Doctor of Medicine Zhilchuk V.E.
Co-researchers	Maksymyak G.I. Zhilchuk A.V.

5. INTRODUCED

5.1. Description of the drug under study

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 with the aim of solving the question of the possibility of registering the drug in Ukraine as a medicinal product.

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

Pharmacological action.

According to preclinical studies, Donovit-VS® exhibits antitumor activity against solid tumors with angiogenesis-dependent growth. The drug also significantly suppresses the process of metastasis, reducing both the number of metastases and their volume. The antitumor and antimetastatic effects are dose-dependent and are 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 antiangiogenic mechanism of action causes antitumor and antimetastatic action only in relation to malignant neoplasms with angiogenesis-dependent growth.

Suggested indications for use.

The drug is supposed to be used in the treatment of oncological diseases as a therapy "supporting" the main treatment; treatment of the consequences of toxic and radiation reactions, as a supportive (symptomatic) therapy of late complicated tumor processes. The drug is supposed to be used at the I-III stage of the tumor process with:

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

Possible contraindications.

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

Special precautions.

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

Method of application and dosage.

Adults with the I-II stage of the tumor process are prescribed 1 tablet 2-3 times a day during the period of preoperative preparation and 5-7 days after the surgical treatment. Postoperative course of treatment - 1-3 months, possible combination with radiation and chemotherapy.

Possible schemes for prescribing the drug under investigation 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 region is possible. The nature of adverse reactions will be clarified in the course of clinical studies.

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.

5.2. Preclinical studies of the drug Donovit-VS

Preclinical studies of the drug "Donovit-VS" (test agent VS-1), 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 pot-bellied" breed. As a result of the conducted studies, the following reports were prepared:

1. "Investigation of the specific antitumor activity of the VS-1 agent (the name of the drug Donovit-VS at the preclinical stage) in relation to 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. "Investigation of the specific pharmacological activity of the drug VS-1 in relation to melanoma B16"

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

5. "Investigation of the 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 agent VS-1 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 agent VS-1 in mice and rats"

10. "Investigation of the cumulative properties and chronic toxicity of the agent VS-1 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 pigs of the Vietnamese fold-bellied breed.

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

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

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

C) VS-1 does not have an antitumor effect against 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 life expectancy of mice with Lewis carcinoma.

E) VS-1 has a pronounced antimetastatic effect against 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 against Lewis carcinoma resistant to cis-DDP. The percentage of inhibition of metastases, estimated by the average number of metastases in the group, was **92.2%.**

F) The advanced hypothesis that VS-1 has a high antitumor effect against 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 turned out to be ineffective against the tumor model L1210 of lymphoid origin.

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

I) The studied test-agent VS-1 at a dose of MTD/2 showed antitumor and antimetastatic activity against Lewis LLC lung carcinoma, which was expressed in the cure of 40% of the animals and in the absence of metastases in 37% of the 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 supplement (BAD). For a number of 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 has been 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 monotherapy and 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 regimen as a "support" therapy for the main treatment; treatment of the consequences of toxic and radiation reactions, supportive (symptomatic) therapy of late complicated tumor processes. The duration of treatment ranged from 2 months to 2.5 years. The improvement was determined by the general well-being of the patients, the stabilization of hemodynamic parameters, the reduction of compression, edema 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 distinct effect, with prolongation of survival, was observed in patients with brain and lung tumors. Thus, the number of positive reactions to treatment was 70%, and in patients with tumors of these localizations - 82%.

The use of BAD Donovit-VS in COPD, bronchial asthma, osteochondrosis, depressive syndromes strengthened the effect of basic drugs, their dose decreased, which allowed to achieve a clinical effect in a shorter time.

Side effects when using the drug Donovit-VS were not observed in any case. Withdrawal from treatment was not accompanied by a withdrawal syndrome. More detailed information on clinical observations of the drug is available on the website of the SPF "Aksomed": aksomed.kiev.ua and: donovit.com .

5.3. Results of the first phase of the clinical study of the drug Donovit-VS ®.

The first phase of clinical research of the drug Donovit-VS ®, tablets produced by Astrapharm LLC, was conducted on the basis of the Rivne regional oncological dispensary. The study included 20 male and female patients aged 18 to 65 years with a diagnosis of colorectal cancer, T_{2-4} N_{0-2} M_{0} after surgical resection of the tumor and 4 courses of chemotherapy. All included patients, by the method of simple randomization, were distributed 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 3 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 draw a conclusion about the good tolerability of the drug under study in all studied treatment schemes. The drug did not have a negative effect on the results of objective clinical and laboratory studies, which allowed us 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 manufactured by Astrapharm LLC, used in patients with colorectal cancer on the background of chemotherapy in comparison with a group of patients receiving only chemotherapy.

Research objectives:

- to study the influence of the researched drug on the degree of toxicity of chemotherapy (according to the CTC NCIC toxicity scale);
- study the impact of the research drug on the patient's quality of life (according to the EORTC QLQ - C 30 scale);

- to compare the treatment results obtained in the main and control groups with the aim of establishing a higher treatment efficiency in the group of patients receiving chemotherapy + Donovit-VS ® in comparison with the group of patients receiving only chemotherapy.

7. DESCRIPTION OF CLINICAL RESEARCH METHODOLOGY

7.1 . Research design

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

7.2. Number of patients (planned and analyzed)

The planned number of patients: 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 were treated in the proctological department of the Rivne regional oncology dispensary and who met the inclusion/exclusion criteria described in the research protocol took part in the study. Patients included in the study were diagnosed with: rectal cancer, disease stage T_{2-4} N_{0-2} $M_{0,}$ or colon cancer, disease stage T_{3-4} N_{1-2} M_0. The diagnosis was confirmed by the data of morphological research. All patients included in the study underwent surgical resection of the tumor and were prescribed chemotherapy according to the FOLFOX-4 regimen.

After clinical evaluation, suitable candidates were given oral and written information about the study drug and the study. All potential research participants were given time to think about their participation in the research and the opportunity to ask questions to the researcher. Written informed consent was obtained from all potential research participants prior to the initiation of any research procedures.

Potential patients underwent screening procedures at Visit 1. Screening was carried out on the 5-7th day after the operation and lasted up to 7 days.

If the patient met all the inclusion/non-inclusion criteria, he was assigned, using a simple randomization method, to one of the treatment groups: main or control. Patients of the main and control groups, starting from the 14th day after the operation, received chemotherapy according to the FOLFOX-4 scheme, in the form of 6 courses with an interval of 14 days. In addition, the patients of the main group, starting from the 14th day after the operation, on the background of chemotherapy received the research drug Donovit-VS®, tablets produced by Astrapharm LLC, 1 tablet 3 times a day for 3 months.

Table 1. Therapy plan in the main and control groups

V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
D (-7-0)	**D0**	**D 14**	**D 28**	**D 42**	**D 56**	**D 70**	**D 90 (±3)**
Screening	**Random**						**Conclusion visit**
	<u>The main group</u> Chemotherapy + Donovit-VS ®						
	1st course CT	**2nd course CT**	**3rd course CT**	**4th course CT**	**5th course CT**	**6th course CT**	
	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓
	<u>Control group</u> Chemotherapy						
	↓	↓	↓	↓	↓	↓	
V - visit D - day							

Six courses of chemotherapy were planned for each patient. Patients who received less than 6 courses of chemotherapy continued to participate in the study, regardless of whether they were in the main or control group.

Registration of patient examination data (Visits) was carried out at the following time points: before treatment, then every 14 days (1-2 days before the next course of CT) for 3 months. The last, final visit was performed on the 90th day from the start of treatment, regardless of how many courses of CT the patient received.

Before the test, each patient underwent a physical examination, chest X-ray, complete blood analysis, biochemical blood analysis, urine analysis, ECG, and functional status was determined on the ECOG scale. Additional assessments prior to the trial included CT or MRI of the abdominal organs performed prior to surgery.

All patients included in the study had a functional status according to the ECOG scale from 0 to 2 points and an expected life expectancy of at least 12 weeks. Additional criteria included sufficient bone marrow reserve (content of leukocytes ≥2.0 x 10^9 cells/l, neutrophils ≥ 1.5 x 10^9 cells/l; platelets ≥100x10^9 cells/l, hemoglobin level ≥100 g/l), as well as sufficient liver and kidney function (AST, ALT did not exceed the upper limit of the norm by more than 2.5 times; total bilirubin did not exceed the upper limit of the norm by more than 1.5 times; creatinine did not exceed the upper limit of the norm by more than 1.25 times). Patients were not included in the study in case of an active infection, as well as any unstable therapeutic or psychiatric condition, which, according to the researcher, could impair the patient's ability to complete the study or prevent participation in it. Pregnant or lactating women could not participate in the study.

During the research, before each course of chemotherapy, the patients underwent a physical examination, registered subjective complaints, performed a comprehensive blood analysis, biochemical blood analysis, urinalysis, ECG, evaluated the toxicity of chemotherapy according to the WHO criteria on the CTC NCIC scale , and determined the functional status on the scale ECOG, in addition, patients filled out the EORTC - QLQ - C 30 quality of life questionnaire on the 2nd, 4th, 6th and 8th visits.

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 took at least one dose of the study drug were assessed for tolerability.

The results of all the patient's examinations were recorded in the primary and secondary medical records (IRF).

7.4. Randomization

Patients were assigned to treatment groups based on a randomization scheme formed on the basis of a table of random numbers obtained by generating random numbers in the MS Excel program.

To carry out the procedure of distribution into treatment groups, the Sponsor provided the researcher with envelopes numbered in accordance with the randomization scheme. The randomization number of the patient (from 01 to 60) was

indicated on the envelopes, and the group to which the patient should be allocated was indicated in the envelope. Randomization numbers were assigned to patients in chronological order in accordance with the assignment of screening numbers to them. The researcher indicated the patient's initials and the date of randomization on the envelope. During the study, a patient screening/randomization log 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: 3-7 days were screening and 3 months - treatment.

7.6. Schedule of research procedures

Registration of studied indicators was carried out before the start of treatment, then every 12 days after each course of CT (after the 6th course - after 20 days) for 3 months.

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

Table 2 - Schedule of research procedures

	Screening	Treatment after surgery (6 courses of CT with an interval of 14 days according to the FOLFOX-4 scheme)						
Data registration points		**1st course CT** [1]	**2nd course CT** [1]	**3rd course CT** [1]	**4th course CT** [1]	**5th course CT** [1]	**6th course CT** [1]	**20 days after the end of the 6th course of CT**
days	**D (-7-0)**	**D0**	**D 14**	**D 28**	**D 42**	**D 56**	**D 70**	**D 90**
Visited	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Anamnesis	*							
Obtaining written informed consent	*							
Pregnancy test	*							
MRI or CT scan AO [2]	*							
R-graph CO [2]	*							
ECG at rest	*		*	*	*	*	*	*
Clinical examination	*	*	*	*	*	*	*	*
- general analysis of urine - general blood analysis - b/x blood analysis	*		*	*	*	*	*	*
Evaluation of the functional state according to the **ECOG scale**	*		*	*	*	*	*	*
Evaluation of the degree of toxicity of therapy according to the CTC NCIC scale			*	*	*	*	*	*
Assessment of quality of life according to the EORTC - QLQ - C 30 scale		*		*		*		*
Evaluation of the patient's compliance with inclusion/exclusion criteria.		*						
Randomization, treatment assignment		*						
Dispensing the researched drug		*		*		*		
Identification and registration of possible AE/AR			*	*	*	*	*	*

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

[2] If the R-graph of the CO and MRI or CT scan of the AO was performed no earlier than 4 weeks before the screening, a repeat examination was not performed in this patient during the screening process.

7.7. Plan of visits

Visit 1 (screening):

- registration of demographic and physical data (age, height, body weight);
- history collection (assessment of all body systems, characteristics of the tumor, type and volume of surgery, therapy during the last 3 months);
- pregnancy test (for women of reproductive age);
- objective examination;
- measurement of blood pressure, heart rate, t body;
- MRI or CT scan of the OBP;
- radiography of chest organs;
- ECG at rest;
- assessment of the functional state of the patient using the ECOG scale;
- general blood analysis;
- general analysis of urine;
- biochemical analysis of blood.

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

- determination of the patient's compliance with the inclusion/non-inclusion criteria based on screening results;
- randomization;
- objective examination;
- measurement of blood pressure, heart rate, t body;
- assessment of the patient's quality of life according to the EORTC - QLQ - C 30 scale;
- appointment of treatment;
- dispensing of the study drug.

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

- objective examination;
- measurement of blood pressure, heart rate, t body;
- registration of ongoing therapy, including accompanying therapy;
- ECG at rest;
- assessment of the functional state of the patient using the ECOG scale;
- assessment of the degree of toxicity of therapy according to the CTC NCIC scale ;
- general blood analysis;
- general analysis of urine;

- biochemical analysis of blood;
- registration of AE/AR.

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

- objective examination;
- measurement of blood pressure, heart rate, t body;
- registration of ongoing therapy, including accompanying therapy;
- ECG at rest;
- assessment of the functional state of the patient using 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 analysis;
- general analysis of urine;
- biochemical analysis of blood;
- registration of AE/AR;
- issuance/accounting of the study drug.

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

- objective examination;
- measurement of blood pressure, heart rate, t body;
- registration of ongoing therapy, including accompanying therapy;
- ECG at rest;
- assessment of the functional state of the patient using the ECOG scale;
- assessment of the degree of toxicity of therapy according to the CTC NCIC scale ;
- general blood analysis;
- general analysis of urine;
- biochemical analysis of blood;
- registration of AE/AR.

Visit 6 (before the 5th course of CT):

- objective examination;
- measurement of blood pressure, heart rate, t body;
- registration of ongoing therapy, including accompanying therapy;
- ECG at rest;
- assessment of the functional state of the patient using 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 - C 30 scale;
- general blood analysis;
- general analysis of urine;
- biochemical analysis of blood;

- registration of AE/AR;
- issuance/accounting of the study drug.

Visit 7 (before the 6th course of CT):

- objective examination;
- measurement of blood pressure, heart rate, t body;
- registration of ongoing therapy, including accompanying therapy;
- ECG at rest;
- assessment of the functional state of the patient using the ECOG scale;
- assessment of the degree of toxicity of therapy according to the CTC NCIC scale ;
- general blood analysis;
- general analysis of urine;
- biochemical analysis of blood;
- registration of AE/AR.

Visit 8 (final):

- objective examination;
- measurement of blood pressure, heart rate, t body;
- registration of ongoing therapy, including accompanying therapy;
- ECG at rest;
- assessment of the functional state of the patient using 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 analysis;
- general analysis of urine;
- biochemical analysis of blood;
- registration of AE/AR

7.8. Research procedures and methods

1). Obtaining informed consent.

Before starting any diagnostic and treatment procedures related to this study, written informed consent to participate in the study was obtained from all potential participants.

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

The fact of discussing the informed consent should have been recorded in the medical history and IRF with the date of signature.

2). History collection.

Anamnesis of life and disease was carried out according to the generally accepted methodology and included: characteristics of the tumor, stage of the disease, type and volume of surgery, results of R-graphy of CO and CT or MRI of the AO before surgery, concomitant diseases, therapy that the patient received during the last 3 months The anamnesis of the patient's life and disease was reflected in the primary documentation and IRF.

3). Pregnancy test.

It was carried out in women of reproductive age, 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 during the entire study and 30 days after the last intake 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 examination.

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 on the first visit was noted. At subsequent visits, data on changes recorded during the inspection were entered into the primary documentation and IRF. Identified changes were given a brief assessment on the subject of their compliance with the AE/AR.

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 a 15-minute rest of the patient, 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). ECG at rest was performed before the start of treatment, then before each course of CT and at the final visit.

In case of significant changes in the results of the ECG, a cardiologist was consulted.

7). R-graphy of CO and MRI or CT of abdominal organs (AO) were performed at the stage of screening or the results of studies conducted no earlier than 4 weeks before screening were taken into account.

8). Assessment of the functional status according to the ECOG scale, intended for determining the working capacity of oncological patients in degrees from 0 to 4, where 0 means that the patient maintains full activity; 4 — cannot perform self-service.

Table 3. ECOG scale

Grades	Sign
0	No symptoms
1	There are symptoms, but daily activity is preserved
2	He spends less than half of the day in bed
3	He spends half of the day and more in bed
4	Does not get up, requires care

9). The toxicity of chemotherapy was assessed using the *Common Toxicity Criteria NCIC* (CTC *NCIC*).

The scale shows 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 starting from the 3rd visit 1-2 days before the next 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	They do not require treatment or blood transfusion	Expressed, requires blood transfusion up to 4 times of 500 ml	A blood transfusion is necessary >, 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	Tolerating more than 2 days	Intolerable, requires treatment	Hemorrhages and dehydration, requiring intravenous fluid infusion
Nausea, vomiting	Absence	Nausea	Vomiting that passes	Vomiting that requires treatment	Unbearable vomiting
State of the oral cavity	No changes	Itching, heartburn, erythema	Erythema, ulcers, free food intake	Ulcers, it is difficult to take food, only liquid food is necessary	It is impossible to take food
Proteinuria	Absence	1+<0.3 g/l	2-3+<3-10 g/l	4+<10 g/l	Nephrotic syndrome
Hematuria	Absence	Microscopic	Macroscopic	Macroscopic + clots	Obstructive uropathy
Pulmonary changes	Absence	X-ray changes are minimal	Moderate symptoms that do not require special treatment	Periodic shortness of breath at rest	Shortness of breath is constant, requires constant stay in bed
Temperature	Normal	Less than 38°C	38°C-40°C	More than 40°C	An increase in temperature with a decrease in blood pressure/collapse
Allergic reactions	Absence	Dermatitis or edema	Bronchospasm not requiring treatment	bronchospasm, requiring treatment	Anaphylactic shock
Skin manifestations	Absence	erythema	Dry peeling, vesicles, itching	Wet peeling, ulcers	Necrosis requiring surgical intervention, dermatitis with peeling
hair	No changes	Minimal hair loss	Moderate	Complete but	Complete, but

			alopecia areata	reversible alopecia	irreversible alopecia
Infection	Absence	local	Medium grade	heavy	Threatening, sepsis
Heart rhythm disorders	Absence	Sinus tachycardia > 100 bpm at rest	Unifocal ventricular extrasystole, atrial fibrillation	Multifocal extrasystole	Ventricular tachycardia
Violations of heart function	Absence	Asymptomatic disorders of cardiac activity	Transient symptomatic dysfunction that does not require treatment	Symptoms - Czech dysfunction, corrected by treatment	Symptoms - Czech dysfunction, not corrected by treatment
Pericarditis	Absence	Asymptomatic fluid accumulation	Symptomatic disorders that do not require treatment	Tamponade, requiring treatment, myocardial function	Tamponade requiring surgical intervention
Neurotoxicity: condition	Vigilance	Passing drowsiness	Drowsiness/sleepless time <50%	Drowsiness/sleepless time >50%	Coma
Peripheral neuropathies	Absence	Paresthesias/or decreased tendon reflexes	Severe paresthesias, moderate weakness	Intolerable paresthesias, loss of motor reactions	Paralysis
Constipation [b]	Absence	rare	Moderate	Abdominal itching	Abdominal distension, vomiting
Pain [c]	Absence	weak	moderate	Strong	Intolerable, requiring the use of drugs

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

10). The assessment of quality of life was carried out 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; scale of the general state of health

and level of quality of life. Also included in the questionnaire are additional symptoms (shortness of breath, sleep disturbance, loss of appetite, constipation, diarrhea, and financial difficulties caused by the disease itself and its treatment). The state of each of the scales was evaluated within 4 gradations: no - 1 point; rather not than not - 2 points; rather yes than no – 3 points; yes - 4 points.

The patient filled out the questionnaire independently at 2, 4, 6 and 8 visits. The researcher calculated the sum of points and entered the data into the IRF.

11). 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 conducted on 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 parameters, the research doctor made a conclusion about its clinical significance.

12). Identification and registration of possible AE/AR

The diagnosis of AE/AR was made on the basis of the patient's complaints, objective examination data, and laboratory research data.

The patient's survey on the occurrence of AE/AR was carried out by the researcher at each visit during the research process.

13). Additional survey methods.

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

8. PATIENT SELECTION CRITERIA

8.1. Criteria for inclusion of patients in the study

Patients meeting the following criteria were included in the study:

- men and women aged 18 to 70;
- diagnosis: colorectal cancer (rectal cancer $T_{2-4}N_{0-2}M_{0,}$ colon cancer $T_{3-4}N_{1-2}M_0$);
- patients after surgical resection of the tumor who are prescribed adjuvant chemotherapy according to the FOLFOX-4 scheme;
- histological or cytological confirmation of colorectal cancer;

- the projected life expectancy is not less than 12 weeks (3 months);
- functional state of the patient before the operation 0-2 points on the ECOG scale;
- for women of reproductive age - a negative pregnancy test result, as well as the use of reliable contraceptives during the research period;
- 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 drug under study;
- pregnancy, lactation;
- previous chemotherapy less than 2.5 months before inclusion in this study;
- 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 the norm by more than 1.25 times;
- transaminases (AST, ALT) exceed the upper limit of the norm by more than 2.5 times; total bilirubin exceeds the upper limit of the norm by more than 1.5 times;
- any unstable therapeutic or psychiatric condition that, in the opinion of the researcher, may impair the patient's ability to complete the study or prevent participation in the study;
- the need to take non-recommended drugs (see section 8.2);
- 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, patients could be removed by the researcher from taking the study drug and from the study as a whole under the following circumstances:

- occurrence in the patient 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 period;
- the need to prescribe to the patient drugs that are inadmissible for use in the framework of this study;
- non-compliance with the treatment regimen by the patient;
- the patient's non-compliance with the procedures prescribed by the protocol.

In case of early withdrawal of the patient from the study, the researcher was recommended to perform Visit 8 procedures for the patient in order to assess the safety of the study therapy.

9. RESEARCH DRUG: LABELING, RECEIVING, ACCOUNTING AND STORAGE

9.1. The drug under study

Name: Donovit-V®.

Pharmaceutical form: tablets.

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

Pharmacotherapeutic group. Antitumor agents.

Physical and 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 provided on the label/packaging of the drug under study: manufacturer's name, address; name of the drug; composition; release form; serial number; storage conditions; release date, expiration date (date, month, hour); designation: "Keep out of the reach of children"; designation: "For clinical research".

9.3. Terms of transfer, registration and return of the drug under study

The study drug was provided to the clinical database by the Sponsor (OOO SPF "Aksomed LTD"). The transfer of the drug was confirmed by the act of transfer. The document indicated the amount of the drug under investigation, the batch 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 in accordance with the randomization scheme on 2, 4 and 6 visits in the amount necessary for treatment within 1 month. Patients brought all used and unused packaging materials, as well as unused tablets, to the clinic during each subsequent visit.

The researcher kept a journal of issuing/returning the drug under study. The journal indicated the quantity of the dispensed/returned drug, the date of issue/return, the patient's randomization number and initials, as well as the full name of the person who dispensed the drug.

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

9.4. Storage conditions

The study drug 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 who received the drug under study were instructed about its storage conditions.

10. TREATMENT

10.1. Treatment scheme.

Patients of the main and control groups received chemotherapy in accordance with international standards for the treatment of colorectal cancer according to the FOLFOX-4 scheme, starting from the 14th day after the operation with an interval of 14 days:

Oxaliplatin 85 mg/m^2 IV (1st day)

Leukovorin 200 mg/m^2 / day. IV (1st and 2nd days)

5-fluorouracil 400 mg/m^2 /day IV (1st 2nd days) by jet

5-fluorouracil 600 mg/m^2/day. intravenously for 22 hours (1st and 2nd days).

In addition, patients of the main group, on the background of chemotherapy, starting from the 14th day after the operation, received the research drug Donovit-VS® tablets produced by Astrapharm LLC, 1 tablet 3 times a day for 3 months.

Six courses of chemotherapy were planned for each patient. When carrying out each subsequent course of chemotherapy, we used standard criteria for the beginning and continuation of treatment: the content of leukocytes ≥2.0 x 10^9 cells/l, neutrophils ≥ 1.5 x10^9 cells/l; platelets ≥100x10^9 cells/l, hemoglobin level ≥100 g/l), transaminases do not exceed the ULN by more than 2.5 times; total bilirubin does not exceed the ULN by more than 1.5 times; creatinine does not exceed ULN by more than 1.25 times, diarrhea and stomatitis are absent or no more than 1st degree, second toxicity - no more than 2nd degree. If the above-mentioned criteria are not met, the chemotherapy was postponed until toxicity decreased to the 1st degree or canceled.

Patients who received less than 6 courses of chemotherapy continued to participate in the study, regardless of whether they were in the main or control group. The last, final visit was performed on the 90th day from the start of treatment, regardless of how many courses of CT the patient received.

10.2. Concomitant therapy

In order to prevent nausea and vomiting, premedication was carried out with antiemetic drugs, in particular 5-HT3 blockers, such as ondansetron, in combination with dexamethasone or methylprednisolone .

As concomitant therapy, patients were also prescribed hepatoprotectors and cardioprotectors according to indications.

In the process of research, it was also allowed to take drugs that are constantly taken by the patient 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 with an immunomodulating effect;
- immunosuppressors;

- biostimulants, bioinhibitors, adaptogens.

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

10.4. Control over the patient's compliance with the scheme of prescribing the drug under study .

Control over the patient's compliance with the prescription of the drug under study was carried out by the researcher 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 tablets, to the clinic during each visit. Data on each dispensing and return of the drug under study were entered in the journal of accounting for the drug under study.

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

$$Kat = \frac{(A - B)}{A} x\ 100\%$$

where:

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

B – is the number of returned tablets.

"Treatment adherence" 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 coefficient of "adherence to treatment" in all patients was more than 80%.

11. VARIABLE PERFORMANCE ASSESSMENTS

Main variable:

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

The toxicity of chemotherapy was evaluated according to the relevant clinical and laboratory indicators (for each one separately), such as: leukopenia, anemia, thrombocytopenia, impaired liver function, diarrhea, nausea, vomiting, condition of the oral cavity, skin manifestations, alopecia, disorders of cardiac activity, etc.

Secondary variable

- level of quality of life of the patient during treatment (according to the questionnaire of the European Organization for Research and Treatment of Cancer EORTC QLQ - C 30).

12. ASSESSMENT OF TOLERABILITY

12.1. List of tolerability indicators

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

- the presence and nature of adverse events, their connection with the drug under study;
- dynamics of vital indicators (blood pressure, heart rate, t body);
- dynamics of ECG data;
- dynamics of laboratory indicators.

12.2. Methods and terms of assessment of tolerability indicators

In the process of the study, careful monitoring of the patient's condition was carried out. For this purpose, during each visit, the researcher asked the patient questions about his well-being, performed a physical examination of the patient, measured blood pressure, heart rate, and body temperature. Diseases, signs or symptoms and/or abnormal laboratory parameters that were observed in the patient before inclusion in the study were not considered adverse reactions if they appeared during the trial, except for those cases when there was a deterioration in the intensity or frequency of their manifestation. Changes in laboratory indicators were considered undesirable phenomena if, according to the researcher, they were not a consequence of the applied chemotherapy.

The 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 participation in the study.

Information about all adverse events that occurred during the study, related and not related to protocol procedures, 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 was assessed: its duration, severity, severity, causality with the drug under study. 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 early 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	Description of the category
Good	During an objective examination, no pathological changes or clinically significant deviations are detected in the dynamics; the patient does not note the appearance of AE/AR.
Satisfactory	During an objective examination, insignificant changes are revealed in the dynamics, which are of a transient nature and do not require additional medical measures and/or insignificant 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 a AE/AR that has a significant negative impact on the patient's condition, requiring discontinuation of the drug and the use of additional medical measures.

13. SIDE EFFECTS/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 the drug, provided that there is at least a minimal probability of a causal relationship between the drug and the adverse reaction, i.e. . a relationship cannot be ruled out.

Adverse effect (AE) is any undesirable medical manifestation in the subject under investigation, which does not necessarily have a causal connection with the use of the drug (changes in laboratory data, symptoms or diseases that coincide in time with the use of the drug under investigation).

A serious adverse reaction or a serious adverse event *is* any undesirable medical manifestation during the use of the study drug (regardless of the dosage) that leads to: death, represents a threat to life, requires hospitalization or an increase in the duration of hospitalization; to long-term or significant loss of working capacity or disability; to congenital anomalies or developmental defects.

A non-serious adverse reaction is an unwanted reaction that does not fall under the category of serious.

Unanticipated adverse reaction – an adverse reaction, the nature or severity of which is not consistent with the available information about the medicinal product (with the investigator's brochure for an unregistered medicinal product or the package insert/summary for a registered medicinal product).

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

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

13.3. Relationship of AE/AR with the study drug

The assessment of the causal 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 inconsistency of the available data, as well as in those cases where they cannot be verified or supplemented;
- **absent** - undesirable clinical manifestation or changes in laboratory parameters are not associated with the use of the drug;
- **possible** - there is a certain temporal relationship with the use of the drug, however, the development of AE/AR can also be explained by a concomitant disease and/or the use of a second drug;

- **probable** - there is a certain temporal relationship with the use of the drug, however, the probability that the development of AE/AR is due to a concomitant disease and/or the use of a second drug is low;
- **Undoubted** - a 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. The outcome of AE/AR

- **convalescence without consequences** - the side effect stopped (symptoms are absent and the patient is not treated for the elimination of this AE/AR);
- **convalescence with consequences** - AE/AR was stopped, but its consequences remained;
- **no changes** - AE/AR did not disappear, symptoms persisted, despite the medical measures taken to eliminate it;
- **worsening** – there was an increase in the symptoms of AE/AR;
- **fatal outcome** - the patient died as a result of this AE/AR.
- **data are missing** - communication with the patient is 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 case of occurrence of AE/AR

In the event of an AE/AR, the investigator had to take measures of a medical nature to stop 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 during the period of the study, AE/AR were registered, it was necessary to monitor until the reaction or its clinically significant signs disappeared.

13.6. Messages about AE/AR

In the event of an unforeseen and/or serious AE/AR, the researcher had to notify the Research Sponsor within 24 hours by phone: (044) 537-78-41 and in writing by e-mail: agn1942@gmail.com . A full report containing all the details of the AE/AR

should be submitted within 5 days to the Sponsor and within 15 days to the Commission on Ethics at Treatment and Prevention Institution.

The researcher was also obliged to inform the Sponsor about all other AE/AR and/or deviations from the norm of laboratory indicators within 5 calendar days from the date when it became known to him.

In the event of the death of the subject or the occurrence of a threat to his life, as a result of taking the study drug, the researcher had to provide information to the Commission on Ethics at the Treatment and Prevention Institution within 7 calendar days from the date when it became known to him. Additional information regarding these cases should be provided to the Ethics Committee within the next 8 calendar days.

14. METHODS OF STATISTICAL DATA ANALYSIS

14.1. Justification of the number of subjects

This parallel, two-group trial with equal group sizes was conducted to prove the superior effectiveness of therapy including chemotherapy + Donovit-VS ® compared to a group of patients receiving only chemotherapy.

The planned test power is 80% (the probability of making a second-order error is 0.2), the two-sided probability of making a first-order error is 0.05.

In this test, the main variables are:

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

Since all the main variables assessing toxicity are quantitative, the following null hypothesis will be tested for each main variable to prove the higher efficiency (assuming that the data are normally distributed):

$$H_0 : \varepsilon \leq \delta \text{ vs } H_a : \varepsilon > \delta, \qquad (4)$$

where: $\delta \geq 0$, is the value of clinically significant differences, at which it can be considered that the treatment scheme, which includes CT+Donovit-VS®, exceeds in effectiveness only CT); ε — differences between groups, which are expected to be observed for this indicator. In the case of a quantitative main variable:

$\varepsilon = n_m$ (main group) – n_c (control group), (5)

where: n_m (main group) is the arithmetic mean of the corresponding main variable for the treatment scheme including Donovit-VS ®, and n_c (control group) is for the control group (without Donovit-VS ®).

It is assumed that any reduction in the level of toxicity in each of the main variables is clinically important. Then, in this study, to prove the higher efficiency in the main group compared to the control group, d was taken equal to 0 ($\delta = 0$).

According to [S.C. Chow, J. Shao, H.Wang. Sample Size Calculations in Clinical Research. — London: Taylor&Francis, 2003. — 358 p.], the sample size for the study of higher efficiency can be estimated using the following expression (for each main variable):

$$n_c = k \times n_m$$

$$n_{main} = \frac{(z_{\alpha/2} + z_{\beta})^2 \times \sigma^2 \times (1+1/k)}{(\varepsilon - \delta)^2} \quad (6)$$

where:

z_α и z_β — corresponding percentage points of SND;

δ — value of clinically important differences;

ε — differences between groups according to a certain main variable (difference of arithmetic means in groups under the assumption that the data are normally distributed);

σ^2 — variance;

k — coefficient for different number of patients in groups (subgroups);

n_m and n_c — the number of patients who are planned to be included in the main and control groups, respectively;

α — the limiting value of the error of the 1st kind (level of significance);

β — is 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 a is taken equal to 0.05 (5%).

The limiting value of the error of the second kind b = 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 — Initial data and sample size estimation results

Statistical indicator	Values
Level of significance α	0.05

Statistical indicator	Values
The value of β	0.2
SNR percentage point for α	1.96
SNR percentage point for β	0.84
The previously estimated standard deviation s	1.3*
The previously estimated variance σ^2	1.69
The value of δ	0
The value of ε	1
Calculated sample size	27
Corrected sample size taking into account the possible dropout of patients from the study	30
The standard deviation is taken on the basis of the 3s rule, based on the assumption that the scores will be normally distributed in the range from 0 to 4 points.	

Thus, to prove the higher efficiency of the treatment scheme used in the main group compared to the treatment scheme used in the control group according to the main variable (the level of CT toxicity for the corresponding clinical and laboratory indicators according to the CTC *NCIC* scale), it is enough to include 30 patients in each group

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

14.2 Plan of statistical analysis

— 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 effectiveness between groups;
— tolerability analysis;
— the number of undesirable/side effects;
— assessment of exceeding efficiency;
— statistical conclusions.

14.3. Analysis of the initial homogeneity of groups

Analysis of homogeneity of groups by age, sex, age, diagnosis, disease severity, concomitant diseases, 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 (M), median (Me), standard deviation (SD), minimum and maximum values; for categorical variables - frequency and proportion in percent).

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

— the hypothesis about the normality of the distribution of the 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 by categorical variables, they were compared using the Pearson chi-square test. If the prerequisites for applying the chi-square test were not met, then Fisher's exact test was used (checks the two-sided hypothesis).

d) Statistical conclusions are drawn regarding the initial homogeneity of the groups according to the specified variables.

14.4. Analysis of effectiveness in groups

a) For quantitative performance indicators, descriptive statistics (n, arithmetic mean, median, standard deviation, minimum and maximum values) were evaluated in each group for each visit.

To assess the dynamics of these indicators, variance analysis was performed using a mixed two-factor model (the dependent variable is the value of the analyzed indicator, the "visit" factor is fixed), the "subject" factor is random. Values at

visits, starting from the next one, were compared with the initial visit for the analyzed variable using a contrast analysis (simple contrasts were used, the initial level was the reference level). The normality of the distribution of variance analysis (VA) residues was checked. If the residuals were not 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 effectiveness between groups

a) For the main variable assessing toxicity (in points), a comparison between groups was performed at each corresponding visit (in accordance with the patient survey scheme) using the Mann-Whitney test or the Student test for independent samples, depending on the normality of the distribution of the compared data sets . Normality was tested using the Shapiro-Wilk test.

b) For other quantitative performance indicators (secondary variables, measured quantitatively), the groups were compared by $dT_{\text{examination i}} = T_{\text{visit i}} - T_{\text{visit 1}}$.
Individual differences $dT_{\text{visit i}}$ were calculated for each subject for each parameter .

If the groups did not differ statistically significantly in the initial state, then the groups were compared by $dT_{\text{visit i}}$ 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 by $dT_{\text{visit i}}$ into account possible initial differences between the groups, a covariance analysis was performed at each moment of time T_i according to the scheme: the dependent variable is dT_i for the corresponding parameter, the factor "Group" — fixed (levels: main and control), covariate — the value of this parameter at the moment of time $T_{\text{visit 1}}$. 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 covariance analysis was checked using the Shapiro-Wilk test. If the residuals are not distributed normally, then the specified analysis was performed in ranks. Conclusions are drawn regarding the differences between the groups.

14.6. Tolerability analysis

a) Results of laboratory tests (indicators of general blood analysis, general urine analysis, blood analysis of blood).

Indicators of descriptive statistics (n, arithmetic mean, median, standard deviation, minimum and maximum values) for each group and visit according to the patient survey scheme. The results for 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, in accordance with the patient survey scheme, and their dynamics in each group were estimated.

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

Indicators of descriptive statistics (n, arithmetic mean, median, standard deviation, minimum and maximum values) for each group and visit according to the patient survey scheme.

c) Data on AE/AR.

Indicators of descriptive statistics (frequency and share in percentages for each group).

d) General tolerance variable.

Indicators of descriptive statistics (frequency and share in percentages for each group).

14.7. Significance levels

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

14.8. Conclusion about the exceeding therapeutic efficiency

The conclusion about the greater effectiveness of therapy including the study drug (main group) compared to therapy without the study drug (control group) was made on the basis of the presence of statistically significant differences when comparing the main variables assessing the degree of toxicity.

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

Patients who took 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 "prohibited" concomitant therapy, etc.) were not included in the efficacy analysis. The tolerability analysis included all patients who took at least one dose of 1 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, with the aim of ensuring their integrity and validity. For this purpose, 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 with the help of built-in means of statistical analysis of electronic spreadsheets in Microsoft Excel and the SPSS 13.1 application program package.

15. RESEARCH RESULTS AND THEIR DISCUSSION

15.1. Description of patients included in the study

60 patients diagnosed with: rectal cancer, disease stage $T_{2-4} N_{0-2} M_{0}$ took part in the study ; colon cancer, disease stage $T_{2-4} N_{1-2} M_{0}$. The presence of a tumor in all patients was verified by MRI or CT before the start of treatment. All patients underwent radical surgical resection of the tumor. The diagnosis in all patients was confirmed by morphological research data.

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

All patients included in the study had a functional status according to ECOG from 0 to 2 points and an expected 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: the main or control group, 30 patients each. The scheme of randomization is given in Appendix A, table. A.1.

Patients of the main and control groups, starting from the 14th day after the operation, received chemotherapy according to the FOLFOX-4 scheme, in the form of 6 courses with an interval of 14 days. In addition, the patients of the main group, starting from the 14th day after the operation, received the research drug Donovit-VS®, tablets manufactured by Astrapharm LLC, 1 tablet 3 times a day for 3 months.

The average number of courses received by patients during this study was 5.93 in the main group and 5.87 in the control group. The reduction in the duration of treatment in 2 patients of the control group was due to the toxicity of chemotherapy (No18 - thrombocytopenia of the 2nd degree after the 4th course of chemotherapy; No26 - diarrhea of the 2nd degree, nausea and vomiting during treatment). In the main group, the reduction in the duration of treatment in 1 patient (No 07) was caused by the refusal to continue treatment after the 4th course of chemotherapy.

The study included patients aged 39 to 69 years (M = 56.8±8.9) with a body weight of 54 to 112 kg (M = 74.6±15.8). 36 (60.0%) men and 24 (40.0%) women were included in the study. The description of patients by age and body weight is given in the **table. 7**.

Table 7 - Characteristics of patients by age and body weight

Parameter*	n	M	Me	SD	MIN	MAX
Age, years	60	56.8	55	8,899	39	69
Body weight, kg*	60	74.6	76	15,819	54	112

15.2. Number of analyzed patients

In this study, there were no cases of patients dropping out of the study due to a serious or unexpected adverse reaction or for any other reason.

Patients who received less than 6 courses of chemotherapy continued to participate in the study, regardless of whether they were in the main or control group.

The last, final visit was performed on the 90th day from the start of treatment, regardless of how many courses of CT the patient received.

All randomized patients completed the study according to the protocol. 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 17 men and 13 women, the control group - 19 men and 11 women. Indicators of descriptive statistics (frequency and share in %), showing the distribution of groups by gender and the results of checking the significance of differences between groups are shown in **Table 8**. The significance of differences between groups was tested using the Pearson chi-square test with Yates correction (see **Table 9**).

Table 8. Distribution of subjects by gender (abs/%)

gender	The main group n=30		Control group n=30	
	n	%	n	%
Male	17	56.7	19	63.3
Female	thirteen	43.3	11	36.7
In total	30	100.0	30	100.0

Table 9. Results of comparison of groups by gender using Pearson's chi-square test

Statistical indicator	Significance
The calculated value of the chi-square criterion	0.069
The number of degrees of freedom	1
Default significance level (alpha)	0.05
The critical value of the chi-square criterion	3.84
Significance level reached (p)	0.7921

Conclusion According to the results of the Pearson chi-square test (Table 9), it can be concluded that the compared groups did not differ statistically significantly by gender ($p = 0.7921$) **.**

The average age of patients in the main group was 56.52 years, in the control group - 57.11 years.

The assessment of the distribution of patients in groups by age categories, using the methods of descriptive statistics, is given in **Table 10**.

Table 10. Distribution of examinees by age category, abs/%

Age, years	The main group n = 30	Control group n = 30
30-39	0	1 (3.3%)
40-49	4 (13.3%)	4 (13.3%)
50-59	8 (26.7%)	5 (16.7%)
60-70	18 (60.0%)	20 (66.7%)

As follows from the data presented in **Table 10**, the largest share in both groups (more than 60%) was made up of subjects over the age of 60.

Analysis of the patients included in the analysis by age and body weight at the time of inclusion in the study using methods of descriptive statistics (n, arithmetic mean, median, standard deviation, minimum and maximum) is shown in **Table 11**. The results of checking the normality of the data distribution using the Shapiro-Wilk test are given in **Appendix A, table. A.2**.

Table 11. Results of a 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	The main group	30	56,52	55	6,550	43	69
	Control group	30	57,11	58	7,314	39	69
Body weight (kg)	The main group	30	73.95	75	12,079	53	98
	Control group	30	75.24	76	17,890	54	112

To compare groups by age and body weight, the Student's test for independent samples was used (**Table 12**), since the data were distributed normally in both groups (**Appendix A, Table A2).**

Table 12. Results of comparison of groups by age and body mass using Student's criterion for independent samples

Indicator	t-statistics	df	p-value	Difference of mean	Conclusion on homogeneity of groups*
Age	-0.329	58	0.743	-0.59	homogeneous
Body mass	-0.327	58	0.745	-1.29	homogeneous
** At a significance level of 0.05.*					

Thus, the main group included patients aged 43 to 69 years (M = 56.5 years; SD = 6.5 years), with a body weight of 53 kg to 98 kg (M = 73.9 kg; SD = 12 ,1 kg).

The control group included patients aged 39 to 69 years (M = 57.1 years; SD = 7.3 years), with a body weight of 54 kg to 112 kg (M = 75.2 kg; SD = 17, 9 kg).

Conclusion Based on the results of the analysis, it can be concluded that the groups did not differ statistically significantly in terms of gender, age and body weight.

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

All patients were diagnosed with rectal cancer, disease stage T_{2-4} $N_{0-2}M_{0}$ or colon cancer, disease stage T_{2-4} N_{1-2} M_0. The distribution of patients in groups depending on tumor localization is presented in **Table 13**.

Table 13. Distribution of patients depending on tumor localization in groups (abs. number, %)

Localization	Main group (n = 30)	Control group (n = 30)	P-value*
The rectum	6 (20.0%)	8 (26.7%)	0.7602
Transverse colon	24 (80.0%)	22 (73.3%)	
** Estimated using Pearson's chi-square test with correction for Yates continuity.*			

As can be seen from Table 13, the majority of patients had a tumor of the colon, while no significant differences between the compared groups were revealed.

All patients, prior to inclusion in the study, underwent radical removal of rectal and colon tumors.

The general condition of the patients before treatment corresponded to 1-2 points on the ECOG scale. Patients led a normal, physically active lifestyle, cared for themselves independently.

Characteristics of the general condition of patients according to the ECOG scale are presented in **Table 14**.

Table 14. Characteristics of the general condition of patients according to the ECOG scale before treatment (abs. number, %)

General condition (points)	The main group (n = 30)	Control group (n = 30)	P-value*
0	-	-	0.4376
1	14 (46.7%)	18 (60.0%)	
2	16 (53.3%)	12 (40.0%)	
3	-	-	
4	-	-	
**The comparison was made using the Pearson chi-square test*			

Conclusion According to the results of the statistical analysis of the data shown in the **table. 13-14** , it is possible to state that initially the groups did not statistically significantly differ in terms of nosological forms, severity of the disease and general condition.

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

Before the beginning of the study, an objective examination of the subjects was conducted, including 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 testified to the absence of exacerbation of chronic diseases, preventing the participation of the subjects in the study. Hemodynamic parameters (heart rate, blood pressure) of both groups of subjects were within the age norm or slightly exceeded the norm. The nature of the accompanying pathology ruled out the possibility of a significant influence on the result of the study.

Hemodynamic parameters and body t did not differ significantly between groups of patients before treatment. The results of the comparative analysis of the groups

before treatment according to these parameters by methods of descriptive statistics are shown in **Table 15.**

Table 15. The results of the analysis of the initial homogeneity of the groups according to the parameters of blood pressure, heart rate, and body t using the methods of descriptive statistics

Indicator	Group	n	M	Me	CO	MIN	MAX
SBR, mm Hg Art.	The main group	30	134.45	135	9,114	110	145
	Control group	30	136.28	132	9,503	110	145
DBP, mm Hg Art.	The main group	30	81.72	80	5,224	70	90
	Control group	30	81.69	82	5,558	65	90
Heart rate, beats/min.	The main group	30	77.32	78	5,248	62	87
	Control group	30	75.34	75	5,404	66	89
t body (°C)	The main group	30	36.72	36.6	0.303	36.0	37.1
	Control group	30	36.84	36.7	0.287	36.1	37.0

Since the SBP, DBP, heart rate, and body temperature data were normally distributed (**Appendix A, table A.3**), the Student's criterion for independent samples was used to compare groups according to these parameters (**table 16**).

Table 16. Results of comparing groups by heart rate using Student's criterion for independent samples

Indicator	t-statistics	df	p-value	Difference of mean	Conclusion on homogeneity of groups*
SBR	-0.761	58	0.449	-1.83	homogeneous
DBR	0.021	58	0.983	0.03	homogeneous
heart rate	1,439	58	0.155	1.98	homogeneous
t bodies	-1.575	58	0.121	-0.12	homogeneous

** At a significance level of 0.05.*

Conclusion Based on the results of the analysis presented in **table. 16**, it is possible to state 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 based on ECG data

According to the protocol, all patients included in the study underwent a standard 12-lead ECG examination. Changes were observed in some patients according to ECG data: signs of left ventricular hypertrophy, diffuse-dystrophic

changes in the myocardium. The results of the analysis of the distribution of patients with the presence/absence of pathology according to the ECG data in groups using the methods of descriptive statistics are shown in the **table** 17.

Table 17. Distribution of patients in groups according to the presence of pathology according to ECG data

Diagnostic criterion	Presence of pathology	The main group n=30		Control group n=30		p-value*
		n	%	n	%	
ECG results	No	21	70.0	24	80.0	0.5510
	There is	9	30.0	6	20.0	
	In total	30	100	60	100	
* Estimated using Pearson's chi-square test with correction for Yates continuity.						

Conclusion According to the results of the statistical analysis of the data shown in the **table. 17**, it can be stated that initially the groups did not statistically significantly differ in the presence of cardiovascular pathology according to ECG data.

15.3.5 Analysis of initial homogeneity of groups according to laboratory parameters of general blood analysis

Before the start of the treatment course, the patients underwent a general blood analysis for the following parameters: erythrocytes, hemoglobin, hematocrit, leukocytes, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and ESR. In the majority of patients, in both groups, the analyzed laboratory parameters were within normal values. In some patients, the laboratory indicators slightly deviated from the norm, but these deviations were determined as clinically insignificant. All observed deviations of laboratory indicators from normal values did not contradict the inclusion/non-inclusion criteria in this study.

The results of the comparative analysis of the parameters of the general blood analysis in the groups using the methods of descriptive statistics are shown in **table 18.** .

Table 18. The results of the comparative analysis of the groups in the initial state according to the parameters of the general blood analysis using the methods of descriptive statistics

Parameter	Group	n	M	Me	SD	MIN	MAX
Leukocytes, $x10^9$ cells/l	The main group	30	6.26	6.4	2,302	3.6	11.2
	Control group	30	6.65	6,7	2,170	3.8	9.7

Parameter	Group	n	M	Me	SD	MIN	MAX
Erythrocytes, x10^{12} cells/l	The main group	30	4.46	4.5	0.357	3.76	4.85
	Control group	30	4.50	4.5	0.378	3.82	4.78
Hematocrit, %	The main group	30	39.98	40.1	2,515	34.8	44.6
	Control group	30	41,18	42.0	2,609	35.3	45.2
Hemoglobin, g/l	The main group	30	129.78	130	13,782	103	146
	Control group	30	128.63	128	12,404	102	140
Platelets, ×10^9 cells/l	The main group	30	238.11	240	50,855	128	311
	Control group	30	235.48	232	47,368	135	278
Neutrophils, %	The main group	30	62.89	63.2	7,169	46.2	69.6
	Control group	30	64.52	65.5	9,337	45.7	85.2
Lymphocytes, %	The main group	30	26,47	26.5	2,421	21.1	29.7
	Control group	30	25,20	24.7	2,892	19.4	32.8
Monocytes, %	The main group	30	4.96	5.1	1,066	4.0	7.5
	Control group	30	5.05	5.2	0.895	3,4	6.4
Eosinophils, %	The main group	30	2.48	2.5	0.428	1.7	3.3
	Control group	30	2.37	2,3	0.363	1.5	2.8
Basophils, %	The main group	30	0.45	0.52	0.322	0.2	1.4
	Control group	30	0.43	0.46	0.280	0.3	0.8
ESR, mm/h	The main group	30	16.9	17	5,262	10	29
	Control group	30	17.5	17	4,970	8	26

According to the results of checking the normality of data distribution (**Appendix A, table A.3**), the Student's criterion for independent samples was used to compare the groups in the initial state according to the parameters of the general blood analysis (**table 19**).

Table 19. The results of the comparison of groups in the initial state according to the parameters of the general blood analysis using the Student's criterion for independent samples

variable	Difference of mean	t	df	p-value	Conclusion on homogeneity of groups*
Leukocytes, x10^9 cells/l	-0.39	0.675	58	0.502	homogeneous
Erythrocytes, x10^{12} /l	-0.04	0.421	58	0.675	homogeneous
Hematocrit, %	-1.20	1,814	58	0.075	homogeneous
Hemoglobin, g/l	1.15	0.339	58	0.735	homogeneous

variable	Difference of mean	t	df	p-value	Conclusion on homogeneity of groups*
Platelets, $\times 10^9$ cells/l	2.63	0.207	58	0.836	homogeneous
Neutrophils, %	-1.63	0.758	58	0.451	homogeneous
Lymphocytes, %	1.27	1,844	58	0.070	homogeneous
Monocytes, %	-0.09	0.354	58	0.725	homogeneous
Eosinophils, %	0.11	1,242	58	0.219	homogeneous
Basophils, %	0.02	0.257	58	0.798	homogeneous
ESR, mm/h	-0.60	0.454	58	0.652	homogeneous
** The conclusion is made at a significance level of 0.05.*					

Conclusion According to the data presented in **table 19**, it is possible to state that the groups, in the initial state, according to the parameters of the general blood analysis (erythrocytes, hemoglobin, hematocrit, leukocytes, platelets, neutrophils, lymphocytes, monocytes, eosinophil's, basophils, and ESR), are not statistically significant differed - were homogeneous .

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

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

The results of a comparative analysis of patients in groups according to indicators of biochemical blood analysis by methods of descriptive statistics are shown in **table 20**.

Table 20. The results of the comparative analysis of the groups in the initial state according to the indicators of biochemical blood analysis using the methods of descriptive statistics

Parameter	Group	n	M	Me	SD	MIN	MAX
ALT, Un/l	The main group	30	24.49	25	3,884	19	34
	Control group	30	26.07	26	4,094	21	39
AST, Un/l	The main group	30	25,33	25	3,665	21	34
	Control group	30	27,19	28	3,673	20	36

Parameter	Group	n	M	Me	SD	MIN	MAX
Total bilirubin, μmol/l	The main group	30	15.43	15.5	1,787	10.7	17.8
	Control group	30	16.04	16.1	1,345	14.4	19.3
Creatinine, μmol/l	The main group	30	73.4	72	12,712	52	96
	Control group	30	72.8	74	11,689	50	88
Glucose, mmol/l	The main group	30	5.13	5.3	0.488	4.2	5.9
	Control group	30	4.92	5.0	0.502	4.0	6.1

According to the results of checking the normality of data distribution (**Appendix A, table A.3**), the Student's criterion for independent samples was used to compare groups in the initial state according to indicators of biochemical blood analysis (**table 21**).

Table 21- Results of comparison of groups in the initial state according to indicators of biochemical blood analysis using the Student's criterion for independent samples

variable	Difference of mean	t	df	p-value	Conclusion on homogeneity of groups*
ALT, Un/l	-1.58	1,534	58	0.131	homogeneous
AST, Un/l	-1.86	1,963	58	0.054	homogeneous
Total bilirubin, μmol/l	-0.61	1,494	58	0.141	homogeneous
Creatinine, μmol/l	0.60	0.190	58	0.849	homogeneous
Glucose, mmol/l	0.21	1,643	58	0.106	homogeneous
* *The conclusion is made at a significance level of 0.05.*					

Conclusion According to the data presented in **table 21**, it is possible to state 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 indicators 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 22** . In all patients, in both groups, analyzed laboratory parameters were within normal values.

Table 22 - The results of the comparative analysis of the groups according to the laboratory indicators of the general analysis of urine by the methods of descriptive statistics

Parameter	Group	n	M	Me	SD	MIN	MAX
Specific weight	The main group	30	1015.5	1015	3,359	1012	1018
	Control group	30	1017.0	1018	3,509	1012	1019
pH	The main group	30	5.40	5.5	0.178	5.2	5.5
	Control group	30	5.32	5,6	0.192	5.1	5.5
Leukocytes, cells in sight	The main group	30	3.5	4	1,450	0	5
	Control group	30	3.3	3	1,651	0	6
Erythrocytes, cells in sight	The main group	30	1.0	1	1,264	0	4
	Control group	30	0.9	1	1,119	0	3
Protein, g/l	The main group	30	0	-	-	0	0
	Control group	30	0	-	-	0	0
Glucose, %	The main group	30	0	-	-	0	0
	Control group	30	0	-	-	0	0
Epithelial, cells in sight	The main group	30	0	-	-	0	0
	Control group	30	0	-	-	0	0
Cylinders, cells in sight	The main group	30	0	-	-	0	0
	Control group	30	0	-	-	0	0
Soli	The main group	30	0	-	-	0	0
	Control group	30	0	-	-	0	0

As can be seen from the **table. In all 22** patients, protein, glucose, epithelium and cylinders, and salts were absent in the urine. Therefore, according to these laboratory indicators, the groups are considered homogeneous, and further comparison of the groups was not carried out.

Since the data of other laboratory parameters (specific gravity, pH, leukocytes and erythrocytes) were distributed normally in the groups (**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 23**).

Table 23 - Results of applying the Student's test for independent samples to compare groups on some laboratory indicators of general urinalysis

Parameter	t	df	p-value	Difference of mean	Conclusion on homogeneity of groups*
Specific weight	1,691	58	0.096	-1.50	homogeneous
pH	1,674	58	0.099	0.08	homogeneous
Leukocytes	0.499	58	0.620	0.20	homogeneous
Erythrocytes	0.325	58	0.747	0.10	homogeneous
** At a significance level of 0.05.*					

Conclusion According to the data presented in the **table. 23** it is possible to state that the groups, in the initial state, did not differ statistically significantly according to the parameters of the general analysis of urine (specific gravity, pH, protein, glucose, epithelial cells, leukocytes, erythrocytes, cylinders, salts) - they 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 the screening (Dsc) and then at each visit, the patient's heart rate, blood pressure, body temperature were measured. Hemodynamic indicators, during the treatment, were within normal values or slightly deviated from the norm in all patients of both groups. Body temperature also did not exceed 37.0°C in most patients of both groups throughout the study, with the exception of 2 patients of the main group and 3 patients of the control group, whose temperature rose above 37.0°C

The results of the descriptive analysis of these parameters in groups are shown in the **table. 24** for the main group and **table. 25** for the control group.

Table 24 - 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, mm Hg	Dsc	30	134.45	135	9,114	110	145
	D14	30	128.91	130	13,398	110	135
	D28	30	129.35	130	13,333	110	135
	D42	30	132.27	130	12,515	110	135
	D56	30	132.92	134	12,898	110	140
	D70	30	130.33	130	12,279	105	140
	D90	30	128.24	130	13,260	110	145
DBR, mmHg	Dsc	30	81.72	80	5,224	70	90
	D14	30	78.45	80	5,964	65	90
	D28	30	82.64	82	6,441	70	90
	D42	30	80.85	80	6,301	75	88
	D56	30	81.52	80	6,169	75	90
	D70	30	80.32	80	6,160	74	88
	D90	30	79.65	80	6,091	72	90
Heart rate, beats/min.	Dsc	30	77.32	78	5,248	62	87
	D14	30	75.23	76	7,412	66	86
	D28	30	74.45	75	7,181	64	86
	D42	30	73.51	72	7,031	62	88
	D56	30	75.38	75	7,318	62	86
	D70	30	74.53	75	7,215	60	85
	D90	30	76.32	76	6,845	65	88
Body temperature, °C	Dsc	30	36.72	36.6	0.303	36.0	37.1
	D14	30	36.61	36.6	0.334	36.5	37.1
	D28	30	36.78	36.7	0.429	36.4	37.2
	D42	30	36,67	36.7	0.441	36.6	38.1
	D56	30	36.65	36.6	0.428	36.5	37.2
	D70	30	36.68	36.6	0.393	36.4	37.3
	D90	30	36.66	36.6	0.376	36.4	37.2

Table 25 - 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	136.28	132	9,503	110	145
	D14	30	130.85	130	10,665	110	140
	D28	30	129.72	130	12,297	110	135
	D42	30	130.44	132	12,602	110	140
	D56	30	132.25	134	12,563	110	145
	D70	30	130.46	132	11,658	105	140
	D90	30	129.21	130	13,210	105	140

DBR, mmHg	Dsc	30	81.69	82	5,558	65	90
	D14	30	80.45	80	6,146	65	90
	D28	30	83.16	85	6,765	70	90
	D42	30	81,83	82	6,080	70	90
	D56	30	82.32	82	6,265	75	95
	D70	30	81.44	80	6,707	74	88
	D90	30	80.27	80	6,309	72	90
Heart rate, beats/min.	Dsc	30	75.34	75	5,404	66	89
	D14	30	73.63	72	7,272	62	88
	D28	30	75.40	75	7,619	64	85
	D42	30	73.62	75	6,961	60	86
	D56	30	75.31	76	7,283	62	85
	D70	30	75.24	75	6,789	62	85
	D90	30	75,82	75	6,759	65	86
Body temperature, °C	Dsc	30	36.84	36.7	0.287	36.1	37.0
	D14	30	36.64	36.6	0.348	36.6	37.0
	D28	30	36.68	36.7	0.353	36.5	37.2
	D42	30	36.89	36.8	0.423	36.4	38.0
	D56	30	36.81	36.8	0.437	36.6	37.2
	D70	30	36.78	36.8	0.431	37.6	37.2
	D90	30	36.84	36.8	0.438	37.6	37.1

To assess the dynamics of hemodynamic indicators and body temperature, a variance analysis (DA) 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 is random) . The results of VA are shown in the **table. 26**.

A comparison of the following levels of the "time" factor with the initial data (Dsc) was also made using a contrast analysis (**tables 27-28**). The normality of the distribution of DA residues was checked using the Shapiro-Wilk test (**Table A.5, Appendix A**).

Table 26. The main results of DA hemodynamic indicators and body temperature

Dependent variable	Factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
The main group						
SBR	Visit	977,362	6	162,894	4,081	0.001
	Patients	25920.767	29	893,820	22,390	0.000
DBR	Visit	336,781	6	56,130	3,965	0.001
	Patients	5390,329	29	185,873	13,128	0.000
heart rate	Visit	288,267	6	48,044	7,102	0.000
	Patients	10112,138	29	348,694	51,542	0.000
Body temperature	Visit	0.507	6	0.084	2,513	0.023
	Patients	26,600	29	0.917	27,306	0.000

Control group						
SBR	Visit	1030,933	6	171,822	3,154	0.006
	Patients	21484.952	29	740,860	13,600	0.000
DBR	Visit	183,495	6	30,583	2,016	0.066
	Patients	5644,481	29	194,637	12,827	0.000
heart rate	Visit	147,248	6	24,541	2,965	0.009
	Patients	9441,352	29	325,564	39,334	0.000
Body temperature	Visit	1,491	6	0.248	7,036	0.000
	Patients	25,943	29	0.895	25,336	0.000

Table 27 - Results of contrast analysis of hemodynamic indicators and body temperature in the main group

Dependent variable	Contrasts	Estimated contrast	Stand. mistake	p-value
SBR	D14 - Dsc	-5,567	1,631	0.001*
	D28 - Dsc	-5.067		0.002*
	D42 - Dsc	-2,200		0.179
	D56 - Dsc	-1,600		0.328
	D70 - Dsc	-4,200		0.011*
	D90 - Dsc	-6,300		0.000*
DDR	D14 - Dsc	-3,167	0.972	0.001*
	D28 - Dsc	0.933		0.338
	D42 - Dsc	-0.833		0.392
	D56 - Dsc	-0.167		0.864
	D70 - Dsc	-1,400		0.151
	D90 - Dsc	-1.967		0.044*
heart rate	D14 - Dsc	-2.033	0.672	0.003*
	D28 - Dsc	-2,800		0.000*
	D42 - Dsc	-3,800		0.000*
	D56 - Dsc	-1,900		0.005*
	D70 - Dsc	-2.767		0.000**
	D90 - Dsc	-0.933		0.166
Body temperature	D14 - Dsc	-0.100	0.047	0.036
	D28 - Dsc	0.067		0.161
	D42 - Dsc	-0.040		0.399
	D56 - Dsc	-0.063		0.183
	D70 - Dsc	-0.030		0.527
	D90 - Dsc	-0.053		0.261
** Statistically significant differences are observed*				

Table 28 - Results of contrast analysis of hemodynamic indicators and body temperature in the control group

Dependent variable	Contrasts	Estimated contrast	Stand. mistake	p-value
SBR	D14 - Dsc	-5,433	1,906	0.005*
	D28 - Dsc	-6,600		0.001*
	D42 - Dsc	-5,800		0.003*
	D56 - Dsc	-4,033		0.036*
	D70 - Dsc	-5,800		0.003*
	D90 - Dsc	-7,100		0.000*
DBR	D14 - Dsc	-1.233	1.006	0.222
	D28 - Dsc	1,500		0.138
	D42 - Dsc	0.133		0.895
	D56 - Dsc	0.600		0.552
	D70 - Dsc	-0.267		0.791
	D90 - Dsc	-1,400		0.166
heart rate	D14 - Dsc	-1,700	0.743	0.023*
	D28 - Dsc	0.133		0.858
	D42 - Dsc	-1.667		0.026*
	D56 - Dsc	0.033		0.964
	D70 - Dsc	-0.067		0.929
	D90 - Dsc	0.533		0.474
Body temperature	D14 - Dsc	-0.197	0.049	0.000*
	D28 - Dsc	-0.160		0.001*
	D42 - Dsc	0.053		0.273
	D56 - Dsc	-0.027		0.583
	D70 - Dsc	-0.057		0.244
	D90 - Dsc	0.0001		1,000
** Statistically significant differences are observed*				

Conclusion: As can be seen from the conducted analysis, hemodynamic indicators in most cases did not change during the observation process in both studied groups of patients. Minor fluctuations in blood pressure, heart rate, and body temperature were noted at different stages of observation, but they were not clinically significant. This indicates the absence of a negative influence of the therapy on hemodynamic indicators and body temperature.

15.4.2. Analysis of the dynamics of general blood analysis indicators

General blood analysis was carried out during screening (Dsc), and then at points D14, D28, D42, D56, D70 and D90.

The results of the analysis of the dynamics of the indicators of the general blood analysis are shown in the **table. 29** for the main group and in **table. 30** for the comparison group.

Table 29. Dynamics of general blood analysis indicators in the process of research in patients of the main group

Indicator	time	n	M	Me	SD	MIN	MAX
Leukocytes, x10 ^{9} cells/l	Dsc	30	6.26	6.4	2,302	3.6	11.2
	D14	30	5.68	5.8	1,862	3.6	7.9
	D28	30	5.32	5.5	1,663	3.6	7.4
	D42	30	5.18	5.1	1,470	3,4	6.8
	D56	30	4.58	4.6	1,352	3.2	6.2
	D70	30	4.64	4.8	1,390	3.2	6.4
	D90	30	4.62	4.6	1,272	3,4	5.8
	[D14 – Dsc]	30	-0.58	-0.6	2,430	0	-3.3
	[D28 – Dsc]	30	-0.94	-0.9	2,012	0	-3.8
	[D42 – Dsc]	30	-1.08	-1.3	2,709	-0.2	-4.4
	[D56 – Dsc]	30	-1.68	-1.8	2,227	-0.4	-5
	[D70 – Dsc]	30	-1.62	-1.6	2,311	-0.4	-4.8
	[D90 – Dsc]	30	-1.64	-1.8	2,326	-0.2	-5.4
Erythrocytes, x10^{12} cells/l	Dsc	30	4.46	4.5	0.357	3.76	4.85
	D14	30	4.28	4.3	0.320	3.62	4.70
	D28	30	4.14	4.2	0.312	3.53	4.13
	D42	30	4.00	4.1	0.326	3.51	4.26
	D56	30	3.95	4.2	0.372	3.52	4.45
	D70	30	3.94	4.0	0.344	3.55	4.23
	D90	30	3.92	4.0	0.369	3.50	4.32
	[D14 – Dsc]	30	-0.18	-0.2	0.567	-0.14	-0.15
	[D28 – Dsc]	30	-0.32	-0.3	0.931	-0.23	-0.72
	[D42 – Dsc]	30	-0.46	-0.4	0.938	-0.25	-0.59
	[D56 – Dsc]	30	-0.51	-0.3	0.587	-0.24	-0.4
	[D70 – Dsc]	30	-0.52	-0.5	1,012	-0.21	-0.62
	[D90 – D0]	30	-0.54	-0.5	1,092	-0.26	-0.53
Hematocrit,%	Dsc	30	39.98	40.1	2,515	34.8	44.6
	D14	30	37,58	39.8	2,501	34.6	42.8
	D28	30	37,19	38.0	2,448	35.7	42.8
	D42	30	36,44	36.5	2,607	33.4	43.3
	D56	30	36.88	36.9	2,458	32.7	43.9
	D70	30	35.08	35.2	2,559	34.2	42.2
	D90	30	36,17	36.4	2,648	34.4	44.9
	[D14 – Dsc]	30	-2.4	-0.3	1,038	-0.2	-1.8
	[D28 – Dsc]	30	-2.79	-2.1	1,335	0.9	-1.8
	[D42 – Dsc]	30	-3.54	-3.6	1,289	-1.4	-1.3
	[D56 – Dsc]	30	-3.1	-3.2	1,236	-2.1	-0.7
	[D70 – Dsc]	30	-4.9	-4.9	1,033	-0.6	-2.4
	[D90 – Dsc]	30	-3.81	-3.7	1,126	-0.4	0.3
Hemoglobin, g/l	Dsc	30	129.78	120	13,335	103	146
	D14	30	127.76	120	13,369	103	144
	D28	30	123.02	118	13,103	102	131

	D42	30	119.89	118	13,217	105	139
	D56	30	115.60	116	13,227	100	135
	D70	30	112.07	115	12,489	100	130
	D90	30	112.23	114	12,864	100	131
	[D14 – Dsc]	30	-2.02	0	1,902	0	-5
	[D28 – Dsc]	30	-6.76	-6	5,511	-1	-10
	[D42 – Dsc]	30	-9.89	-2	6,356	2	-12
	[D56 – Dsc]	30	-14,18	-15	5,348	-3	-18
	[D70 – Dsc]	30	-17.71	-20	7,222	-3	-20
	[D90 – Dsc]	30	-17.55	-20	9,097	-3	-20
Platelets, $\times 10^9$ cells/l	Dsc	30	238.11	240	50,855	128	311
	D14	30	223.02	226	46,358	164	305
	D28	30	215.04	220	47,609	157	305
	D42	30	213.91	218	41,330	135	263
	D56	30	210.82	214	42,783	99	247
	D70	30	197.90	205	40,337	98	249
	D90	30	195.84	202	38,480	100	230
	[D14 – Dsc]	30	-15.09	-14	8,795	36	-6
	[D28 – Dsc]	30	-23.07	-20	9,448	29	-6
	[D42 – Dsc]	30	-24.2	-22	10,479	7	-48
	[D56 – Dsc]	30	-27.29	-26	11,444	-29	-64
	[D70 – Dsc]	30	-40,21	-35	10,690	-30	-62
	[D90 – Dsc]	30	-42.27	-38	12,354	-28	-81
Neutrophils,%	Dsc	30	62.89	63.2	7,169	46.2	69.6
	D14	30	61.94	62.1	6,727	44.3	68.3
	D28	30	61.55	60.8	6,440	43.8	67.6
	D42	30	60,90	59.0	6,316	40.4	67.6
	D56	30	60.02	58.7	6,190	40.9	67.5
	D70	30	59.84	58.3	6,880	40.6	66.7
	D90	30	58,31	58.1	6,946	40.2	66.1
	[D14 – Dsc]	30	-0.95	-1.1	0.891	-1.3	-1.9
	[D28 – Dsc]	30	-1.34	-2.4	0.985	-2.0	-2.4
	[D42 – Dsc]	30	-1.99	-4.2	2,179	-2.0	-5.8
	[D56 – Dsc]	30	-2.87	-4.5	1,747	-2.1	-5.3
	[D70 – Dsc]	30	-3.05	-4.9	1,445	-2.9	-5.6
	[D90 – Dsc]	30	-4.58	-5.1	1,809	-3.5	-6.0
Lymphocytes, %	Dsc	30	26,47	26.5	2,421	21.1	29.7
	D14	30	26.86	26.7	2,883	18.5	30.6
	D28	30	27,31	27.5	3,113	18.6	31.5
	D42	30	26.95	27.1	2,907	18.4	32.1
	D56	30	27.40	27.6	3,240	19.8	31.5
	D70	30	28.79	28.9	3,054	19.9	30.1
	D90	30	29.43	29.6	3,359	18.2	32.3
	[D14 – Dsc]	30	0.39	0.2	1,218	-2.6	0.9
	[D28 – Dsc]	30	0.84	1.0	2,060	-2.5	1.8

	[D42 – Dsc]	30	0.48	0.6	1,591	-2.7	2.4
	[D56 – Dsc]	30	0.93	1.1	1,169	-1.3	1.8
	[D70 – Dsc]	30	2.32	2.4	0.897	-1.2	0.4
	[D90 – Dsc]	30	2.96	3.1	1,420	-2.9	2.6
Monocytes, %	Dsc	30	4.96	5.1	1,066	4.0	7.5
	D14	30	4.91	5.0	1,217	3.2	8.2
	D28	30	5.22	5.3	1,226	3.8	8.3
	D42	30	4.91	4.9	1,136	2.8	8.0
	D56	30	5.03	5.1	1,159	3.2	8.1
	D70	30	5.16	5.2	1,106	3.5	7.9
	D90	30	5.04	5.0	1,312	3,4	8.2
	[D14 – Dsc]	30	-0.05	-0.1	0.379	-0.8	0.7
	[D28 – Dsc]	30	0.26	0.2	0.464	-0.2	0.8
	[D42 – Dsc]	30	-0.05	-0.2	0.324	-1.2	0.5
	[D56 – Dsc]	30	0.07	0	0.492	-0.8	0.6
	[D70 – Dsc]	30	0.2	0.1	0.345	-0.5	0.4
	[D90 – Dsc]	30	0.08	-0.1	0.355	-0.6	0.7
Eosinophils, %	Dsc	30	2.48	2.5	0.428	1.7	3.3
	D14	30	2.31	2.4	0.537	1,2	4.1
	D28	30	2.97	3.0	0.602	1,2	4.5
	D42	30	2.85	2.9	0.677	1.4	5.3
	D56	30	2.30	2.5	0.590	1.0	5.2
	D70	30	2.23	2.4	0.474	1.1	4.7
	D90	30	2.34	2,3	0.460	1.4	4.8
	[D14 – Dsc]	30	-0.17	-0.1	0.432	-0.5	0.8
	[D28 – Dsc]	30	0.49	0.5	0.511	-0.5	1,2
	[D42 – Dsc]	30	0.37	0.4	0.497	-0.3	2.0
	[D56 – Dsc]	30	-0.18	0	0.429	-0.7	1.9
	[D70 – Dsc]	30	-0.25	-0.1	0.455	-0.6	1.4
	[D90 – Dsc]	30	-0.14	-0.2	0.468	-0.3	1.5
Basophils, %	Dsc	30	0.45	0.52	0.322	0.2	1.4
	D14	30	0.40	0.42	0.384	0.2	1.8
	D28	30	0.43	0.45	0.280	0.1	1.6
	D42	30	0.53	0.50	0.255	0.1	1.3
	D56	30	0.54	0.55	0.325	0.2	1.7
	D70	30	0.56	0.58	0.299	0.1	1.6
	D90	30	0.58	0.58	0.301	0.1	1.7
	[D14 – Dsc]	30	-0.05	-0.1	0.135	0	0.4
	[D28 – Dsc]	30	-0.02	-0.07	0.149	-0.1	0.2
	[D42 – Dsc]	30	0.08	-0.02	0.343	-0.1	-0.1
	[D56 – Dsc]	30	0.09	0.03	0.347	0	0.3
	[D70 – Dsc]	30	0.11	0.06	0.384	-0.1	0.2
	[D90 – Dsc]	30	0.13	0.06	0.379	-0.1	0.3
ESR, mm/h	Dsc	30	16.9	17	5,262	10	29
	D14	30	16.8	17	6,138	12	35

	D28	30	18.0	18	6,365	10	38
	D42	30	15.9	16	6,114	9	36
	D56	30	14.3	14	5,789	9	29
	D70	30	15.4	15	5,885	11	31
	D90	30	15.6	16	5,459	10	28
	[D14 – Dsc]	30	-0.1	0	0.403	2	6
	[D28 – Dsc]	30	1.1	1	0.673	0	9
	[D42 – Dsc]	30	-1	-1	0.720	-1	7
	[D56 – Dsc]	30	-2.6	-3	0.422	-1	0
	[D70 – Dsc]	30	-1.5	-2	0.374	1	2
	[D90 – Dsc]	30	-1.3	-1	0.277	0	-1

Table 30. Dynamics of indicators of general blood analysis in the process of research in patients of the control group

Indicator	time	n	M	Me	SD	MIN	MAX
Leukocytes, x10 ^{9} cells/l	Dsc	30	6.65	6,7	2,170	3.8	9.7
	D14	30	5,12	5.4	1,760	3.7	7.6
	D28	30	4.68	4.8	1,905	2.9	7.4
	D42	30	4.03	5.0	1,779	2.6	6.2
	D56	30	3.91	4.6	1,459	2.6	5.2
	D70	30	3.84	4.0	1,355	2.4	5.0
	D90	30	3.47	3.3	1,320	2.0	4.8
	[D14 – Dsc]	30	-1.53	-1.3	0.896	-0.1	-2.1
	[D28 – Dsc]	30	-1.97	-1.9	1,109	-0.9	-2.3
	[D42 – Dsc]	30	-2.62	-1.7	1,238	-1.2	-3.5
	[D56 – Dsc]	30	-2.74	-2.1	1,306	-1.2	-4.5
	[D70 – Dsc]	30	-2.81	-2.7	1,275	-1.4	-4.7
	[D90 – Dsc]	30	-3.18	-3.4	1,290	-1.8	-4.9
Erythrocytes, x10^{12} cells/l	Dsc	30	4.50	4.5	0.378	3.82	4.78
	D14	30	4.19	4.2	0.401	3.57	4.89
	D28	30	4.18	4.2	0.385	3.51	4.42
	D42	30	3.56	3.8	0.373	3.51	4.36
	D56	30	3.65	3.5	0.357	3.52	4.45
	D70	30	3.64	3.6	0.340	3.54	4.38
	D90	30	3.72	4.0	0.352	3.51	4.52
	[D14 – Dsc]	30	-0.31	-0.3	0.406	-0.25	0.11
	[D28 – Dsc]	30	-0.32	-0.3	0.311	-0.31	-0.36
	[D42 – Dsc]	30	-0.94	-0.7	0.288	-0.31	-0.98
	[D56 – Dsc]	30	-0.85	-1	0.306	-0.3	-0.90
	[D70 – Dsc]	30	-0.86	-0.9	0.388	-0.28	-0.95
	[D90 – D0]	30	-0.78	-0.8	0.215	-0.31	-0.86
Hematocrit,%	Dsc	30	41,18	42.0	2,609	35.3	45.2
	D14	30	39,28	40.0	2,773	35.3	42.8
	D28	30	39.85	41.4	2,659	34.9	42.8
	D42	30	38.67	39.7	2,815	34.8	43.3

	D56	30	36.64	36.8	2,609	34.7	43.9
	D70	30	38,29	38.5	2,734	35.5	42.2
	D90	30	37,43	37.6	3,015	33.4	44.9
	[D14 – Dsc]	30	-1.9	-2	1,224	0.0	-2.4
	[D28 – Dsc]	30	-1.33	-0.6	0.966	-0.4	-2.4
	[D42 – Dsc]	30	-2.51	-2.3	0.861	-0.5	-1.9
	[D56 – Dsc]	30	-4.54	-5.2	0.764	-0.6	-1.3
	[D70 – Dsc]	30	-2.89	-3.5	1,114	0.2	-3.0
	[D90 – D0]	30	-3.75	-4.4	1,062	-1.9	-0.3
Hemoglobin, g/l	Dsc	30	128.63	125	13,570	102	140
	D14	30	124.41	122	13,672	100	141
	D28	30	121.02	116	13,400	95	139
	D42	30	117.89	112	13,315	93	136
	D56	30	102.60	110	13,269	95	134
	D70	30	100.07	110	12,889	97	132
	D90	30	101.23	110	12,467	97	131
	[D14 – Dsc]	30	-4.22	-3	0.604	-5	1
	[D28 – Dsc]	30	-7.61	-9	0.694	-7	-10
	[D42 – Dsc]	30	-10.74	-11	0.755	-9	-14
	[D56 – Dsc]	30	-26.03	-22	0.367	-7	-29
	[D70 – Dsc]	30	-28.56	-26	0.502	-5	-32
	[D90 – Dsc]	30	-27.40	-28	0.617	-5	-32
Platelets, $\times 10^9$ cells/l	Dsc	30	235.48	232	47,368	135	278
	D14	30	219.30	224	49,225	139	305
	D28	30	215.32	220	48,417	152	305
	D42	30	196.91	202	45,125	142	263
	D56	30	165.49	175	42,336	94	247
	D70	30	158.92	164	41,702	72	209
	D90	30	147.65	150	39,778	82	201
	[D14 – Dsc]	30	-16,18	-8	6,113	4	27
	[D28 – Dsc]	30	-20.16	-12	5,894	17	27
	[D42 – Dsc]	30	-38.57	-30	4,370	7	-15
	[D56 – Dsc]	30	-69.99	-57	5,480	-41	-31
	[D70 – Dsc]	30	-76.56	-68	3,338	-63	-69
	[D90 – Dsc]	30	-87.83	-82	6,884	-53	-77
Neutrophils,%	Dsc	30	64.52	65.5	9,337	45.7	85.2
	D14	30	63.75	64.1	7,447	42.3	84.9
	D28	30	63.49	64.0	6,715	40.5	78.3
	D42	30	62,83	63.5	6,480	40.2	75.7
	D56	30	62,18	61.8	5,905	40.6	75.4
	D70	30	61.94	60.9	6,129	39.6	74.2
	D90	30	60,67	60.2	5,884	39.4	72.1
	[D14 – Dsc]	30	-0.77	-1.4	4,337	-0.3	-3.4
	[D28 – Dsc]	30	-1.03	-1.5	5,027	-5.2	-6.9
	[D42 – Dsc]	30	-1.69	-2	5,129	-5.5	-9.5

	[D56 – Dsc]	30	-2.34	-3.7	5,696	-5.1	-9.8
	[D70 – Dsc]	30	-2.58	-4.6	5,703	-6.1	-11.0
	[D90 – Dsc]	30	-17.85	-18.6	5,883	-9.3	-28.1
Lymphocytes, %	Dsc	30	25,20	24.7	2,892	19.4	32.8
	D14	30	25.44	25.8	3,044	17.4	35.2
	D28	30	27.45	27.7	2,784	20.5	34.6
	D42	30	26,41	26.6	2,816	19.4	32.2
	D56	30	25,39	25.6	2,893	19.6	33.2
	D70	30	26.86	26.9	2,691	20.3	30.4
	D90	30	26.15	26.4	2,704	18.7	31.6
	[D14 – Dsc]	30	0.24	1.1	0.754	-2.0	2.4
	[D28 – Dsc]	30	2.25	3.0	0.336	1.1	1.8
	[D42 – Dsc]	30	1.21	1.9	0.401	0.0	-0.6
	[D56 – Dsc]	30	0.19	0.9	0.116	0.2	0.4
	[D70 – Dsc]	30	1.66	2,2	0.269	0.9	-2.4
	[D90 – Dsc]	30	0.95	1.7	0.278	-0.7	-1.2
Monocytes, %	Dsc	30	5.05	5.2	0.895	3,4	6.4
	D14	30	4.85	4.9	0.962	3.2	7.2
	D28	30	4.93	5.0	1,033	3.5	8.2
	D42	30	4.91	5.0	0.932	3.1	7.9
	D56	30	5.02	5.0	0.877	3.2	8.0
	D70	30	5.11	5.2	0.880	3.3	7,8
	D90	30	4.98	5.1	0.894	3.3	8.1
	[D14 – Dsc]	30	-0.2	-0.3	0.266	-0.2	0.8
	[D28 – Dsc]	30	-0.12	-0.2	0.315	0.1	1.8
	[D42 – Dsc]	30	-0.14	-0.2	0.411	-0.3	1.5
	[D56 – Dsc]	30	-0.03	-0.2	0.377	-0.2	1.6
	[D70 – Dsc]	30	0.06	0	0.402	-0.1	1.4
	[D90 – Dsc]	30	-0.07	-0.1	0.416	-0.1	1.7
Eosinophils, %	Dsc	30	2.37	2,3	0.363	1.5	2.8
	D14	30	2.32	2.4	0.654	1.3	4.5
	D28	30	2.65	2.8	0.672	1.0	4.5
	D42	30	2.47	2.5	0.590	1.4	4.8
	D56	30	2.34	2,3	0.693	1.5	5.2
	D70	30	2.21	2,2	0.612	1.1	4.9
	D90	30	2.29	2,3	0.633	1.4	4.8
	[D14 – Dsc]	30	-0.05	0.1	0.293	-0.2	1.7
	[D28 – Dsc]	30	0.28	0.5	0.380	-0.5	1.7
	[D42 – Dsc]	30	0.10	0.2	0.305	-0.1	2.0
	[D56 – Dsc]	30	-0.03	0	0.363	0	2.4
	[D70 – Dsc]	30	-0.16	-0.1	0.440	-0.4	2.1
	[D90 – Dsc]	30	-0.08	0	0.461	-0.1	2.0
Basophils, %	Dsc	30	0.43	0.46	0.280	0.3	0.8
	D14	30	0.46	0.48	0.411	0.2	1.4
	D28	30	0.53	0.51	0.462	0.2	1.5

	D42	30	0.51	0.50	0.509	0.3	1.7
	D56	30	0.55	0.57	0.422	0.2	1.4
	D70	30	0.50	0.52	0.410	0.2	1,2
	D90	30	0.53	0.52	0.431	0.2	1,2
	[D14 – Dsc]	30	0.03	0.02	0.153	-0.1	0.6
	[D28 – Dsc]	30	0.1	0.05	0.202	-0.1	0.7
	[D42 – Dsc]	30	0.08	0.04	0.222	0.0	0.9
	[D56 – Dsc]	30	0.12	0.11	0.266	-0.1	0.6
	[D70 – Dsc]	30	0.07	0.06	0.183	-0.1	0.4
	[D90 – Dsc]	30	0.1	0.06	0.190	-0.1	0.4
ESR, mm/h	Dsc	30	17.5	17	4,970	8	26
	D14	30	18.3	19	5,984	9	38
	D28	30	18.5	19	5,602	10	34
	D42	30	16.9	17	5,550	9	31
	D56	30	16.7	17	5,441	12	29
	D70	30	16.5	17	5,478	12	32
	D90	30	16.8	17	5,716	10	32
	[D14 – Dsc]	30	0.8	2	3,400	1	12
	[D28 – Dsc]	30	1.0	2	2,500	2	8
	[D42 – Dsc]	30	-0.6	0	1,135	1	5
	[D56 – Dsc]	30	-0.8	0	0.501	4	3
	[D70 – Dsc]	30	-1.0	0	0.580	4	6
	[D90 – Dsc]	30	-0.7	0	0.497	2	6

Graphically, the dynamics of the average values of some parameters of the general blood analysis are shown in **fig. 1-3**.

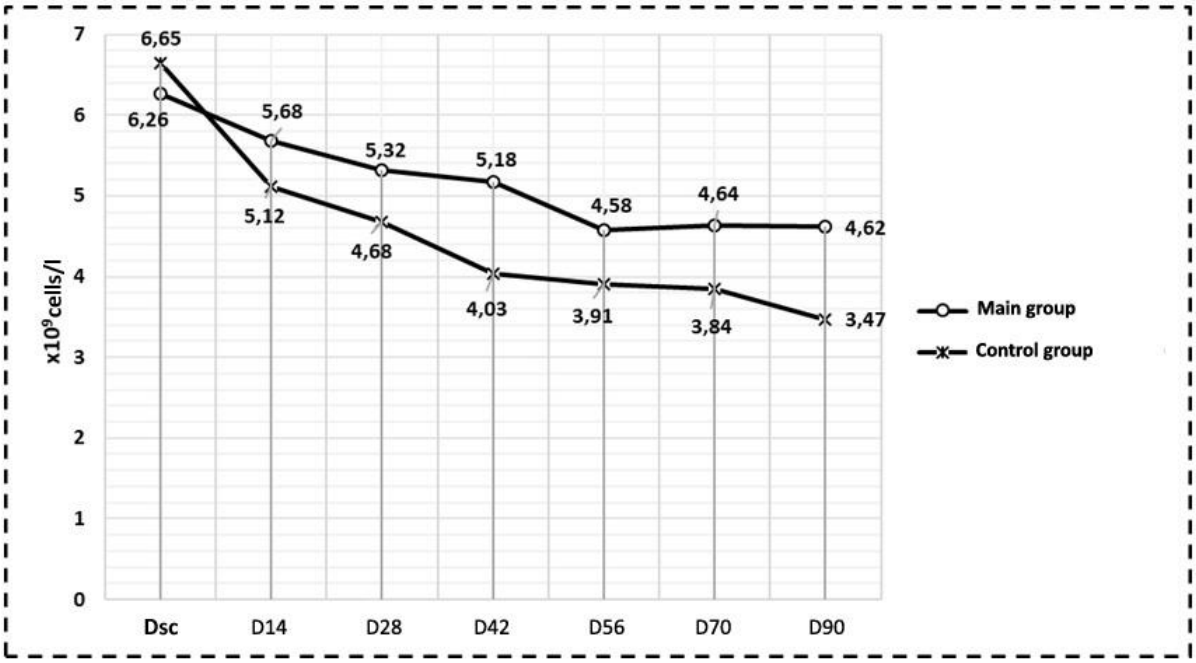

Fig. 1 – Dynamics of the indicator "Leukocytes" in groups

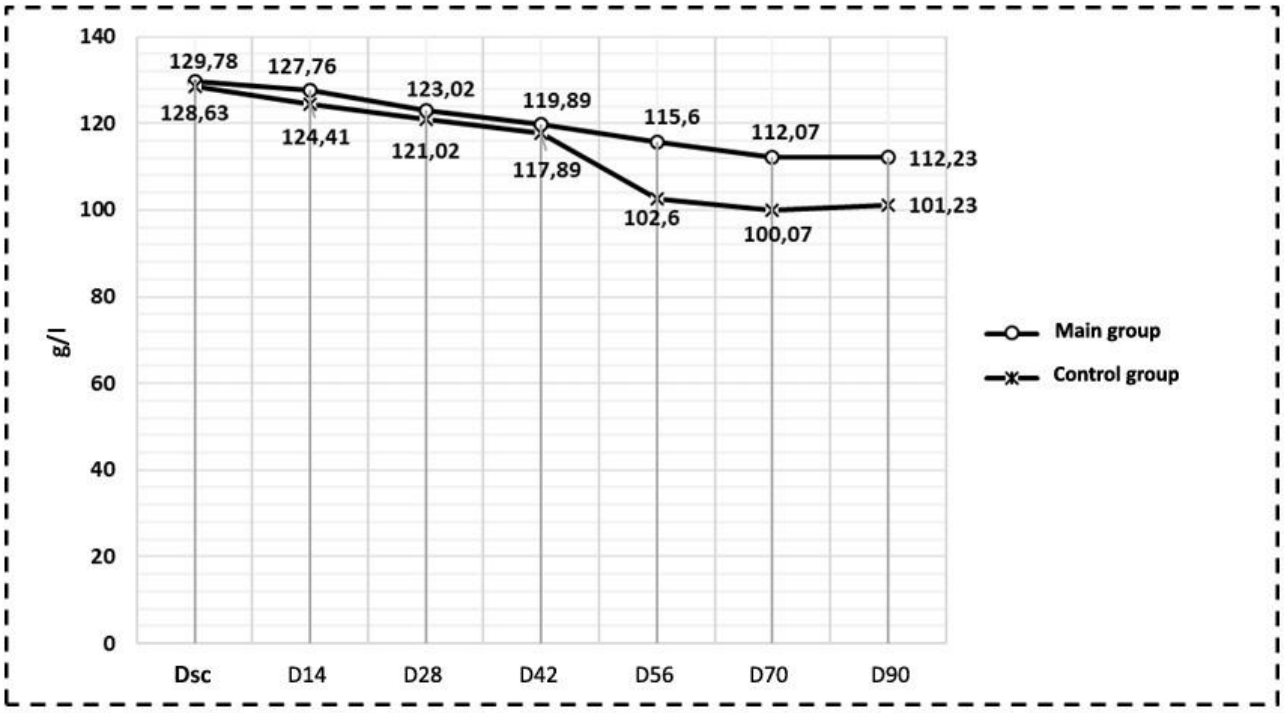

Fig. 2 – Dynamics of the indicator "Hemoglobin" in groups

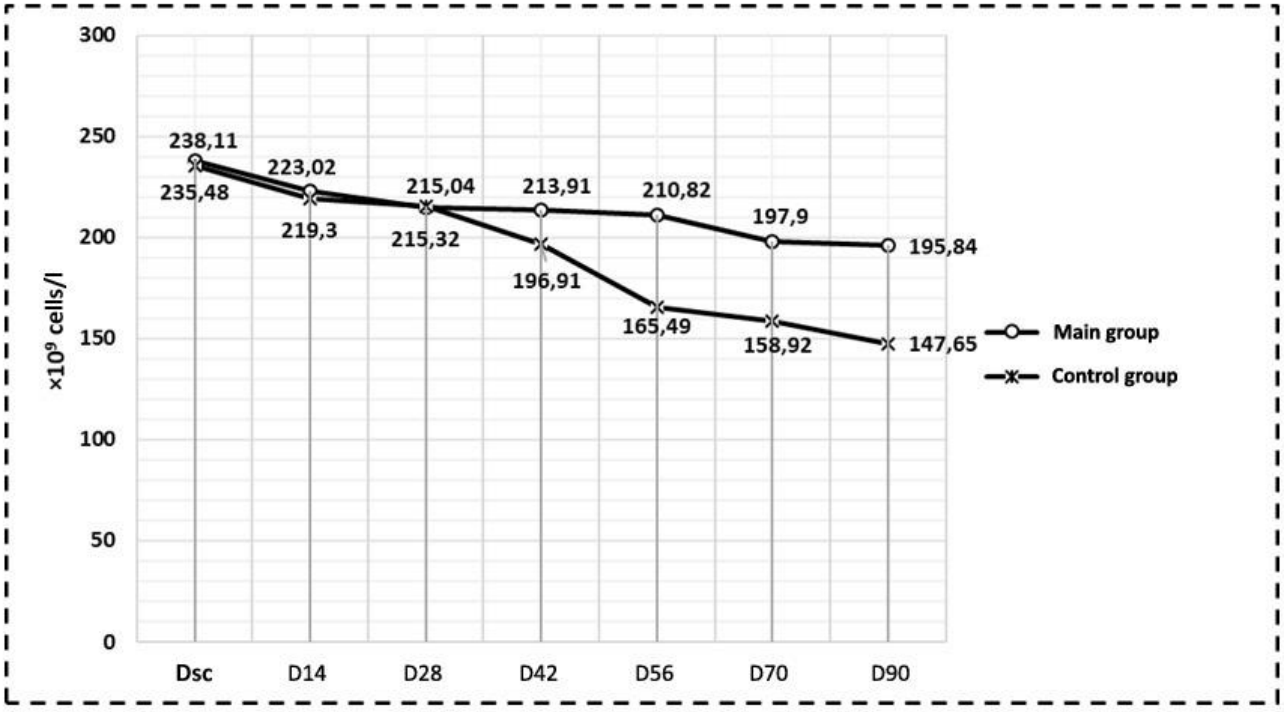

Fig. 3 – Dynamics of the indicator "Platelets" in groups

As can be seen from the graphs, already after the first course of chemotherapy, and then at all stages of observation, a decrease in the level of leukocytes, hemoglobin and platelets was noted in patients of both groups. These changes corresponded to the toxicity profile of the chemotherapeutic drugs used and indicated a negative effect of chemotherapeutic drugs on the hematopoietic system. It should be noted that the changes in the above indicators in the main group were of a less pronounced nature.

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, D14, D28, D42, D56, D70, D90), the "subjects" factor is random) . The results of DA are shown in the **table. 31 - 32** .

A comparison of the following levels of the "visit" factor with the initial data (Dscreening) was also performed using the contrast analysis of the **table. 33 - 34** . The normality of the distribution of DA residues was checked using the Shapiro-Wilk test (**Table A.6 of Appendix A**).

Table 31 - The main results of DA indicators of general blood analysis in the main group

Dependent variable	Factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning
Leukocytes	Visit	71,948	6	11,991	2,728	0.015
	Patients	288,755	29	9,957	2,266	0.001
Erythrocytes	Visit	7,209	6	1,201	2,662	0.017
	Patients	145,848	29	5,029	11,141	0.000
Hematocrit	Visit	415,528	6	69,255	1,514	0.187
	Patients	6522,544	29	224,915	16,283	0.000
Hemoglobin	Visit	2426,996	6	404,499	11,628	0.000
	Patients	21923,182	29	755,972	21,731	0.000
Platelets	Visit	37903.067	6	6317,178	5,894	0.000
	Patients	478645.643	29	16505.022	15,398	0.000
Neutrophils	Visit	3890,337	6	648,390	1,726	0.148
	Patients	18266,357	29	629,874	17,219	0.000
Lymphocytes	Visit	214,666	6	35,778	1,662	0.177
	Patients	1332,562	29	45,950	14,464	0.000
Monocytes	Visit	2,674	6	0.446	1,470	0.250
	Patients	136,383	29	4,703	36,624	0.000
Eosinophils	Visit	15,423	6	2,570	1,608	0.156
	Patients	56,030	29	1,932	11,731	0.000
Basophils	Visit	0.906	6	0.151	3,809	0.001
	Patients	10,130	29	0.349	8,816	0.000
ESR	Visit	274,533	6	45,756	1,597	0.161
	Patients	3280.595	29	113,124	21,256	0.000

Table 32 - The main results of DA indicators of general blood analysis in the control group

Dependent variable	Factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning
Leukocytes	Visit	219,395	6	36,566	8,827	0.000
	Patients	239,755	29	8,267	1,996	0.004
Erythrocytes	Visit	20,884	6	3,481	5,287	0.000
	Patients	223,958	29	7,723	11,729	0.000
Hematocrit	Visit	416,349	6	69,392	1,364	0.310
	Patients	2665,872	29	91,927	4,457	0.000
Hemoglobin	Visit	6714.044	6	1119,007	13,118	0.000
	Patients	17992.653	29	620,436	7,273	0.000
Platelets	Visit	208995.295	6	34832.549	20,465	0.000
	Patients	522312.957	29	18010.792	10,582	0.000
Neutrophils	Visit	6837,896	6	1139,649	1,715	0.109
	Patients	21439.579	29	739,296	18,756	0.000
Lymphocytes	Visit	127,757	6	21,293	1,280	0.345
	Patients	741,859	29	25,581	5,863	0.000
Monocytes	Visit	1,618	6	0.270	1,127	0.449
	Patients	113,763	29	3,923	16,391	0.000
Eosinophils	Visit	3,498	6	0.583	1,474	0.175
	Patients	34,050	29	1,174	5,587	0.000
Basophils	Visit	0.337	6	0.056	2,771	0.008
	Patients	11,043	29	0.381	12,003	0.000
ESR	Visit	115,124	6	19,187	1,764	0.103
	Patients	3309,524	29	114,122	22,390	0.000

Table 33 - Results of the contrast analysis of indicators of general blood analysis in the main group

Dependent variable	Contrasts	Estimated contrast	Stand. mistake	p-value*
Leukocytes	D14 - Dsc	-0.997	0.541	0.045*
	D28 - Dsc	-1,140		0.031*
	D42 - Dsc	-1,193		0.022*
	D56 - Dsc	-1.697		0.002*
	D70 - Dsc	-1,610		0.003*
	D90 - Dsc	-1.643		0.003*
Erythrocytes	D14 - Dsc	-0.203	0.173	0.243
	D28 - Dsc	-0.330		0.059
	D42 - Dsc	-0.353		0.043*
	D56 - Dsc	-0.383		0.027*

	D70 - Dsc	-0.523		0.003*
	D90 - Dsc	-0.557		0.002*
Hematocrit	D14 - Dsc	-1.357	0.960	0.431
	D28 - Dsc	-1.757		0.274
	D42 - Dsc	-2,513		0.109
	D56 - Dsc	-3.043		0.085
	D70 - Dsc	-3,190		0.061
	D90 - Dsc	-2.777		0.076
Hemoglobin	D14 - Dsc	-1.503	1,523	0.325
	D28 - Dsc	-2,750		0.140
	D42 - Dsc	-2.983		0.125
	D56 - Dsc	-6,157		0.000*
	D70 - Dsc	-9,707		0.000*
	D90 - Dsc	-9,530		0.000*
Platelets	D14 - Dsc	-15,067	8,453	0.076
	D28 - Dsc	-17,100		0.057
	D42 - Dsc	-24,200		0.005
	D56 - Dsc	-27,300		0.000*
	D70 - Dsc	-40,333		0.000*
	D90 - Dsc	-42,300		0.000*
Neutrophils	D14 - Dsc	-1.527	1,562	0.341
	D28 - Dsc	-1,760		0.232
	D42 - Dsc	-1.867		0.176
	D56 - Dsc	-2.127		0.132
	D70 - Dsc	-2.227		0.087
	D90 - Dsc	-2,560		0.070
Lymphocytes	D14 - Dsc	0.383	0.460	0.606
	D28 - Dsc	0.830		0.193
	D42 - Dsc	0.483		0.495
	D56 - Dsc	0.930		0.125
	D70 - Dsc	1,323		0.089
	D90 - Dsc	1,460		0.056
Monocytes	D14 - Dsc	-0.053	0.093	0.765
	D28 - Dsc	0.257		0.056
	D42 - Dsc	-0.053		0.765
	D56 - Dsc	0.073		0.529
	D70 - Dsc	0.207		0.077
	D90 - Dsc	0.053		0.565
Eosinophils	D14 - Dsc	-0.170	0.105	0.307
	D28 - Dsc	0.293		0.203
	D42 - Dsc	0.360		0.078
	D56 - Dsc	-0.183		0.182
	D70 - Dsc	-0.247		0.120
	D90 - Dsc	-0.140		0.183
Basophils	D14 - Dsc	-0.040	0.051	0.437
	D28 - Dsc	-0.017		0.746
	D42 - Dsc	0.083		0.107
	D56 - Dsc	0.097		0.062
	D70 - Dsc	0.117		0.024*
	D90 - Dsc	0.137		0.009*

ESR	D14 - Dsc	-0.100	0.596	0.867
	D28 - Dsc	1,100		0.166
	D42 - Dsc	-1.033		0.185
	D56 - Dsc	-1.667		0.071
	D70 - Dsc	-1.267		0.139
	D90 - Dsc	-1.333		0.096
** Statistically significant differences are observed* *The conclusion is made at a significance level of 0.05*				

Table 34 - Results of the contrast analysis of indicators of the general blood analysis in the control group

Dependent variable	Contrasts	Estimated contrast	Stand. mistake	p-value*
Leukocytes	D14 - Dsc	-1.537	0.526	0.004*
	D28 - Dsc	-1.987		0.000*
	D42 - Dsc	-1.733		0.001*
	D56 - Dsc	-2,167		0.000*
	D70 - Dsc	-2,810		0.000*
	D90 - Dsc	-3,533		0.000*
Erythrocytes	D14 - Dsc	-0.303	0.210	0.149
	D28 - Dsc	-0.330		0.117
	D42 - Dsc	-0.943		0.000*
	D56 - Dsc	-0.847		0.000*
	D70 - Dsc	-0.757		0.000*
	D90 - Dsc	-0.490		0.020*
Hematocrit	D14 - Dsc	-1.303	1,173	0.306
	D28 - Dsc	-1.267		0.357
	D42 - Dsc	-1.527		0.233
	D56 - Dsc	-1,850		0.145
	D70 - Dsc	-1,900		0.123
	D90 - Dsc	-2,160		0.052
Hemoglobin	D14 - Dsc	-3,223	2,385	0.178
	D28 - Dsc	-4,603		0.100
	D42 - Dsc	-6,733		0.059
	D56 - Dsc	-13,033		0.000*
	D70 - Dsc	-15,613		0.000*
	D90 - Dsc	-15,437		0.000*
Platelets	D14 - Dsc	-16,167	10,652	0.131
	D28 - Dsc	-18,200		0.075
	D42 - Dsc	-38,567		0.000*
	D56 - Dsc	-70,000		0.000*
	D70 - Dsc	-76,600		0.000*
	D90 - Dsc	-87,833		0.000*
Neutrophils	D14 - Dsc	-0.753	1,621	0.298
	D28 - Dsc	-0.920		0.243
	D42 - Dsc	-1.067		0.187
	D56 - Dsc	-1.327		0.134

	D70 - Dsc	-1,440		0.098
	D90 - Dsc	-1.649		0.058
Lymphocytes	D14 - Dsc	0.243	0.539	0.652
	D28 - Dsc	1,257		0.107
	D42 - Dsc	0.813		0.213
	D56 - Dsc	0.200		0.711
	D70 - Dsc	1,270		0.086
	D90 - Dsc	0.970		0.174
Monocytes	D14 - Dsc	-0.223	0.126	0.079
	D28 - Dsc	-0.120		0.343
	D42 - Dsc	-0.153		0.226
	D56 - Dsc	-0.043		0.732
	D70 - Dsc	0.057		0.654
	D90 - Dsc	-0.083		0.510
Eosinophils	D14 - Dsc	-0.043	0.118	0.715
	D28 - Dsc	0.177		0.061
	D42 - Dsc	0.110		0.354
	D56 - Dsc	-0.030		0.800
	D70 - Dsc	-0.143		0.228
	D90 - Dsc	-0.077		0.518
Basophils	D14 - Dsc	0.023	0.046	0.613
	D28 - Dsc	0.100		0.031*
	D42 - Dsc	0.083		0.072
	D56 - Dsc	0.117		0.012*
	D70 - Dsc	0.073		0.113
	D90 - Dsc	0.100		0.031*
SOE	D14 - Dsc	0.733	0.583	0.210
	D28 - Dsc	0.967		0.099
	D42 - Dsc	-0.633		0.279
	D56 - Dsc	-0.833		0.155
	D70 - Dsc	-1.033		0.078
	D90 - Dsc	-0.733		0.210
** Statistically significant differences are observed* *The conclusion is made at a 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 group, a statistically significant decrease in the level of leukocytes after the first course of chemotherapy, erythrocytes and platelets after the third course of chemotherapy, and hemoglobin after the fourth course of chemotherapy compared to the initial data was revealed.

2. In the control group, there was also a statistically significant decrease in the level of leukocytes after the first course of chemotherapy, erythrocytes and platelets, after the third course of chemotherapy, and hemoglobin after the fourth course of chemotherapy compared to the initial data.
3. Changes in other hematological indicators in both groups were not statistically and clinically significant throughout the study.

15.4.3. Analysis of the comparison of the dynamics of hematological indicators 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 performed by dT_i differences and with the help of the Mann-Whitney test, because individual differences dT_i were not distributed normally in both groups (see **Tables A.7-A.8 of Appendix A**).

The results of the analysis of the comparison of the dynamics of hematological parameters between the groups are shown in **Table 35.**

Table 35. Comparison of groups using the Mann-Whitney criterion on the dynamics of hematological indicators

Indicator	dTi	U of Mann-Whitney	Wilcoxon W	Z-statistics	p-value (two-way)	Differences between groups
Leukocytes	dT14	345,000	815,000	-2,291	0.021	Significant
	dT28	348,000	812,000	-2.553	0.001	Significant
	dT42	396,500	861,500	-2,791	0.000	Significant
	dT56	406,500	871,500	-2,444	0.000	Significant
	dT70	361,000	826,000	-2,517	0.001	Significant
	dT90	300,000	765,000	-2,619	0.001	Significant
Erythrocytes	dT14	445,000	910,000	-0.125	0.900	Not significant
	dT28	449,000	914,000	-0.025	0.980	Not significant
	dT42	343,000	808,000	-1,990	0.047	Not significant
	dT56	375,000	840,000	-1,496	0.135	Not significant
	dT70	435,500	900,500	-0.275	0.783	Not significant
	dT90	423,000	888,000	-0.513	0.608	Not significant
Hematocrit	dT14	435,500	900,500	-0.318	0.751	Not significant
	dT28	417,500	882,500	-0.688	0.492	Not significant
	dT42	422,500	887,500	-0.549	0.583	Not significant
	dT56	414,000	879,000	-0.657	0.511	Not significant

	dT70	394,500	859,500	-0.950	0.342	Not significant
	dT90	432,000	897,000	-0.342	0.732	Not significant
Hemoglobin	dT14	416,500	881,500	-0.709	0.478	Not significant
	dT28	390,500	855,500	-1.066	0.286	Not significant
	dT42	404,000	869,000	-0.811	0.418	Not significant
	dT56	494,000	859,000	-2,911	0.000	Significant
	dT70	487,000	850,000	-2.989	0.000	Significant
	dT90	498,500	853,500	-2,799	0.000	Significant
Platelets	dT14	411,000	876,000	-0.800	0.424	Not significant
	dT28	447,000	912,000	-0.060	0.952	Not significant
	dT42	327,500	792,500	-1.984	0.047	Significant
	dT56	314,500	779,500	-2,194	0.028	Significant
	dT70	348,500	813,500	-2.545	0.000	Significant
	dT90	337,000	802,000	-2,713	0.000	Significant
Neutrophils	dT14	352,000	817,000	-1.656	0.098	Not significant
	dT28	409,500	874,500	-0.625	0.532	Not significant
	dT42	405,500	870,500	-0.683	0.494	Not significant
	dT56	401,500	866,500	-0.729	0.466	Not significant
	dT70	330,000	795,000	-1.795	0.073	Not significant
	dT90	347,000	812,000	-1.541	0.123	Not significant
Lymphocytes	dT14	438,000	903,000	-0.318	0.750	Not significant
	dT28	352,500	817,500	-1.852	0.064	Not significant
	dT42	425,000	890,000	-0.513	0.608	Not significant
	dT56	402,000	867,000	-1.273	0.203	Not significant
	dT70	403,500	868,500	-0.760	0.447	Not significant
	dT90	319,000	784,000	-2.103	0.035	Not significant
Monocytes	dT14	396,500	861,500	-1.016	0.309	Not significant
	dT28	355,500	820,500	-1.597	0.110	Not significant
	dT42	411,500	876,500	-0.716	0.474	Not significant
	dT56	404,500	869,500	-0.790	0.430	Not significant
	dT70	406,000	871,000	-0.727	0.467	Not significant
	dT90	414,500	879,500	-0.608	0.543	Not significant
Eosinophils	dT14	379,000	844,000	-1.556	0.120	Not significant
	dT28	368,000	833,000	-1.254	0.210	Not significant
	dT42	341,500	806,500	-1.659	0.097	Not significant
	dT56	332,000	797,000	-2,295	0.022	Significant
	dT70	391,500	856,500	-0.989	0.323	Not significant
	dT90	449,000	914,000	-0.016	0.987	Not significant
Basophils	dT14	379,500	844,500	-1,870	0.062	Not significant
	dT28	391,500	856,500	-1.662	0.097	Not significant
	dT42	450,000	915,000	0.000	1,000	Not significant
	dT56	448,000	913,000	-0.042	0.966	Not significant
	dT70	445,000	910,000	-0.106	0.916	Not significant

	dT90	435,000	900,000	-0.329	0.742	Not significant
ESR	dT14	441,500	906,500	-0.186	0.852	Not significant
	dT28	413,500	878,500	-0.679	0.497	Not significant
	dT42	445,000	910,000	-0.125	0.900	Not significant
	dT56	349,500	814,500	-1.833	0.067	Not significant
	dT70	429,000	894,000	-0.431	0.667	Not significant
	dT90	426,500	891,500	-0.457	0.648	Not significant

Conclusion Based on the data presented **in table. 35**, it is possible to draw conclusions:

1. A significantly more pronounced decrease in the level of leukocytes was revealed, starting from the first course of CT, in patients of the control group, compared to the main group.
2. A significantly more pronounced decrease in the level of hemoglobin was revealed, starting from the fourth course of CT, in patients of the control group, compared to the main group.
3. A significantly more pronounced decrease in the level of platelets was revealed, starting from the third course of CT, in patients of the control group, compared to the main group.
4. The groups did not differ significantly in other hematological indicators.

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

Further analysis of indicators was carried out with the construction of a table of frequencies. Pearson's χ^2 test (or Fisher's exact test) was used to compare frequencies. The results of this analysis are shown in **table. 36**.

Table 36. 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	28	93.3	1,000
		Outside the norm	2	6,7	2	6,7	
	D14	It's normal	26	86.7	20	66.7	0.125
		Outside the norm	4	13.3	10	33.3	
	D28	Norm	24	80.0	14	47.7	0.015**
		Outside the norm	6	20.0	16	53.3	
	D42	Norm	24	80.0	14	47.7	0.015**
		Outside the norm	6	20.0	16	53.3	
	D56	Norm	24	80.0	14	47.7	0.015**

		Outside the norm	6	20.0	16	53.3	
	D70	Norm	24	80.0	14	47.7	0.015**
		Outside the norm	6	20.0	16	53.3	
	D90	Norm	25	83.3	14	47.7	0.006**
		Outside the norm	5	16.7	16	53.3	
Hemoglobin	Dsc	It's normal	29	96.7	29	96.7	1,000
		Outside the norm	1	3.3	1	3.3	
	D14	It's normal	29	96.7	29	96.7	1,000
		Outside the norm	1	3.3	1	3.3	
	D28	Norm	28	93.3	25	83.3	0.052
		Outside the norm	2	6,7	5	16.7	
	D42	Norm	28	93.3	23	76.7	0.146
		Outside the norm	2	6,7	7	23.3	
	D56	Norm	28	93.3	23	76.7	0.146
		Outside the norm	2	6,7	7	23.3	
	D70	Norm	28	93.3	23	76.7	0.146
		Outside the norm	2	6,7	7	23.3	
	D90	Norm	28	93.3	23	76.7	0.146
		Outside the norm	2	6,7	7	23.3	
Platelets	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D14	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D28	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D42	Norm	27	90.0	20	66.7	0.0575
		Outside the norm	3	10.0	10	33.3	
	D56	Norm	27	90.0	20	66.7	0.0575
		Outside the norm	3	10.0	10	33.3	
	D70	Norm	27	90.0	20	66.7	0.0575
		Outside the norm	3	10.0	10	33.3	
	D90	Norm	27	90.0	20	66.7	0.0575
		Outside the norm	3	10.0	10	33.3	
Neutrophils	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D14	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D28	Norm	28	93.3	22	73.3	0.0797
		Outside the norm	2	6,7	8	27.7	
	D42	Norm	26	86.7	20	66.7	0.125
		Outside the norm	4	13.3	10	33.3	
	D56	Norm	26	86.7	20	66.7	0.125
		Outside the norm	4	13.3	10	33.3	

	D70	Norm	26	86.7	20	66.7	0.125
		Outside the norm	4	13.3	10	33.3	
	D90	Norm	26	86.7	23	76.7	0.506
		Outside the norm	4	13.3	7	23.3	
Erythrocytes	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D14	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D28	Norm	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	
	D56	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D70	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D90	Outside the norm	0	0	0	0	
		Norm	30	100.0	30	100.0	1,000
Hematocrit	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D14	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D28	Norm	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	
	D56	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D70	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D90	Norm	30	100.0	22	73.3	
Lymphocytes	Dsc	It's normal	29	96.7	30	100.0	1,000
		Outside the norm	1	3.3	0	0	
	D14	It's normal	29	96.7	29	96.7	1,000
		Outside the norm	1	3.3	1	3.3	
	D28	Norm	30	100.0	28	93.3	0.492
		Outside the norm	0	0	2	6,7	
	D42	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D56	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D70	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
Monocytes	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D14	It's normal	30	100.0	29	96.7	1,000
		Outside the norm	0	0	1	3.3	
	D28	Norm	29	96.7	29	96.7	1,000
		Outside the norm	1	3.3	1	3.3	
	D42	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D56	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D70	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
Eosinophils	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D14	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D28	Norm	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	
	D56	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D70	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
Basophils	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D14	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D28	Norm	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	
	D56	Norm	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D70	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
ESR	Dsc	It's normal	29	96.7	29	96.7	1,000
		Outside the norm	1	3.3	1	3.3	
	D14	It's normal	29	96.7	28	93.3	1,000

		Outside the norm	1	3.3	2	6,7	
	D28	Norm	28	93.3	29	96.7	1,000
		Outside the norm	2	6,7	1	3.3	
	D42	Norm	29	96.7	30	100.0	1,000
		Outside the norm	1	3.3	0	0	
	D56	Norm	30	100.0	29	96.7	1,000
		Outside the norm	0	0	1	3.3	
	D70	Norm	30	100.0	29	96.7	1,000
		Outside the norm	0	0	1	3.3	
	D90	Norm	30	*100.0*	29	96.7	1,000
**Evaluated using Fisher's exact test.* ***There are significant differences between groups*							

As can be seen from table 36, in the majority of patients, the parameters of the general blood analysis, throughout the study, were within the physiological norm. The toxic effect of the applied chemotherapy was mainly manifested in a decrease in the level of such indicators as: leukocytes, hemoglobin and platelets. Thus, a decrease in the number of leukocytes (<4.0x10 ^{9} cells/l) was observed in 6 (20.0%) patients of the main group and in 16 (53.3%) patients of the control group. A decrease in the level of hemoglobin (<110 g/l) was observed in 2 (6.7%) patients of the main group and in 7 (23.3%) patients of the control group. A decrease in the number of platelets (<100 x10^{9} cells/l) was observed in 3 (10.0%) patients of the main group and in 10 (33.3%) patients of the control group.

A higher frequency of development of leukopenia, anemia, and thrombocytopenia was noted in patients of the control group, compared to the main group, but a significantly higher frequency of development between the groups was revealed only for leukopenia.

Figures 4-9 show the frequency of leukopenia, anemia, and thrombocytopenia in patients of the main and control groups during the study.

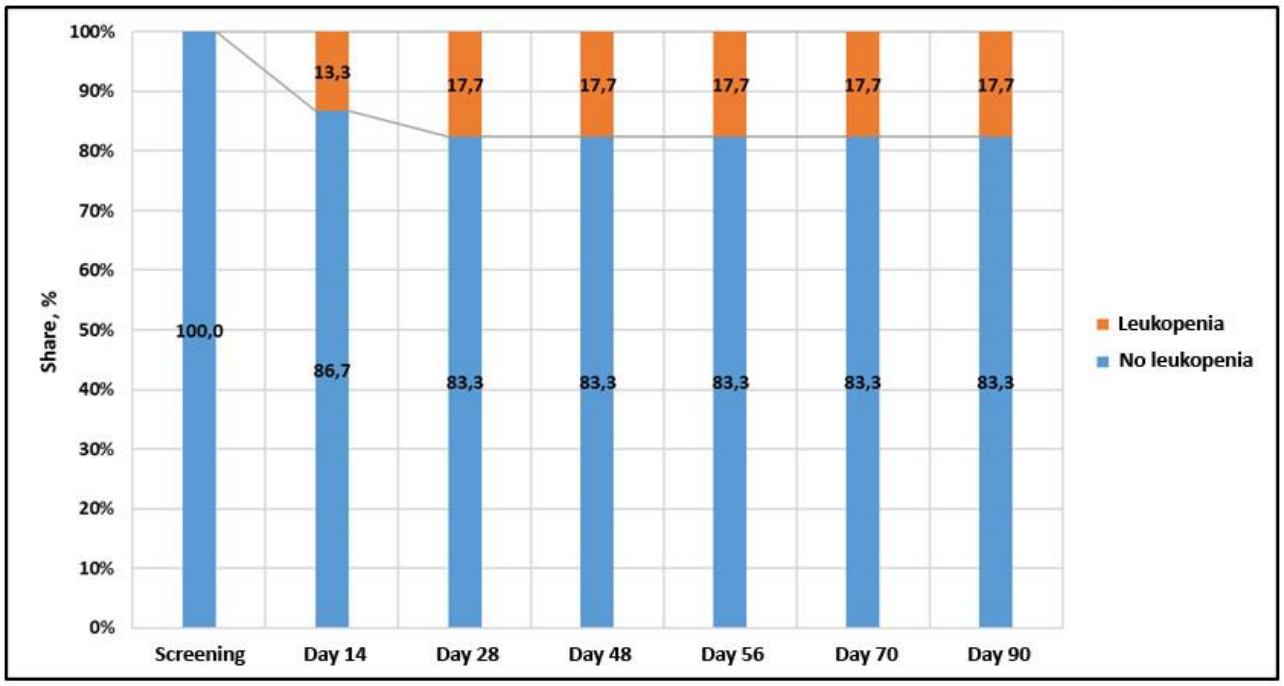

Fig. 4 – Frequency of development of leukopenia in the main group

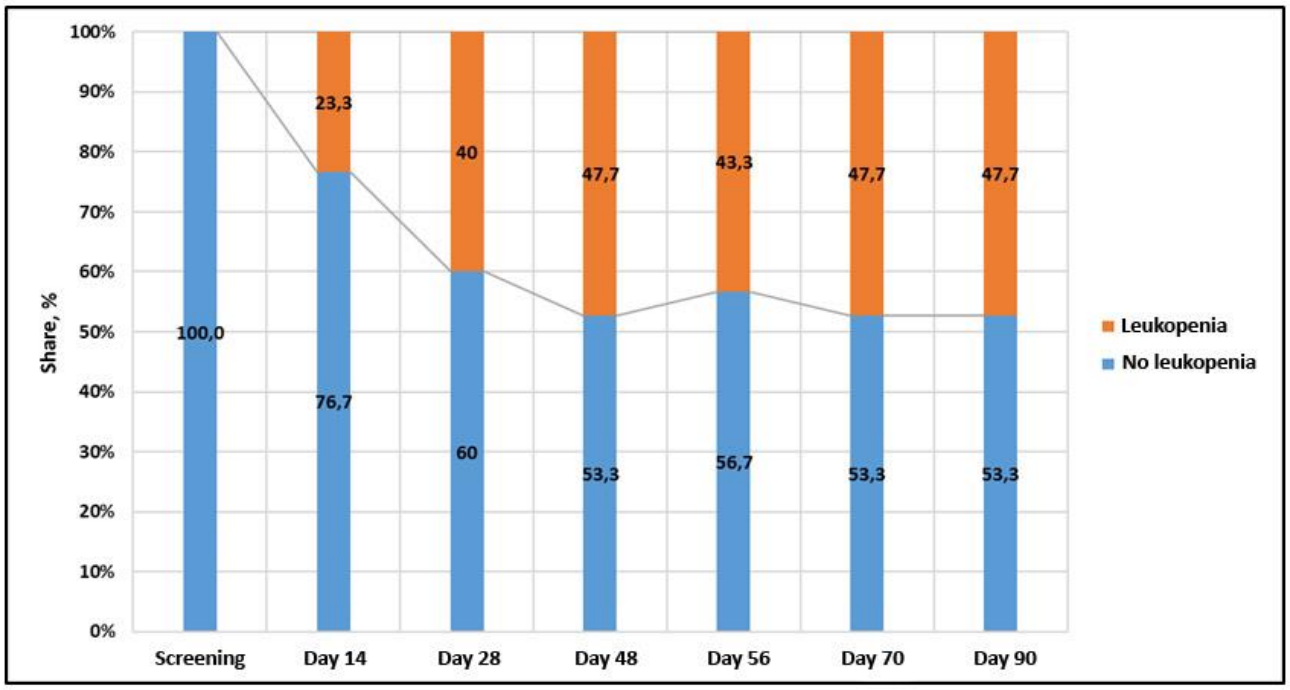

Fig. 5 – The frequency of leukopenia in the control group

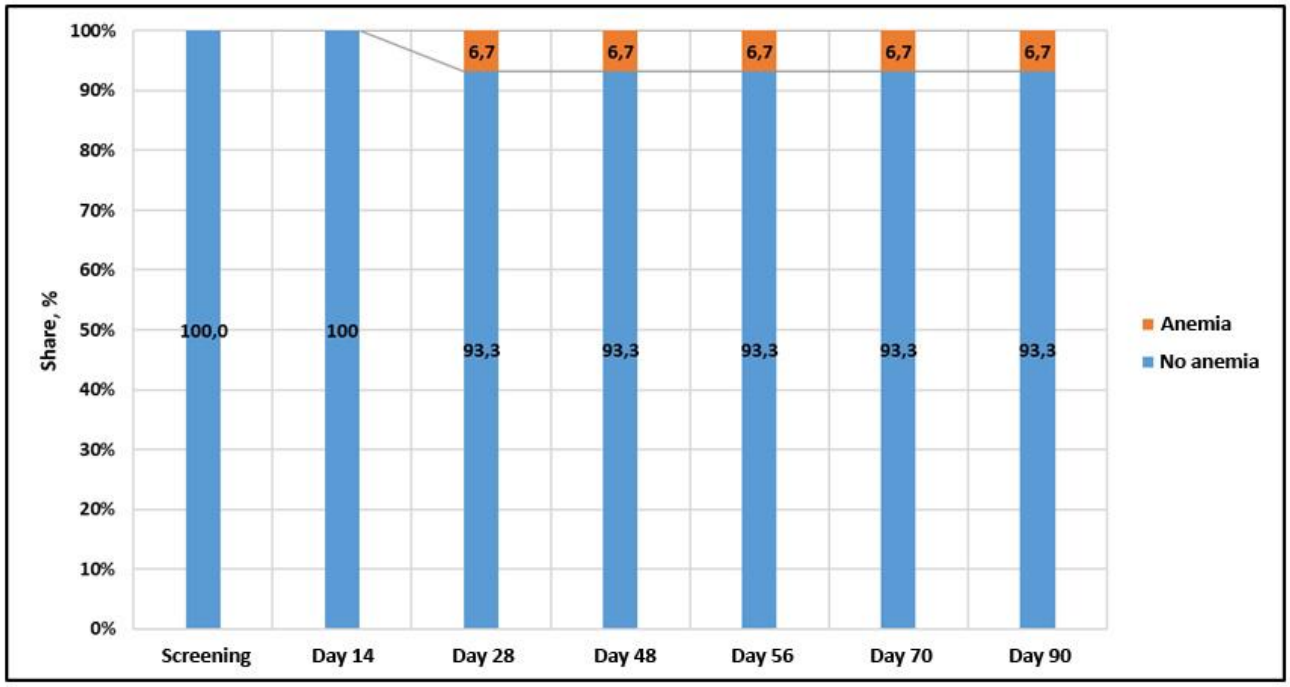

Fig. 6 – The frequency of anemia in the main group

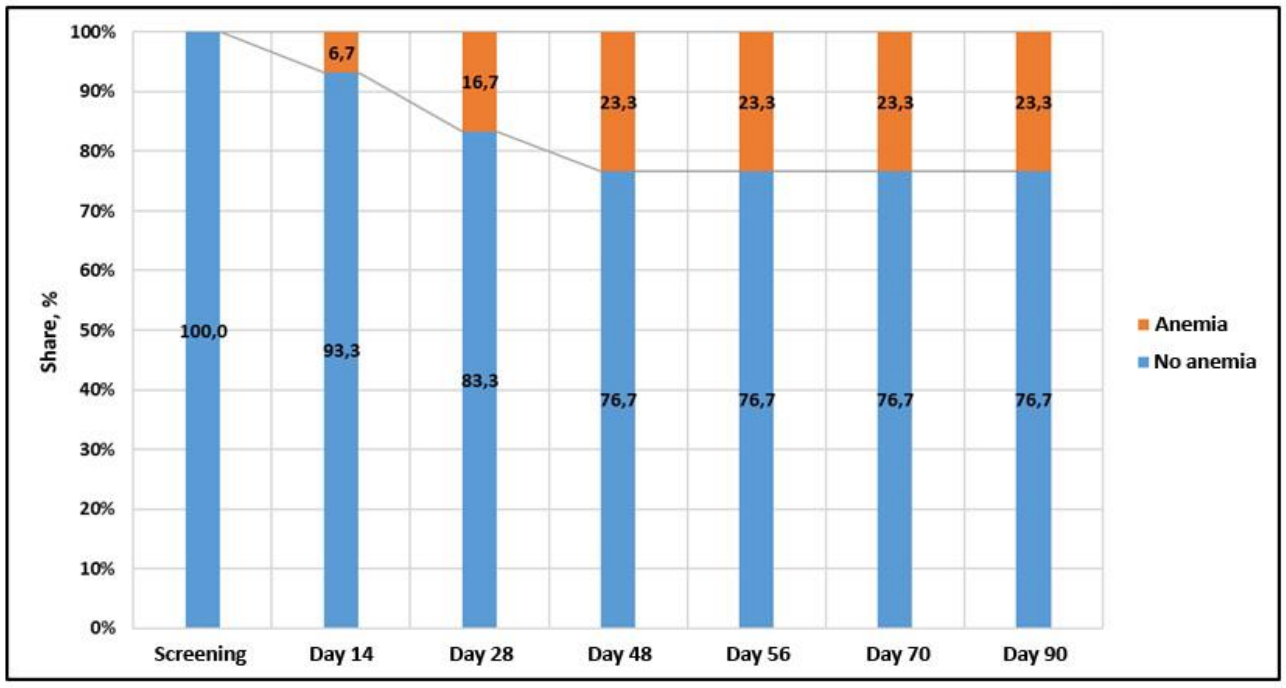

Fig. 7 – The frequency of anemia in the control group

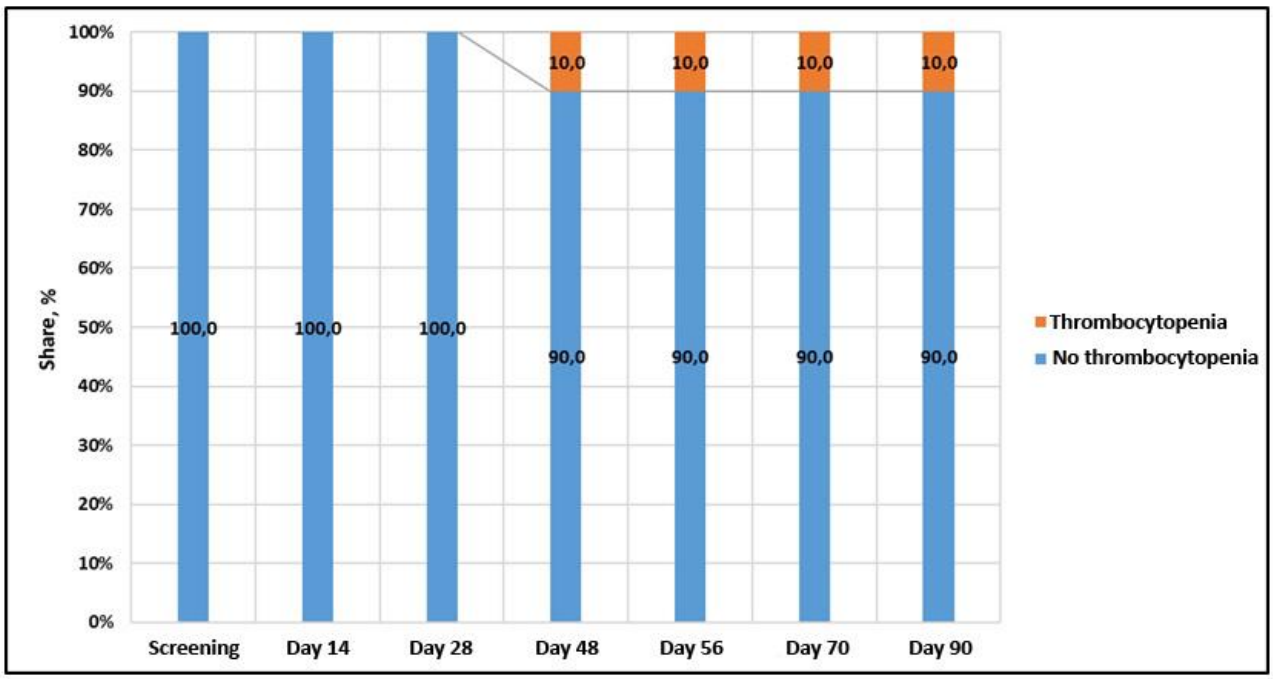

Fig. 8 – Frequency of development of thrombocytopenia in the main group

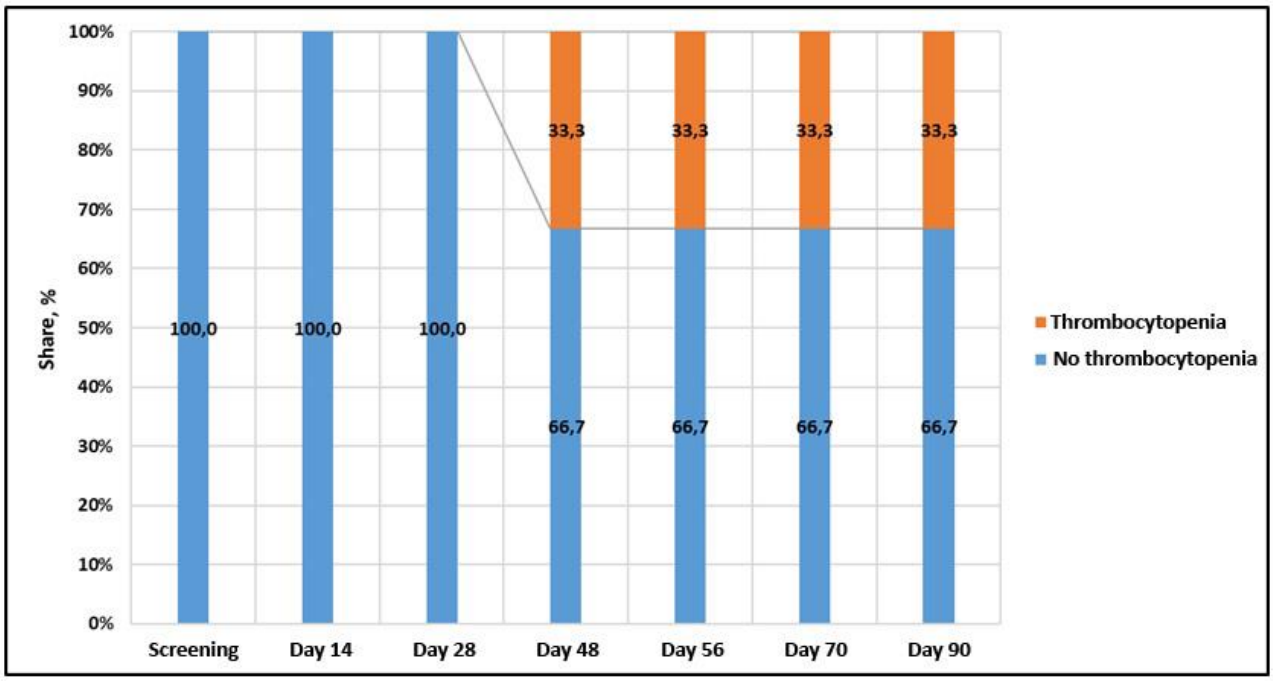

Fig. 9 – Frequency of development of thrombocytopenia in the control group

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

According to other indicators, the differences between the groups are not significant.

15.4.4. Analysis of the dynamics of biochemical blood analysis parameters

Biochemical analysis of blood (ALT, AST, total bilirubin, creatinine, glucose) was carried out during screening (Dsc), and then after each course of chemotherapy.

The results of the analysis of the dynamics of the indicators of biochemical analysis of blood, by the method of descriptive statistics, are shown in the **table. 37** for the main group and in **table. 38** for the comparison group.

Table 37 - Dynamics of indicators of biochemical blood analysis in the process of research in patients of the main group

Parameter	time	n	M	Me	SD	MIN	MAX
ALT, Un/l	Dsc	30	24.49	25	3,884	19	34
	D14	30	26.08	26	4,576	19	34
	D28	30	26.99	27	4,811	20	32
	D42	30	29.59	28	4,827	21	27
	D56	30	32,11	25	4,513	22	40
	D70	30	33.45	26	4,799	24	40
	D90	30	34,42	28	4,542	24	38
	[D14 – Dsc]	30	1.59	1	-	0	0
	[D28 – Dsc]	30	2.5	2	0.347	1	-2
	[D42 – Dsc]	30	5.1	3	0.775	2	-7
	[D56 – Dsc]	30	7.62	0	0.654	3	6
	[D70 – Dsc]	30	8.96	1	0.215	5	6
	[D90 – Dsc]	30	9.93	3	0.226	4	5
AST, Un/l	Dsc	30	25,33	25	3,665	21	34
	D14	30	25,14	25	4,230	21	35
	D28	30	28.57	28	4,906	23	37
	D42	30	28.78	28	4,891	24	38
	D56	30	30.03	30	3,631	24	38
	D70	30	32,14	30	4,233	27	36
	D90	30	35,33	34	3,835	31	38
	[D14 – Dsc]	30	-0.19	0	0.387	0	1
	[D28 – Dsc]	30	3.24	3	0.382	2	3
	[D42 – Dsc]	30	3.45	3	0.265	3	4
	[D56 – Dsc]	30	4.7	5	0.311	3	4
	[D70 – Dsc]	30	6.81	5	0.589	2	6
	[D90 – D0]	30	10	9	0.679	4	10
Total bilirubin, μmol/l	Dsc	30	15.43	15.5	1,787	10.7	17.8
	D14	30	16.38	17.1	3,518	12.1	20.9
	D28	30	17.68	17.4	3,918	14.5	19.5
	D42	30	17.25	17.2	3,657	14.2	19.3
	D56	30	18.46	18.6	3,427	14.2	22.2

	D70	30	18.67	18.5	3,453	14.6	23.1
	D90	30	18.55	18.3	3,221	14.1	24.3
	[D14 – Dsc]	30	0.95	1.6	0.971	1.4	3.1
	[D28 – Dsc]	30	2.25	1.9	1,164	1.7	3.8
	[D42 – Dsc]	30	1.82	1.7	1,439	1.5	3.5
	[D56 – Dsc]	30	3.03	3.1	1,562	3.5	4.4
	[D70 – Dsc]	30	3.24	3	1,620	3.9	5.3
	[D90 – Dsc]	30	3.12	2.8	1,843	3,4	6.5
Creatinine, μmol/l	Dsc	30	73.4	72	12,712	52	96
	D14	30	72.5	70	10,367	62	98
	D28	30	72.8	70	9,725	61	89
	D42	30	73.3	74	10,886	52	90
	D56	30	75.4	72	10,160	54	91
	D70	30	77.5	72	10,033	62	92
	D90	30	78.2	72	10,180	61	95
	[D14 – Dsc]	30	-0.9	-2	7,324	2	10
	[D28 – Dsc]	30	-0.6	-2	8,357	-7	9
	[D42 – Dsc]	30	-0.1	2	7,235	-6	0
	[D56 – Dsc]	30	2.0	0	6,896	-5	2
	[D70 – Dsc]	30	4.1	0	10,370	-4	10
	[D90 – Dsc]	30	4.8	0	8,347	-1	9
Glucose, μmol/l	Dsc	30	5.13	5.3	0.488	4.2	5.9
	D14	30	4.82	4.9	0.594	3.8	5.7
	D28	30	4.86	4.9	0.677	4.4	5.8
	D42	30	5.02	5.0	0.585	4.0	6.1
	D56	30	5.03	5.0	0.587	4.2	6.0
	D70	30	5,12	5.1	0.538	4.3	5.9
	D90	30	4.95	5.0	0.645	4.2	5.7
	[D14 – Dsc]	30	-0.31	-0.4	0.124	-0.4	-0.2
	[D28 – Dsc]	30	-0.27	-0.4	0.136	0.2	-0.1
	[D42 – Dsc]	30	-0.11	-0.3	0.250	-0.2	0.2
	[D56 – Dsc]	30	-0.10	-0.3	0.076	0	0.1
	[D70 – Dsc]	30	-0.01	-0.2	0.069	0	0.1
	[D90 – Dsc]	30	-0.18	-0.3	0.084	0	-0.2

Table 38 - Dynamics of indicators of biochemical blood analysis in the process of research in patients of the control group

Parameter	time	n	M	Me	CO	MIN	MAX
ALT, Un/l	Dsc	30	26.07	26	4,094	21	39
	D14	30	28.53	28	4,497	21	43
	D28	30	30.45	28	4,799	22	48
	D42	30	35,32	34	6,373	22	55
	D56	30	38,49	36	7,337	26	59

	D70	30	40.53	42	7,120	27	58
	D90	30	38,42	38	7,326	22	60
	[D14 – Dsc]	30	2.46	2	1.125	0	4
	[D28 – Dsc]	30	4.38	2	2,225	1	9
	[D42 – Dsc]	30	9.25	8	5,126	1	16
	[D56 – Dsc]	30	12.42	10	6,440	5	20
	[D70 – Dsc]	30	14.46	16	6,317	6	19
	[D90 – Dsc]	30	12.35	12	7,218	1	21
AST, Un/l	Dsc	30	27,19	28	3,673	20	36
	D14	30	26,14	26	4,637	23	42
	D28	30	29.57	30	4,096	24	48
	D42	30	35.78	35	5,943	30	46
	D56	30	37.03	37	7,373	35	49
	D70	30	38,14	36	7,732	34	54
	D90	30	40.33	40	7,810	34	57
	[D14 – Dsc]	30	-1.05	-2	1,309	3	6
	[D28 – Dsc]	30	2.38	2	2,709	4	12
	[D42 – Dsc]	30	8.59	7	1,304	7	10
	[D56 – Dsc]	30	9.84	9	1,402	13	15
	[D70 – Dsc]	30	10.95	8	1,576	14	18
	[D90 – D0]	30	13,14	12	2,052	14	21
Total bilirubin, μmol/l	Dsc	30	16.04	16.1	1,345	14.4	19.3
	D14	30	17.38	17.8	2,653	12.1	20.3
	D28	30	17.68	17.8	3,693	13.5	19.5
	D42	30	18.15	18.3	3,178	12.2	27.2
	D56	30	20.46	21.2	3,650	12.2	31.2
	D70	30	21.67	22.5	5,332	13.8	37.1
	D90	30	21.81	24.8	5,739	13.1	35.3
	[D14 – Dsc]	30	1.34	1.7	1,096	-2.3	1
	[D28 – Dsc]	30	1.64	1.7	2,225	-0.9	0.2
	[D42 – Dsc]	30	2.11	2,2	0.986	-2.2	7.9
	[D56 – Dsc]	30	4.42	5.1	1,113	-2.2	11.9
	[D70 – Dsc]	30	5.63	6.4	1,479	-0.6	17.8
	[D90 – Dsc]	30	5.77	8.7	1,603	-1.3	16
Creatinine, μmol/l	Dsc	30	72.8	74	11,689	50	88
	D14	30	72.9	74	10,132	58	82
	D28	30	73.1	80	10,059	60	91
	D42	30	74.8	70	9,562	59	94
	D56	30	76.5	72	11,004	64	89
	D70	30	78.6	74	11,022	61	92
	D90	30	79.3	74	11,064	61	91
	[D14 – Dsc]	30	0.1	0	4,314	-6	8
	[D28 – Dsc]	30	0.3	6	1,315	3	10
	[D42 – Dsc]	30	2	-4	1,106	6	9
	[D56 – Dsc]	30	3.7	-2	3,886	1	14
	[D70 – Dsc]	30	5.8	0	2,718	4	11

	[D90 – Dsc]	30	6.5	0	2,817	3	11
Glucose, μmol/l	Dsc	30	4.92	5.0	0.502	4.0	6.1
	D14	30	4.76	4.8	0.671	3.6	5.9
	D28	30	5.01	5.0	0.656	4.5	5.8
	D42	30	4.84	4.9	0.624	4.1	6.0
	D56	30	5.23	5.4	0.616	3.8	6.4
	D70	30	4.82	4.9	0.664	3.8	6.2
	D90	30	4.84	4.8	0.597	4.0	6.2
	[D14 – Dsc]	30	-0.16	-0.2	0.276	-0.4	-0.2
	[D28 – Dsc]	30	0.09	0	0.311	0.5	-0.3
	[D42 – Dsc]	30	-0.08	-0.1	0.261	0.1	-0.1
	[D56 – Dsc]	30	0.31	0.4	0.319	-0.2	0.3
	[D70 – Dsc]	30	-0.10	-0.1	0.175	-0.2	0.1
	[D90 – Dsc]	30	-0.08	-0.2	0.120	0	0.1

Graphically, the dynamics of average values is shown in **Fig. 10 - 13** .

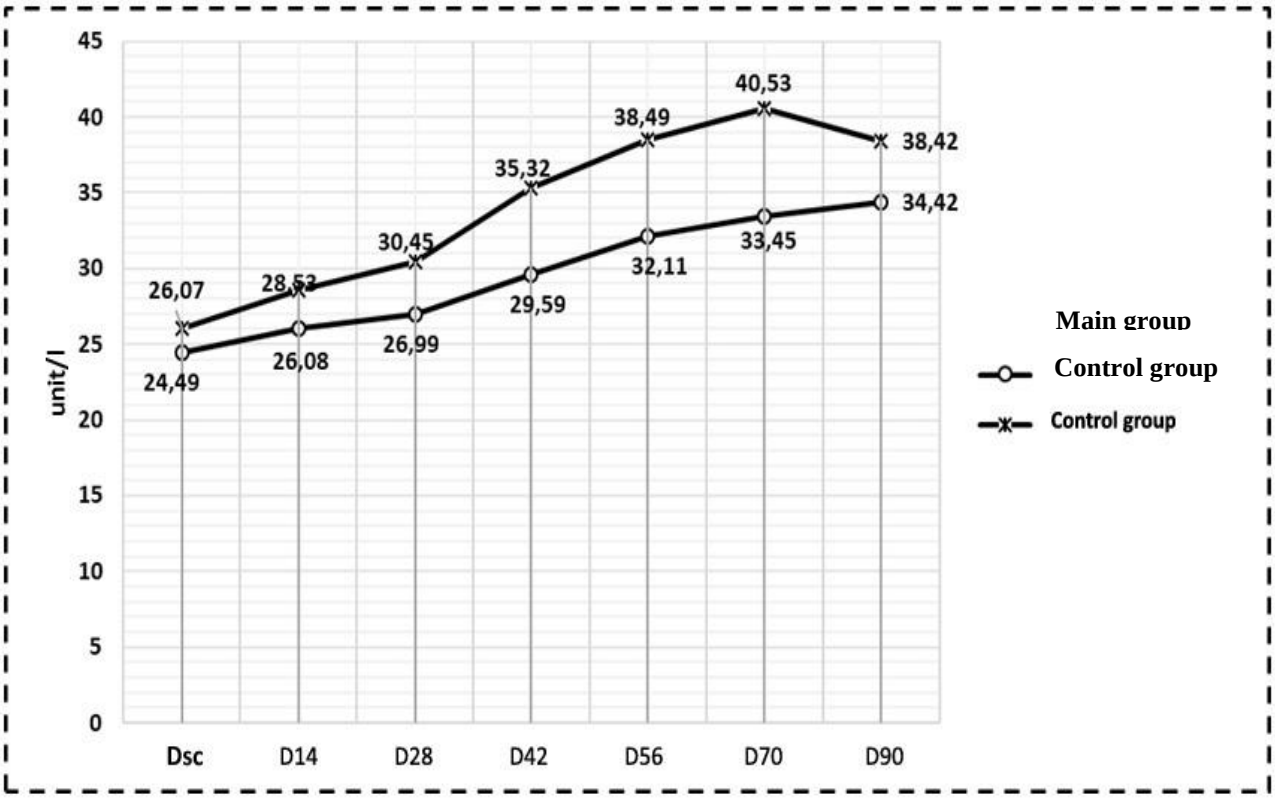

Fig. 10 – Dynamics of average ALT values in groups

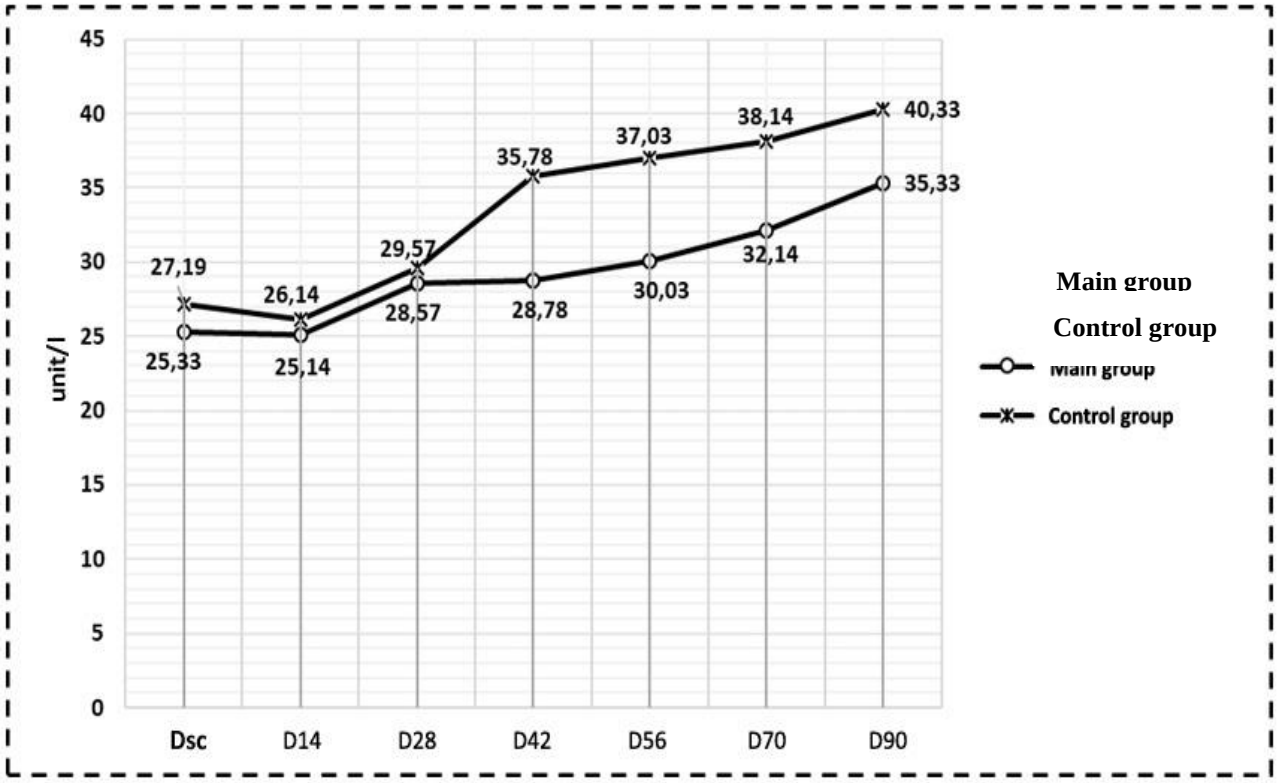

Fig. 11 – Dynamics of average AST values in groups

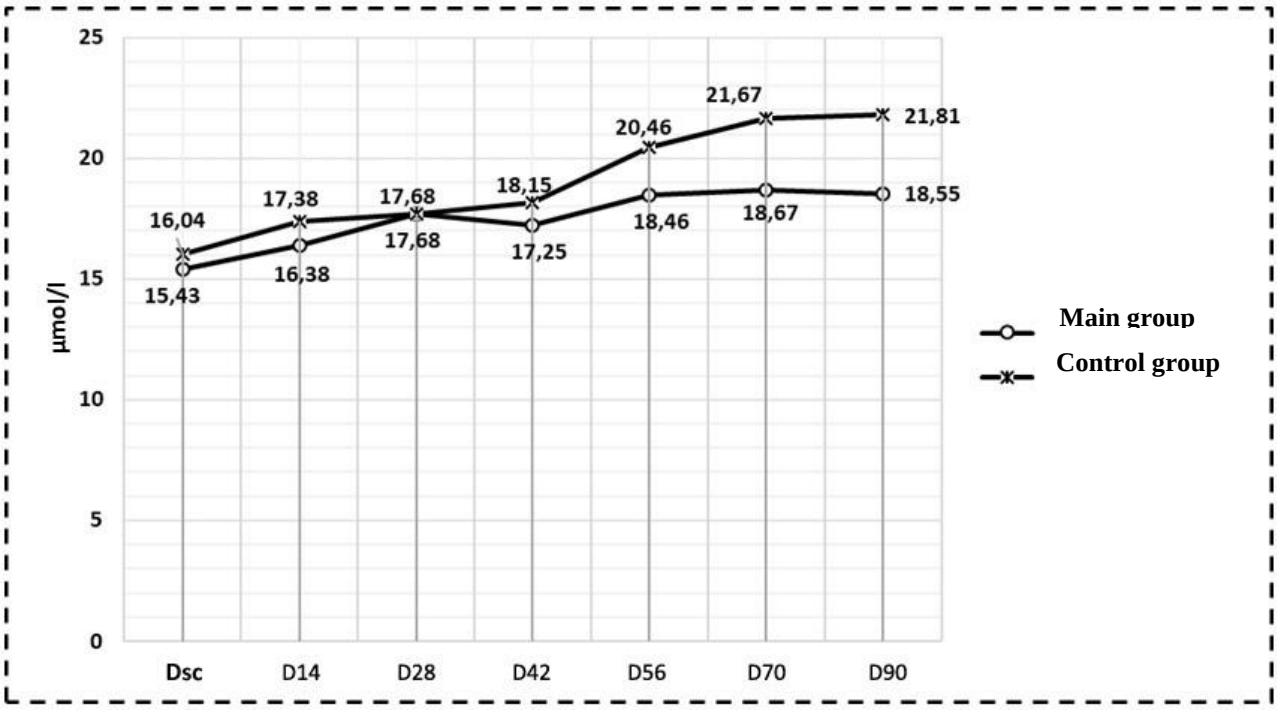

Fig. 12 – Dynamics of average values of total bilirubin in groups

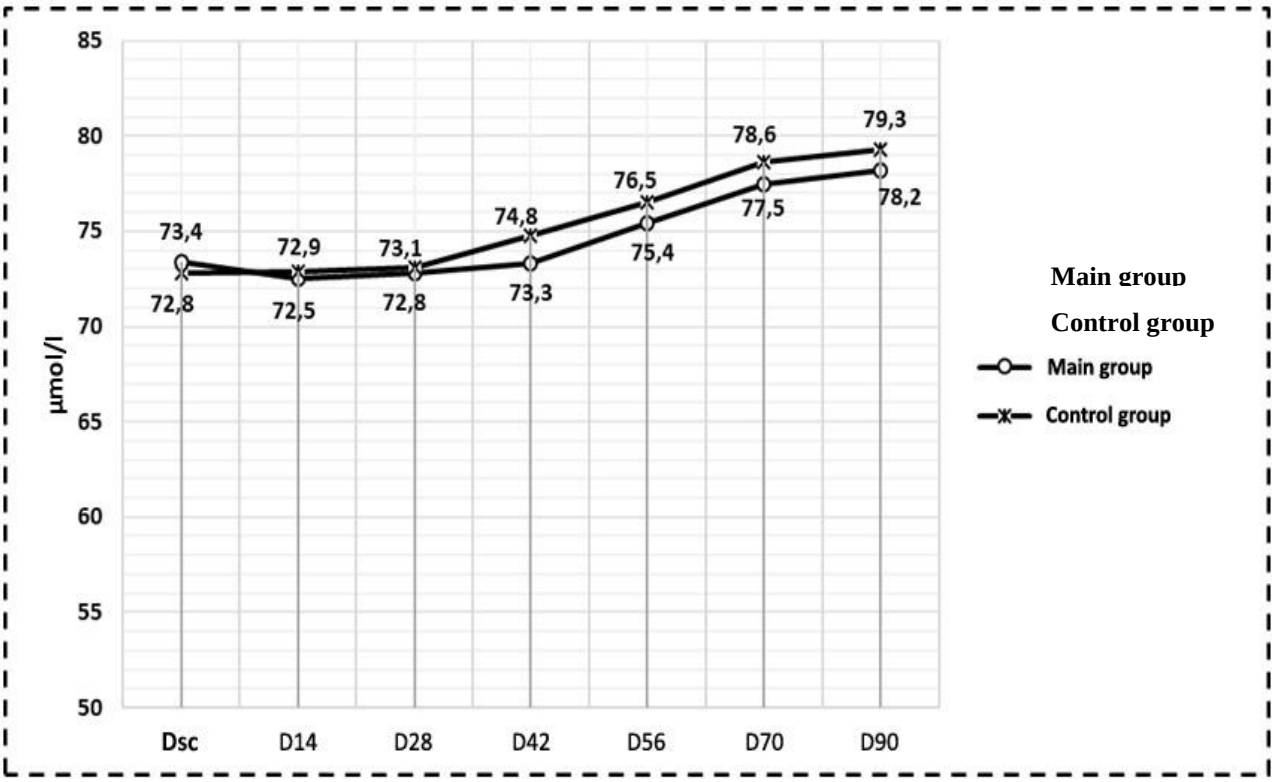

Fig. 13 – Dynamics of average creatinine values in groups

As can be seen from the graphs, an increase in the level of ALT, AST and bilirubin was noted in the patients of the main and control groups. These changes indicated a negative effect of chemopreparations on the hepatobiliary system. It should be noted that the changes in the above indicators in the main group were of a less pronounced nature.

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, D14, D28, D42, D56, D70, D90) and the "subjects" factor is random). The results of DA are shown in the **table. 39 - 40**.

A comparison of the following levels of the "visit" factor with the initial data (Dsc) was also performed using the contrast analysis of the **table. 41 - 42**. The normality of the distribution of VA residues was checked using the Shapiro-Wilk test (**Table A.9 of Appendix A**).

Table 39 - The main results of VA indicators of biochemical blood analysis in the main group

Dependent variable	Factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
ALT	Visit	363,293	6	60,549	5,772	0.000
	Patients	2474,961	29	85,343	8,136	0.000
AST	Visit	2369,242	6	394,874	33,013	0.000
	Patients	1657,631	29	57,160	4,779	0.000
Total bilirubin	Visit	267,412	6	44,569	1,814	0.098
	Patients	1526,253	29	52,629	11,116	0.000
Creatinine	Visit	127,199	6	21,200	1,888	0.066
	Patients	19802.629	29	682,849	70,468	0.000
Glucose	Visit	2,519	6	,420	1,765	0.139
	Patients	58,663	29	2,023	10,912	0.000

Table 40 - The main results of VA indicators of biochemical blood analysis in the control group

Dependent variable	Factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
ALT	Visit	6576,545	6	1096,091	17,509	0.000
	Patients	12631.300	29	435,562	6,958	0.000
AST	Visit	5845.959	6	974,326	52,390	0.000
	Patients	3459,851	29	119,305	1,615	0.123
Total bilirubin	Visit	1240,136	6	206,689	17,729	0.000
	Patients	3011,152	29	103,833	8,907	0.000
Creatinine	Visit	1549,881	6	258,313	1,857	0.072
	Patients	15556,539	29	536,432	14,240	0.000
Glucose	Visit	4,660	6	0.777	1,521	0.170
	Patients	79,399	29	2,738	15,940	0.000

Table 41 - Results of contrast analysis of indicators of biochemical blood analysis in the main group

Dependent variable	Contrasts	Estimated contrast	Stand. mistake	p-value*
ALT	D_{14} - Dsc	0.897	0.836	0.258
	D_{28} - Dsc	1,510		0.060
	D_{42} - Dsc	2,127		0.000*
	D_{56} - Dsc	2,647		0.000*
	D_{70} - Dsc	2,960		0.001*
	D_{90} - Dsc	3,937		0.000*

AST	D_{14} - Dsc	-0.187	0.893	0.835
	D_{28} - Dsc	1,253		0.104
	D_{42} - Dsc	3,453		0.000*
	D_{56} - Dsc	4,720		0.000*
	D_{70} - Dsc	6,820		0.000*
	D_{90} - Dsc	10,010		0.000*
Total bilirubin	D_{14} - Dsc	0.950	0.562	0.293
	D_{28} - Dsc	1,233		0.169
	D_{42} - Dsc	1,500		0.109
	D_{56} - Dsc	2,000		0.080
	D_{70} - Dsc	2,133		0.070
	D_{90} - Dsc	2,202		0.055
Creatinine	D_{14} - Dsc	-0.907	0.804	0.261
	D_{28} - Dsc	-1.087		0.057
	D_{42} - Dsc	0.407		0.614
	D_{56} - Dsc	-1.003		0.214
	D_{70} - Dsc	-0.907		0.261
	D_{90} - Dsc	-1,203		0.136
Glucose	D_{14} - Dsc	-0.300	0.111	0.008*
	D_{28} - Dsc	-0.267		0.018*
	D_{42} - Dsc	-0.100		0.370
	D_{56} - Dsc	-0.090		0.419
	D_{70} - Dsc	-0.007		0.952
	D_{90} - Dsc	-0.173		0.121
** Statistically significant differences are observed* *The conclusion is made at a significance level of 0.05*				

Table 42 - Results of contrast analysis of indicators of biochemical blood analysis in the control group

Dependent variable	Contrasts	Estimated contrast	Stand. mistake	p-value*
ALT	D_{14} - Dsc	1,463	2,043	0.230
	D_{28} - Dsc	1,687		0.125
	D_{42} - Dsc	3,250		0.000*
	D_{56} - Dsc	4,467		0.000*
	D_{70} - Dsc	4,487		0.000*
	D_{90} - Dsc	4,367		0.000*
AST	D_{14} - Dsc	-1.067	1,113	0.339
	D_{28} - Dsc	1,370		0.069

	D_{42} - Dsc	8,600		0.000*
	D_{56} - Dsc	9,833		0.000*
	D_{70} - Dsc	10,913		0.000*
	D_{90} - Dsc	13,113		0.000*
Total bilirubin	D_{14} - Dsc	1.007	0.882	0.437
	D_{28} - Dsc	1,243		0.364
	D_{42} - Dsc	1,590		0.222
	D_{56} - Dsc	1,717		0.140
	D_{70} - Dsc	1,830		0.087
	D_{90} - Dsc	2,163		0.052
Creatinine	D_{14} - Dsc	-0.300	1,585	0.850
	D_{28} - Dsc	2,197		0.053
	D_{42} - Dsc	-2,020		0.063
	D_{56} - Dsc	0.703		0.658
	D_{70} - Dsc	0.803		0.613
	D_{90} - Dsc	0.493		0.756
Glucose	D_{14} - Dsc	-0.160	0.107	0.137
	D_{28} - Dsc	0.083		0.437
	D_{42} - Dsc	-0.093		0.384
	D_{56} - Dsc	0.210		0.154
	D_{70} - Dsc	-0.107		0.320
	D_{90} - Dsc	-0.083		0.437
** Statistically significant differences are observed* *The conclusion is made at a significance level of 0.05*				

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

1. In the main group, a statistically significant increase in the level of ALT and AST was revealed after the third course of CT.
2. In the control group, a statistically significant increase in the level of ALT and AST was revealed after the third course of CT.
3. Changes in other biochemical indicators in both groups were within the physiological norm and were not statistically and clinically significant.

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

Since in the initial state the groups did not differ statistically significantly according to the indicators of the biochemical blood analysis, the comparison between the groups was performed according to the differences in dT_i with the help of the Mann-Whitney test, because individual differences dT_i are not distributed normally in both groups (see **Tables A.10-A.11 of Appendix A**). The results of this comparison are shown in **Table 43.**

Table 43. Comparison of groups using the Mann-Whitney criterion on the dynamics of indicators of biochemical blood analysis

Indicator	dTi	U of Mann-Whitney	Wilcoxon W	Z-statistics	p-value (two-way)	Differences between groups
ALT	dT14	362,000	827,000	-1.637	0.102	Not significant
	dT28	440,500	905,500	-0.167	0.867	Not significant
	dT42	375,000	840,000	-1,204	0.229	Not significant
	dT56	445,500	810,500	-1,604	0.150	Not significant
	dT70	383,500	748,500	-1.582	0.179	Not significant
	dT90	441,000	816,000	-1.652	0.136	Not significant
AST	dT14	424,000	889,000	-0.570	0.569	Not significant
	dT28	446,000	911,000	-0.068	0.946	Not significant
	dT42	400,500	865,500	-1.741	0.105	Not significant
	dT56	433,500	898,500	-1.815	0.075	Not significant
	dT70	320,000	785,000	-1.924	0.054	Not significant
	dT90	355,500	820,500	-1,398	0.162	Not significant
Total bilirubin	dT14	412,500	877,500	-0.684	0.494	Not significant
	dT28	436,500	901,500	-0.223	0.824	Not significant
	dT42	448,500	913,500	-0.025	0.980	Not significant
	dT56	402,500	867,500	-0.746	0.456	Not significant
	dT70	359,000	824,000	-1,404	0.160	Not significant
	dT90	305,500	770,500	-1,518	0.134	Not significant
Creatinine	dT14	448,000	913,000	-0.068	0.945	Not significant
	dT28	486,000	851,000	-1.615	0.091	Not significant
	dT42	362,500	827,500	-1,498	0.134	Not significant
	dT56	439,500	904,500	-0.204	0.838	Not significant
	dT70	447,000	912,000	-0.057	0.955	Not significant
	dT90	401,000	866,000	-0.931	0.352	Not significant
Glucose	dT14	392,500	857,500	-1.147	0.251	Not significant
	dT28	425,500	890,500	-1,421	0.175	Not significant
	dT42	440,500	905,500	-0.165	0.869	Not significant
	dT56	405,500	870,500	-0.728	0.467	Not significant
	dT70	400,000	865,000	-0.998	0.318	Not significant
	dT90	449,500	914,500	-0.008	0.993	Not significant
	dT90	362,000	827,000	-1.637	0.102	Not significant

Conclusion: based on the results of the analysis given in table. 42, it is possible to state that the groups did not differ statistically significantly in terms of 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 table of frequencies. Fisher's exact test was used to compare frequencies. The results of this analysis are shown in **table. 44**.

Table 44. Results of the analysis of indicators of biochemical blood analysis

Indicator	time	Category	Main group (n = 30)		Control group (n = 30)		p-value*
			n	%	n	%	
ALT, Un/l	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D14	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D28	Norm	29	96.7	27	90.0	1,000
		Outside the norm	1	3.3	3	10.0	
	D42	Norm	26	86.7	22	73.3	0.103
		Outside the norm	4	13.3	8	26.7	
	D56	Norm	26	86.7	22	73.3	0.103
		Outside the norm	4	13.3	8	26.7	
	D70	Norm	26	86.7	22	73.3	0.103
		Outside the norm	4	13.3	8	26.7	
	D90	Norm	27	90.0	24	80.0	0.103
		Outside the norm	3	10.0	6	20.0	
AST, Un/l	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D14	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D28	Norm	30	100.0	28	93.3	1,000
		Outside the norm	0	0	2	6,7	
	D42	Norm	26	86.7	22	73.3	0.103
		Outside the norm	4	13.3	8	26.7	
	D56	Norm	26	86.7	22	73.3	0.103

		Outside the norm	4	13.3	8	26.7	
	D70	Norm	26	86.7	22	73.3	0.103
		Outside the norm	4	13.3	8	26.7	
	D90	Norm	26	86.7	27	90.0	0.103
		Outside the norm	4	13.3	3	10.0	
Total bilirubin, μmol/l	Dsc	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D14	It's normal	30	100.0	30	100.0	1,000
		Outside the norm	0	0	0	0	
	D28	Norm	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	
	D56	Norm	30	100.0	27	90.0	0.237
		Outside the norm	0	0	3	10.0	
	D70	Norm	30	100.0	27	90.0	0.237
		Outside the norm	0	0	3	10.0	
	D90	Norm	30	100.0	27	90.0	0.237
		Outside the norm	0	0	3	10.0	
** Estimated using Fisher's exact test.*							

As can be seen from table 44, in the majority of patients, indicators of biochemical blood analysis, throughout the study, were within the physiological norm. The toxic effect of the applied chemotherapy was mainly manifested in the increase in the level of such indicators as: ALT and AST. Thus, an increase in the level of ALT and AST was observed in 4 (13.3%) patients of the main group and in 8 (26.7%) patients of the control group. Elevation of bilirubin – in 3 (10.0%) patients of the control group.

Conclusion There was no significant difference in the frequency of ALT, AST and bilirubin elevation in patients between groups.

15.4.6. Analysis of dynamics of general urine analysis parameters.

General analysis of urine (specific gravity, pH, protein, glucose, leukocytes, erythrocytes, cylinders, epithelial cells, salts). conducted during 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. 45** for the main group and in the **table. 46** for the control group.

Table 45 - Dynamics of indicators of the general analysis of urine in the process of research in patients of the main group

Parameter	time	n	M	Me	SD	MIN	MAX
Specific weight	Dsc	30	1015.5	1015	3,359	1012	1018
	D14	30	1016.7	1016	3,362	1014	1020
	D28	30	1015.5	1015	3,197	1014	1021
	D42	30	1015.2	1015	3,214	1012	1020
	D56	30	1017.9	1018	4,044	1014	1022
	D70	30	1016.7	1018	3,344	1014	1023
	D90	30	1016.5	1016	3,218	1012	1019
	[D14 – Dsc]	30	1,2	1	0.650	0	2
	[D28 – Dsc]	30	0	0	0.322	2	3
	[D42 – Dsc]	30	-0.3	0	0.570	0	2
	[D56 – Dsc]	30	2.4	3	0.456	2	4
	[D70 – Dsc]	30	1,2	3	0.634	2	5
	[D90 – Dsc]	30	1.0	1	0.135	0	1
pH	Dsc	30	5.40	5.5	0.178	5.2	5.5
	D14	30	5.50	5.5	0.282	5.0	5.7
	D28	30	5.60	5.5	0.300	4.8	5.9
	D42	30	5.63	5,6	0.316	4.9	6.0
	D56	30	5.66	5,6	0.312	5.0	5.8
	D70	30	5.52	5.5	0.350	5.2	5.9
	D90	30	5.54	5.5	0.336	5.0	6.0
	[D14 – Dsc]	30	0.1	0	0.233	-0.2	0.2
	[D28 – Dsc]	30	0.2	0	0.328	-0.4	0.4
	[D42 – Dsc]	30	0.23	0.1	0.338	-0.3	0.5
	[D56 – Dsc]	30	0.26	0.1	0.351	-0.2	0.3
	[D70 – Dsc]	30	0.12	0	0.376	0	0.4
	[D90 – D0]	30	0.14	0	0.320	-0.2	0.5
Leukocytes, cells in sight	Dsc	30	3.5	4	1,450	0	5
	D14	30	3.2	3	1,190	0	7
	D28	30	3.5	3	1,141	0	7
	D42	30	4.0	4	1,577	0	7
	D56	30	3.1	3	1,189	0	6
	D70	30	3.0	3	1,208	0	7
	D90	30	3,4	3	1,166	0	7
	[D14 – Dsc]	30	-0.3	-1	0.302	0	2
	[D28 – Dsc]	30	0	-1	0.307	0	2
	[D42 – Dsc]	30	0.5	0	0.325	0	2
	[D56 – Dsc]	30	-0.4	-1	0.160	0	1
	[D70 – Dsc]	30	-0.5	-1	0.275	0	2
	[D90 – Dsc]	30	-0.1	-1	0.250	0	2

Erythrocytes, cells in sight	Dsc	30	1.0	1	1,264	0	4
	D14	30	2.0	2	1,372	0	5
	D28	30	2,2	2	1,304	0	5
	D42	30	2.1	2	1,386	0	4
	D56	30	2,2	2	1,315	0	4
	D70	30	2.1	2	1,367	0	4
	D90	30	2.1	2	1,390	0	4
	[D14 – Dsc]	30	1.0	1	0.109	0	1
	[D28 – Dsc]	30	1,2	1	0.125	0	1
	[D42 – Dsc]	30	1.1	1	-	0	0
	[D56 – Dsc]	30	1,2	1	-	0	0
	[D70 – Dsc]	30	1.1	1	-	0	0
	[D90 – Dsc]	30	1.1	1	-	0	0
	[D90 – Dsc]	30	1.0	1	0.114	0	1

Table 46 - Dynamics of indicators of the general analysis of urine in the process of research in patients of the control group

Parameter	time	n	M	Me	SD	MIN	MAX
Specific weight	Dsc	30	1017.0	1018	3,509	1012	1019
	D14	30	1016.7	1016	3,238	1014	1020
	D28	30	1015.5	1015	3,116	1014	1021
	D42	30	1015.2	1015	3,250	1012	1020
	D56	30	1017.9	1018	3,887	1014	1022
	D70	30	1016.7	1018	3,349	1014	1023
	D90	30	1016.5	1016	3,216	1012	1019
	[D14 – Dsc]	30	-0.3	-2	0.256	1	2
	[D28 – Dsc]	30	-1.5	-3	0.314	0	2
	[D42 – Dsc]	30	-1.8	-3	0.179	0	1
	[D56 – Dsc]	30	0.9	0	0.214	2	3
	[D70 – Dsc]	30	-0.3	0	0.216	2	4
	[D90 – Dsc]	30	-0.5	-2	-	0	0
pH	Dsc	30	5.32	5,6	0.192	5.1	5.5
	D14	30	5.52	5.5	0.216	5.0	5.7
	D28	30	5.60	5.5	0.301	4.8	5.9
	D42	30	5.56	5,6	0.309	4.9	6.0
	D56	30	5.61	5,6	0.315	5.0	5.8
	D70	30	5.58	5,6	0.401	5.2	5.9
	D90	30	5.55	5,6	0.433	5.0	6.0
	[D14 – Dsc]	30	0.2	-0.1	0.348	-0.1	0.2
	[D28 – Dsc]	30	0.28	-0.1	0.400	-0.3	0.4
	[D42 – Dsc]	30	0.24	0	0.403	-0.2	0.5
	[D56 – Dsc]	30	0.29	0	0.419	-0.1	0.3
	[D70 – Dsc]	30	0.26	0	0.445	0.1	0.4
	[D90 – D0]	30	0.23	0	0.392	-0.1	0.5
Leukocytes, cells in sight	Dsc	30	3.3	3	1,651	0	6
	D14	30	3.2	3	1,790	0	7
	D28	30	3.5	3	1,892	0	7
	D42	30	4.0	4	1,863	0	7
	D56	30	3.1	3	1,609	0	6

	D70	30	3.0	3	1,714	0	7
	D90	30	3,4	3	1,745	0	7
	[D14 – Dsc]	30	-0.1	0	0.107	0	1
	[D28 – Dsc]	30	0.2	0	0.126	0	1
	[D42 – Dsc]	30	0.7	1	0.104	0	1
	[D56 – Dsc]	30	-0.2	0	-	0	0
	[D70 – Dsc]	30	-0.3	0	0.087	0	1
	[D90 – Dsc]	30	0.1	0	0.095	0	1
Erythrocytes, cells in sight	Dsc	30	0.9	1	1,119	0	3
	D14	30	1.6	2	1,235	0	5
	D28	30	1.9	2	1,260	0	5
	D42	30	2.1	2	1,076	0	4
	D56	30	2,2	2	1,420	0	6
	D70	30	2.0	2	1,110	0	4
	D90	30	2.1	2	1,115	0	4
	[D14 – Dsc]	30	0.7	1	0.281	0	2
	[D28 – Dsc]	30	1	1	0.275	0	2
	[D42 – Dsc]	30	1,2	1	0.170	0	1
	[D56 – Dsc]	30	1.3	1	0.345	0	3
	[D70 – Dsc]	30	1.1	1	0.165	0	1
	[D90 – Dsc]	30	1,2	1	0.153	0	1
	[D90 – Dsc]	30	0.7	1	0.204	0	2

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

For the rest of the parameters, an analysis of the significance of changes during the study period was performed.

To evaluate the dynamics of general urinalysis indicators, 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, D90) and the "subjects" factor is random). The results of VA are shown in the **table. 47 - 48**.

A comparison of the following levels of the "visit" factor with the initial data (Dsc) was also performed using the contrast analysis **of tables 49 - 50**. The normality of the distribution of VA residues was checked using the Shapiro-Wilk test (**Table A.12 of Appendix A**).

Table 47 - The main results of DA indicators of the general analysis of urine in the main group

Dependent variable	Factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
Specific weight	Visit	155,314	6	25,886	8,050	0.000
	Patients	1665,124	29	57,418	17,855	0.000
pH	Visit	1,383	6	0.231	4,411	0.000
	Patients	9,224	29	0.318	6,086	0.000
Leukocytes, cells in sight	Visit	20,057	6	3,343	8,707	0.000
	Patients	246,208	29	8,490	22,114	0.000
Erythrocytes, cells in sight	Visit	29,200	6	4,867	9,475	0.000
	Patients	258,195	29	8,903	17,334	0.000

Table 48 - The main results of DA indicators of the general analysis of urine in the control group

Dependent variable	Factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
Specific weight	Visit	143,324	6	23,887	6,848	0.000
	Patients	1732,171	29	59,730	17,123	0.000
pH	Visit	1,776	6	0.296	3,773	0.001
	Patients	7,575	29	0.261	3,330	0.000
Leukocytes, cells in sight	Visit	19,714	6	3,286	8,662	0.000
	Patients	243,848	29	8,409	22,168	0.000
Erythrocytes, cells in sight	Visit	32,057	6	5,343	8,159	0.000
	Patients	183,124	29	6,315	9,643	0.000

Table 49 - Results of the contrast analysis of indicators of the general analysis of urine in the main group

Dependent variable	Contrasts	Estimated contrast	Stand. mistake	p-value*
Specific weight	D14 - Dsc	1,167	0.463	0.013*
	D28 - Dsc	0.000		1,000
	D42 - Dsc	-0.267		0.565
	D56 - Dsc	2,367		0.000*
	D70 - Dsc	1,167		0.013*
	D90 - Dsc	1,000		0.032*
pH	D14 - Dsc	0.097	0.059	0.103
	D28 - Dsc	0.197		0.001*
	D42 - Dsc	0.230		0.000*
	D56 - Dsc	0.257		0.000*

	D70 - Dsc	0.123		0.038*
	D90 - Dsc	0.140		0.019*
Leukocytes, cells in sight	D14 - Dsc	-0.300	0.160	0.062
	D28 - Dsc	0.000		1,000
	D42 - Dsc	0.500		0.002*
	D56 - Dsc	-0.400		0.013*
	D70 - Dsc	-0.500		0.002*
	D90 - Dsc	-0.100		0.533
Erythrocytes, cells in sight	D14 - Dsc	0.933	0.185	0.000*
	D28 - Dsc	1,133		0.000*
	D42 - Dsc	1,033		0.000*
	D56 - Dsc	1,133		0.000*
	D70 - Dsc	1,033		0.000*
	D90 - Dsc	1,033		0.000*
** Statistically significant differences are observed* *The conclusion is made at a significance level of 0.05*				

Table 50 - Results of the contrast analysis of indicators of the general analysis of urine in the control group

Dependent variable	Contrasts	Estimated contrast	Stand. mistake	p-value*
Specific weight	D14 - Dsc	-0.333	0.482	0.490
	D28 - Dsc	-1,500		0.002*
	D42 - Dsc	-1.767		0.000*
	D56 - Dsc	0.867		0.074
	D70 - Dsc	-0.333		0.490
	D90 - Dsc	-0.533		0.270
pH	D14 - Dsc	0.197	0.072	0.007*
	D28 - Dsc	0.277		0.000*
	D42 - Dsc	0.237		0.001*
	D56 - Dsc	0.293		0.000*
	D70 - Dsc	0.260		0.000*
	D90 - Dsc	0.230		0.002*
Leukocytes, cells in sight	D14 - Dsc	-0.100	0.159	0.530
	D28 - Dsc	0.200		0.210
	D42 - Dsc	0.700		0.000*
	D56 - Dsc	-0.200		0.210
	D70 - Dsc	-0.300		0.061
	D90 - Dsc	0.100		0.530
Erythrocytes, cells in sight	D14 - Dsc	0.600	0.209	0.005
	D28 - Dsc	0.900		0.000*
	D42 - Dsc	1,100		0.000*
	D56 - Dsc	1,200		0.000*
	D70 - Dsc	1,033		0.000*
	D90 - Dsc	1,100		0.000*
** Statistically significant differences are observed* *The conclusion is made at a significance level of 0.05*				

Conclusion As can be seen from the conducted analysis, in some cases statistically significant changes were observed in the course of treatment according to the analyzed indicator of the general urine analysis, but they were not clinically significant.

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 toxicity of chemotherapy during treatment. It was assumed that the use of the research drug Donovit-VS®, against the background of adjuvant 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 evaluated after each course of chemotherapy according to the CTC *NCIC* toxicity scale .

Of the 60 patients who received postoperative chemotherapy according to the FOLFOX-4 scheme, complications developed in 100.0% of patients, but in most cases they were of a mild nature. Toxic reactions of the applied chemotherapy regimen were predictable, manageable and corresponded mainly to the 1st and 2nd degrees of toxicity on the CTC *NCIC scale.* Grade 3 toxicity was observed only in 2 patients (3.3%). *None of the patients, according to any of the parameters, did not have grade 4 toxicity throughout the study.*

Gastrointestinal toxicity was noted most often in patients, its manifestations of the 1st and 2nd degree were noted in 45 (75.0%) patients and 3rd degree - in 1 (1.7%). Neurotoxicity was the second most frequent complication and was observed in 32 patients (53.3%), but only in 2 (3.3%) patients it reached the 2nd degree. Hematological toxicity of the 1st degree was revealed in 26 patients (43.3%), 2nd degree - in 6 (10.0%) - and 3rd degree - in 1 patient. Hepatotoxicity of the 1st degree developed in 7 patients (23.3%), in 5 (16.7%) patients this complication had the 2nd degree of severity. Cutaneous manifestations were observed in 10 patients. Reduction of courses of adjuvant treatment due to the development of toxic effects - in 2 patients (5.0%).

It should be noted that none of the patients, both in the main and control groups, had allergic reactions, deterioration of the heart and lungs, heart rhythm disturbances,

stomatitis, proteinuria, hemorrhagic manifestations and complications in the form of infections during the study.

The absence of cardiological toxicity of chemotherapy was confirmed by ECG data, which was performed on patients after each course of chemotherapy.

15.5.2. Analysis of hematological toxicity in groups

Hematological toxicity was detected in 11 (36.7%) patients of the main group and in 22 (86.7%) patients of the control group. The most frequent complication of chemotherapy from the blood system was the development of leukopenia, anemia, and thrombocytopenia.

Leukopenia of the 1st degree was detected in 6 (20.0%) patients of the main group and in 11 (36.7%) of the control patients, of the 2nd degree - in 4 (13.3%) of the control patients and of the 3rd degree - in 1 (3.3%) control patient. Anemia of the 1st degree was observed in 2 (6.7%) patients of the main group and in 7 (23.3%) patients of the control group. Thrombocytopenia of the 1st degree in 3 (10.0%) patients of the main group and in 9 (30.0%) patients of the control group, and of the 2nd degree - in 1 (3.3%) patient of the control group.

The frequency of occurrence and the percentage ratio of hematological toxicity of chemotherapy in the groups are presented in the table. 51.

Table 51 - Analysis of hematological toxicity of chemotherapy in groups

Parameter	**degree toxicity**	**The main group n=30**		**Control group n=30**		**P-value***
		n	**%**	**n**	**%**	
Leukopenia	1	6	20.0	11	36.7	0.015**
	2	0	0	4	13.3	
	3	0	0	1	3.3	
Anemia	1	2	6,7	7	23.3	0.148
	2	0	0	0	0	
	3	0	0	0	0	
Thrombocytopenia	1	3	10.0	9	30.0	0.107
	2	0	0	1	3.3	
	3	0	0	0	0	

***** *The analysis was performed using Fisher's exact test*
The conclusion is made at a significance level of 0.05
****** *Statistically significant differences are observed*

Conclusion

1. A higher number of patients with pathological changes in hematological indicators was noted in the control group compared to the main group.
2. A significantly higher frequency of leukopenia was revealed in patients of the control group compared to the main group. For other indicators, the differences are not significant.

15.5.3. Analysis of hepatotoxicity in groups

Hepatotoxicity manifested itself most often in the form of an increase in transaminases. An increase in the level of ALT and AST of the 1st degree of toxicity was observed in 3 (10.0%) patients of the main group and in 5 (16.7%) patients of the control group, in 1 (3.3%) of the main patient and in 3 (10, 0%) patients of the control group had an increase in transaminases of the 2nd degree of severity. Elevation of bilirubin – in 3 (10.0%) patients of the control group.

Table 52 - Analysis of hepatotoxicity in groups

Parameter	degree toxicity	The main group n=30		Control group n=30		P-value*
		n	%	n	%	
ALT	1	3	10.0	4	13.3	0.181
	2	1	3.3	4	13.3	
	3	0	0	0	0	
AST	1	3	10.0	5	16.7	0.333
	2	1	3.3	3	10.0	
	3	0	0	0	0	
Bilirubin	1	0	0	3	10.0	0.237
	2	0	0	0	0	
	3	0	0	0	0	
**The analysis was performed using Fisher's exact test* *Conclusion at the significance level of 0.05*						

Conclusion

1. There was no significant difference in the number of patients with elevated ALT, AST, and bilirubin levels in the control group compared to the primary group.

15.5.4. Analysis of the toxicity of chemotherapy based on objective examination data and subjective complaints

During the study, at each visit, the patient's mucous membranes and skin were examined; palpation and percussion of the abdomen were performed; auscultation of the heart and lungs. When examining and interviewing patients, the presence and severity of the following symptoms were taken into account: allergic reactions, skin manifestations, heart and lung conditions, heart rhythm disorders, nausea, vomiting, dyspeptic phenomena, oral cavity condition, hair coat condition, hemorrhagic phenomena. The state of the nervous system was evaluated.

Nausea and vomiting were the most frequent complications of chemotherapy from the gastrointestinal tract. All 30 patients (100%) of the control group and 13 (43.3%) patients of the main group complained of nausea and bleeding urges of varying intensity throughout the treatment. The severity of these symptoms, in most patients, corresponded to the 1st degree of toxicity according to CTC *NCIC*, and only in 3 (10.0%) patients of the control group, the severity of vomiting corresponded to the 2nd degree of toxicity.

Diarrhea of the 1st and 2nd degree of toxicity was observed in 12 (40.0%) patients of the main group and in 15 (50.0%) patients of the control group, of the 3rd degree - in 1 (3.3%) patient of the control group.

Constipation of the 1st-2nd degree after the 1st and 2nd course of chemotherapy was observed in 3 (10.0%) patients of the main group and in 5 (16.7%) patients of the control group.

Peripheral polyneuropathy of the 1st degree was observed in 13 (43.3.0%) primary patients and in 15 (50.0%) control patients. In 2 (6.7%) patients of the control group, severe paresthesia and weakness were observed (toxicity of the 2nd degree).

On the part of the skin, there was palmo-plantar syndrome in 4 (13.3%) patients of the main group and in 6 (20.0%) patients of the control group.

Minimal hair loss (alopecia) was observed in all patients, both the main and control groups.

The analysis of the toxicity of chemotherapy in groups is presented in the **table. 53**.

Table 53 - Analysis of toxicity of chemotherapy in groups

Parameter	degree toxicity	The main group n=30		Control group, n=30		P-value*
		n	%	n	%	
Nausea/vomiting	1	thirteen	43.3	27	90.0	0.0003**
	2	0	0	3	10.0	
	3	0	0	0	0	
Diarrhea	1	10	33.3	10	33.3	0.401
	2	2	6,7	5	16.7	
	3	0	0	1	3.3	
Constipation	1	3	10.0	5	16.7	0.707
	2	0	0	0	0	
	3	0	0	0	0	
Peripheral polyneuropathy	1	thirteen	43.3	15	50.0	0.439
	2	0	0	2	6,7	
	3	0	0	0	0	
Skin manifestations	1	4	13.3	6	20.0	0.731
	2	0	0	0	0	
	3	0	0	0	0	
Alopecia	1	30	100.0	30	100.0	1,000
	2	0	0	0	0	
	3	0	0	0	0	

**Analysis was performed using Fisher's exact test*
***Statistically significant differences are observed*
Conclusion at the significance level of 0.05

Conclusion . Analyzing the results presented **in the table. 53, it** can be concluded that the control group had a statistically significantly higher number of patients who experienced nausea/vomiting as a result of chemotherapy.

The differences between the groups were not significant for the rest of the indicators.

Summing up, it can be stated that the overall toxicity profile for the group of patients receiving the study drug Donovit-VS® on the background of chemotherapy was less pronounced than in the group receiving only chemotherapy. This indicates a positive effect of the drug Donovit-VS® on 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. 14-15.**

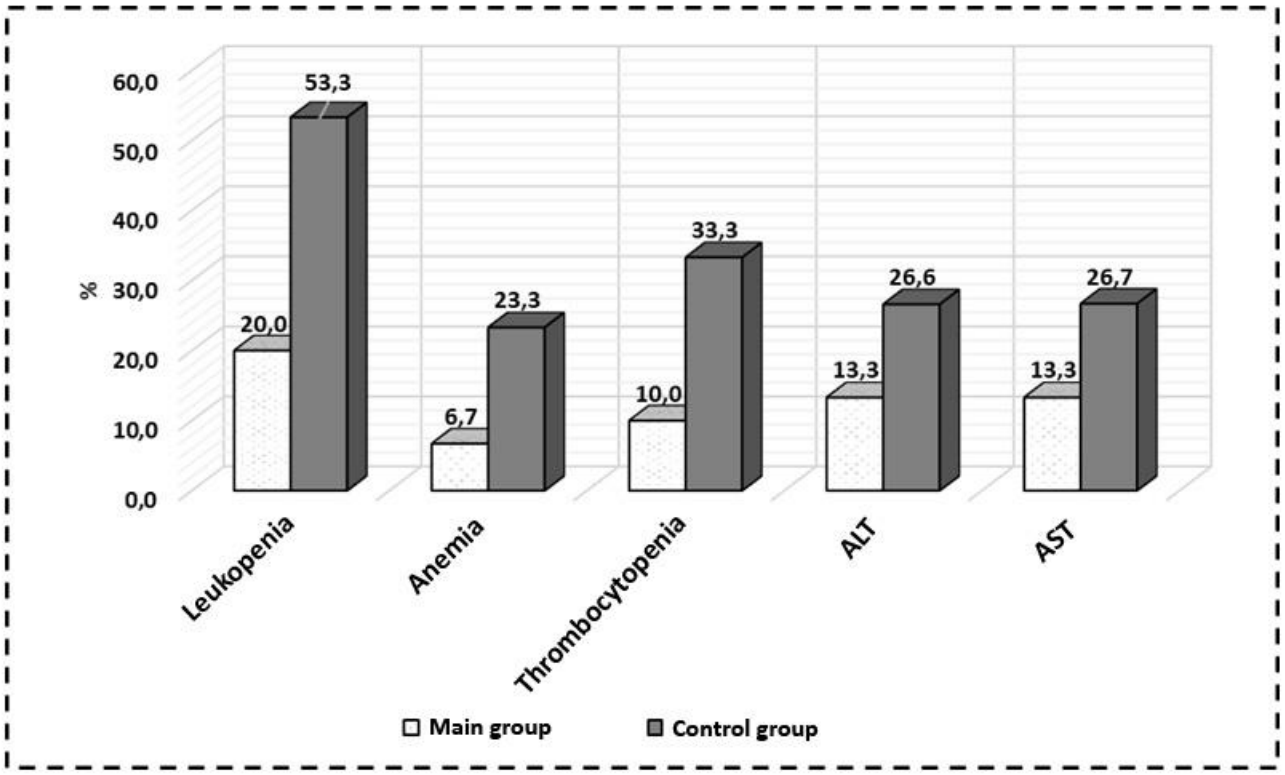

Fig. 14 - Analysis of hematological toxicity and hepatotoxicity of chemotherapy in groups

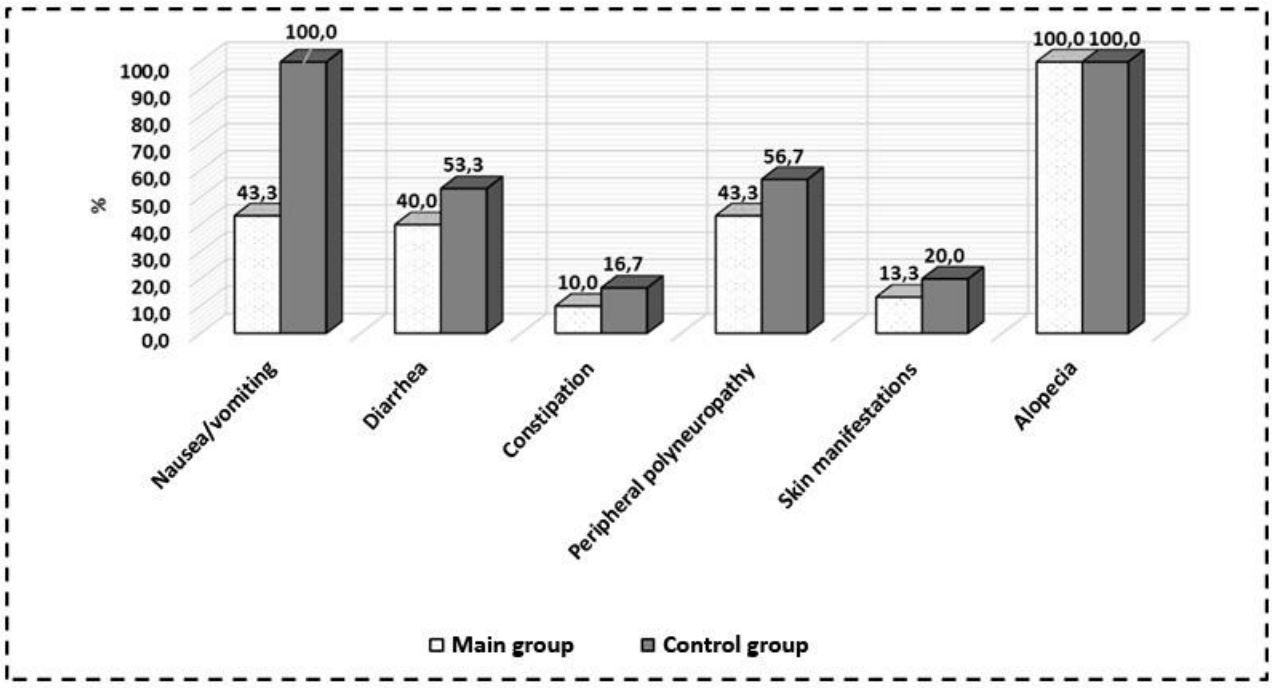

Fig. 15 - Analysis of non-hematological toxicity of chemotherapy in groups

15.6. Assessment of quality of life

Determining the quality of life in research is one of the important criteria for evaluating the effectiveness of treatment in oncology. In this study, the Quality of Life Assessment Questionnaire of the European Organization for Cancer Research and Treatment EORTC QLQ-C30 was used for assessment. The 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; the quality of life scale and the general health status scale. Also included in the questionnaire are additional symptoms (shortness of breath, sleep disturbance, loss of appetite, constipation, diarrhea, and financial difficulties caused by the disease itself and its treatment).

The state of each of the scales was evaluated within 4 gradations: no - 1 point; rather not than not - 2 points; rather yes 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 formula:

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

A higher index also represented a higher level for the quality of life scale and general health status, while a higher index for the functional and symptomatic scales and individual questions represented a higher level of symptom severity.

The level of quality of life was assessed in all patients before the start of chemotherapy, then after the 2nd, 4th and 6th courses (Days 0, 28, 56, 90).

Statistical analysis of the data of the EORTC QLQ-C30 questionnaire, obtained before treatment, revealed no significant differences in indicators in patients of the main and control groups (see **Tables 54-55**).

Table 54. Results of the comparative analysis of groups in the initial state according to the data of the EORTC QLQ-C30 questionnaire, obtained before treatment with the help of descriptive statistics methods

Parameter	Group	n	M	Me	SD	MIN	MAX
General health status	The main group	30	68,66	66.6	14,224	33.3	83.3
	Control group	30	69.42	66.6	14,019	33.3	83.3
General assessment of quality of life	The main group	30	71.31	66.6	14,172	33.3	83.3
	Control group	30	70.58	66.6	15,691	33.3	83.3
Physical function	The main group	30	53.85	50.0	19,597	33.3	100
	Control group	30	54,35	50.0	20,981	33.3	100
Role function	The main group	30	66.95	66.6	25,985	33.3	100
	Control group	30	66.85	66.6	25,992	33.3	100
Emotional function	The main group	30	72.41	66.6	15,157	33.3	83.3
	Control group	30	73.20	66.6	16,853	33.3	83.3
Cognitive function	The main group	30	55,27	50.0	24,931	33.3	100
	Control group	30	57.30	50.0	25,276	33.3	100
Social function	The main group	30	67.27	66.6	25,782	33.3	100
	Control group	30	66.16	66.6	25,435	33.3	100
Fatigue	The main group	30	57.60	66.6	14,320	33.3	66.6
	Control group	30	58.50	66.6	13,846	33.3	66.6
Nausea/vomiting	The main group	30	0.00	0	-	0	0
	Control group	30	0.00	0	-	0	0
Pain	The main group	30	0.00	0	-	0	0
	Control group	30	0.00	0	-	0	0
Sleep disorders	The main group	30	33,13	33.3	18,184	0	66.6
	Control group	30	32,43	33.3	17,256	0	66.6
Loss of appetite	The main group	30	32,37	33.3	17,190	0	66.6
	Control group	30	32,13	33.3	17,079	0	66.6
Constipation	The main group	30	20,25	16.6	8,081	0	33.3
	Control group	30	22.25	16.6	10,187	0	33.3
Diarrhea	The main group	30	0.00	0	-	0	0
	Control group	30	0.00	0	-	0	0
Financial difficulties	The main group	30	50.33	50.0	19,882	33.3	100
	Control group	30	50.47	50.0	20,063	33.3	100

Since the data of the EORTC QLQ-C30 questionnaire were not normally distributed, the Mann-Whitney criterion was used to compare the groups according to these parameters in the initial state (**Table 55**).

Table 55 - Comparison of groups in the initial state using the Mann-Whitney test according to the data of the EORTC QLQ-C30 questionnaire

Indicator	U of Mann-Whitney	Wilcoxon W	Z-statistics	p-value (two-way)	Homogeneity of groups*
General health status	344,000	809,000	-1,591	0.112	Homogeneous
General assessment of quality of life	396,500	861,500	-0.805	0.421	Homogeneous
Physical function	448,000	913,000	-0.031	0.976	Homogeneous
Role function	447,500	912,500	-0.038	0.970	Homogeneous
Emotional function	443,000	908,000	-0.115	0.908	Homogeneous
Cognitive function	429,000	894,000	-0.336	0.737	Homogeneous
Social function	428,000	893,000	-0.336	0.737	Homogeneous
Fatigue	431,500	896,500	-0.362	0.717	Homogeneous
Nausea/vomiting	-	-	-	1,000	Homogeneous
Pain	-	-	-	1,000	Homogeneous
Sleep disorders	444,500	909,500	-,084	0.933	Homogeneous
Loss of appetite	449,000	914,000	-,015	0.988	Homogeneous
Constipation	406,500	871,500	-,648	0.517	Homogeneous
Diarrhea	-	-	-	1,000	Homogeneous
Financial difficulties	447,500	912,500	-0.050	0.960	Homogeneous
**The conclusion is made at a significance level of 0.05*					

The analysis of the data obtained during the treatment showed a progressive decrease in the quality of life in both groups. The changes associated with the clinical picture (symptomatics), which is a consequence of the general effect of CT on the body, prevailed. High values had such indicators as fatigue, nausea, vomiting, loss of appetite. An increased value of the diarrhea indicator was revealed. The indicators of general health status and physical functioning were also relatively low. Patients were concerned about such asthenic manifestations as malaise, general weakness, increased fatigue, and reduced work capacity. Individual perception by patients of the presence of a serious oncological disease caused a change in the emotional background. The development of dyssomnic disorders was also noted. It should be noted that in the group of patients taking chemotherapy + Donovit-VS®, the decrease in the quality of life in most indicators was less pronounced.

The average score on the "quality of life" subscale of patients before the start of chemotherapy was 71.32 in the main group and 70.57 in the control group. In the

course of treatment, a progressive decrease in this indicator was noted in both groups. So, after the 6th course of chemotherapy, the average score in the main group was 64.41 points, and in the control group - 59.94.

On the scale of "general state of health", the situation was similar. The average score before the start of chemotherapy was 68.67 in the main group and 69.42 in the control group. In the course of treatment, a progressive decrease was noted, and after the 6th course of chemotherapy, the average score of the general state of health in the main group was 59.85, and in the control group - 53.64.

Table 56 - Dynamics of quality of life according to the EORTC QLQ-C30 scale (in points) in the main group

Parameter	time	n	M	Me	SD	Min	Max
General health status	D0	30	68,66	66.6	14,224	33.3	83.3
	D28	30	65.24	66.6	14,114	33.3	83.3
	D56	30	63.12	66.6	13,147	16.6	66.6
	D90	30	64.41	66.6	13,205	16.6	66.6
General assessment of quality of life	D0	30	71.31	66.6	14,172	33.3	83.3
	D28	30	67.83	66.6	14,225	33.3	83.3
	D56	30	63.54	66.6	12,974	33.3	66.6
	D90	30	64,45	66.6	12,740	33.3	66.6
Physical function	D0	30	53.85	66.6	19,597	33.3	100
	D28	30	64.24	66.6	18,144	33.3	100
	D56	30	73,24	66.6	16,087	33.3	100
	D90	30	72.17	66.6	15,855	33.3	100
Role function	D0	30	66.95	66.6	25,985	33.3	100
	D28	30	65.32	66.6	25,232	33.3	100
	D56	30	64.74	66.6	24,362	33.3	100
	D90	30	64.51	66.6	25,126	33.3	100
Emotional function	D0	30	72.41	66.6	15,157	33.3	83.3
	D28	30	69.15	66.6	10,143	33.3	83.3
	D56	30	70.37	66.6	19,084	33.3	100
	D90	30	71.43	66.6	20,237	33.3	100
Cognitive function	D0	30	55,27	50.0	24,931	33.3	100
	D28	30	54.60	50.0	25,090	33.3	66.6
	D56	30	53,57	50.0	24,893	33.3	100
	D90	30	53.27	50.0	25,116	33.3	100
Social function	D0	30	67.27	66.6	25,782	33.3	100
	D28	30	70.20	66.6	25,423	33.3	100
	D56	30	72.70	66.6	24,411	33.3	100
	D90	30	74.37	66.6	24,916	33.3	100
Fatigue	D0	30	57.60	50.0	14,320	33.3	66.6
	D28	30	74.30	83.3	16,510	66.6	100
	D56	30	80.40	83.3	16,609	66.6	100
	D90	30	81.30	83.3	17,074	66.6	100
Nausea/vomiting	D0	30	0.00	0	-	0	0

	D28	30	72.30	83.3	12,933	66.6	100
	D56	30	72.13	83.3	12,565	66.6	100
	D90	30	75.53	83.3	14,991	66.6	100
Pain	D0	30	0.00	0	-	0	0
	D28	30	48,29	50.0	29,763	0	66.6
	D56	30	46.05	50.0	28,784	0	66.6
	D90	30	44,36	50.0	29,454	0	66.6
Sleep disorders	D0	30	33,13	33.3	18,184	0	66.6
	D28	30	48,26	50.0	27,021	0	66.6
	D56	30	50,31	50.0	23,709	0	66.6
	D90	30	54.01	50.0	19,819	0	66.6
Loss of appetite	D0	30	32,37	33.3	17,190	0	66.6
	D28	30	50.17	50.0	23,876	33.3	100
	D56	30	55.40	50.0	25,987	33.3	100
	D90	30	55,60	50.0	24,981	33.3	100
Constipation	D0	30	20,25	16.6	8,081	0	33.3
	D28	30	21,16	16.6	9,115	0	33.3
	D56	30	22,28	16.6	14,845	0	66.6
	D90	30	22.68	16.6	9,763	0	33.3
Diarrhea	D0	30	0.00	0	-	0	0
	D28	30	43.10	50.0	22,155	33.3	100
	D56	30	43.23	50.0	22,259	33.3	100
	D90	30	43.90	50.0	22,810	33.3	100
Financial difficulties	D0	30	50.33	50.0	19,882	33.3	100
	D28	30	50.07	50.0	20,149	33.3	100
	D56	30	49.93	50.0	21,056	33.3	100
	D90	30	48.73	50.0	20,552	33.3	100

Table 57 - Dynamics of quality of life according to the EORTC QLQ-C30 scale (in points) in the control group

Parameter	time	n	M	Me	SD	Min	Max
General health status	D0	30	69.42	66.6	14,019	33.3	83.3
	D28	30	61.86	66.6	13,714	33.3	83.3
	D56	30	58,26	66.6	12,874	16.6	66.6
	D90	30	56,59	66.6	12,558	16.6	66.6
General assessment of quality of life	D0	30	70.58	66.6	15,691	33.3	83.3
	D28	30	64.46	66.6	14,701	16.6	83.3
	D56	30	59.84	66.6	12,883	16.6	66.6
	D90	30	58.86	66.6	12,490	33.3	66.6
Physical function	D0	30	54,35	50.0	20,981	33.3	100
	D28	30	72.97	83.3	17,946	33.3	100
	D56	30	79.61	83.3	16,716	33.3	100

	D90	30	81.44	83.3	16,574	33.3	100
Role function	D0	30	66.85	66.6	25,992	33.3	100
	D28	30	65.51	66.6	25,003	33.3	100
	D56	30	65.12	66.6	25,340	33.3	100
	D90	30	66,87	66.6	24,622	33.3	100
Emotional function	D0	30	73.20	83.3	16,853	33.3	83.3
	D28	30	71.59	83.3	15,859	33.3	83.3
	D56	30	70.13	83.3	20,884	33.3	100
	D90	30	73.97	83.3	20,103	33.3	100
Cognitive function	D0	30	57.30	66.6	25,276	33.3	100
	D28	30	56,23	66.6	25,200	33.3	100
	D56	30	55,63	50.0	25,225	33.3	100
	D90	30	55.40	50.0	25,341	33.3	100
Social function	D0	30	66.16	66.6	25,435	33.3	100
	D28	30	72.70	83.3	23,876	33.3	100
	D56	30	77.37	83.3	23,814	33.3	100
	D90	30	84.90	83.3	22,721	33.3	100
Fatigue	D0	30	58.50	66.6	13,846	33.3	66.6
	D28	30	82.50	83.3	14,974	66.6	100
	D56	30	88.60	83.3	15,669	66.6	100
	D90	30	90.83	100.0	15,982	66.6	100
Nausea/vomiting	D0	30	0.00	0	-	0	0
	D28	30	85.73	83.3	16,574	66.6	100
	D56	30	86.70	83.3	16,212	66.6	100
	D90	30	85.40	83.3	16,376	66.6	100
Pain	D0	30	0.00	0	-	0	0
	D28	30	50.10	50.0	28,340	0	66.6
	D56	30	47,11	50.0	29,616	0	66.6
	D90	30	44,43	50.0	29,432	0	66.6
Sleep disorders	D0	30	32,43	33.3	17,256	0	66.6
	D28	30	47.54	50.0	26,803	0	66.6
	D56	30	54.14	50.0	19,992	0	66.6
	D90	30	54.71	50.0	18,146	0	66.6

Loss of appetite	D0	30	32,13	33.3	17,079	0	66.6
	D28	30	51.07	50.0	25,970	33.3	100
	D56	30	53,63	50.0	24,679	33.3	100
	D90	30	55.93	50.0	26,337	33.3	100
Constipation	D0	30	22.25	16.6	10,187	0	33.3
	D28	30	21.52	16.6	10,093	0	33.3
	D56	30	20.90	16.6	9,662	0	66.6
	D90	30	21.88	16.6	9,983	0	33.3
Diarrhea	D0	30	0.00	0	-	0	0
	D28	30	45.50	50.0	22,393	33.3	100
	D56	30	43.10	50.0	22,973	33.3	100
	D90	30	40.17	50.0	19,453	33.3	100
Financial difficulties	D0	30	50.47	50.0	20,063	33.3	100
	D28	30	51.30	50.0	19,670	33.3	100
	D56	30	49.73	50.0	20,228	33.3	100
	D90	30	50.90	50.0	19,654	33.3	100

Graphically, the dynamics of quality of life indicators are presented in **fig. 16-18.**

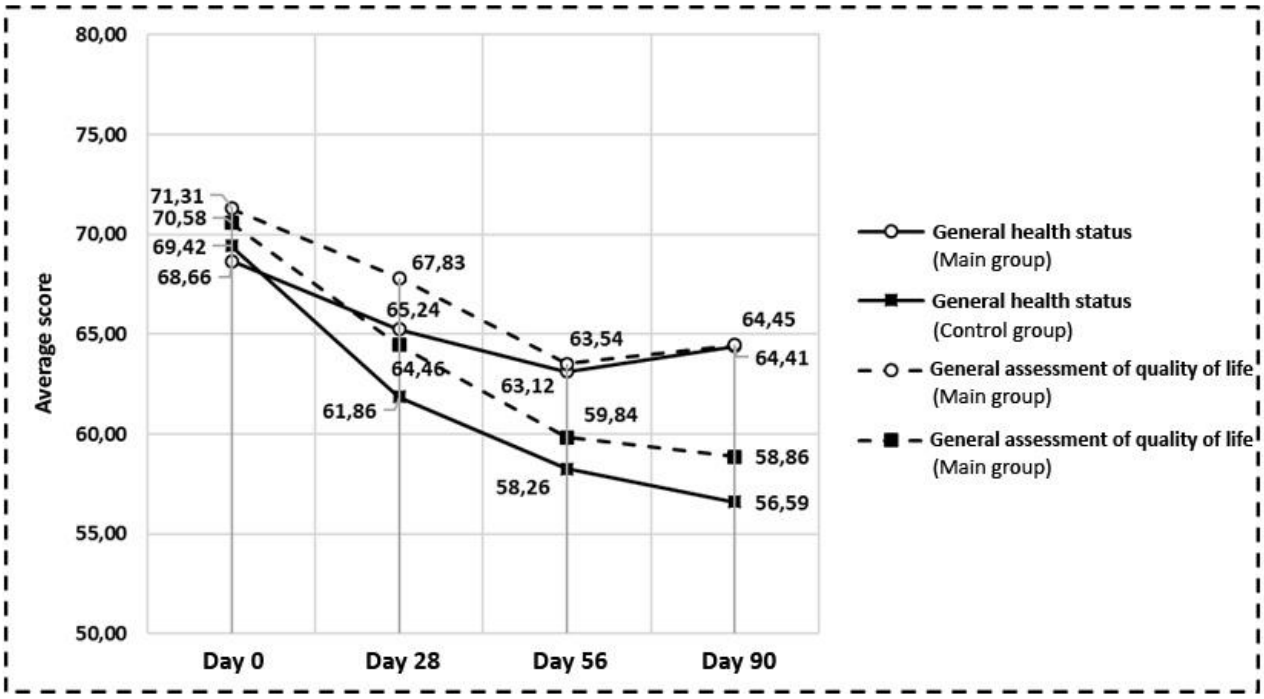

Fig. 16 – Dynamics of indicators "General health status" and "General assessment of quality of life"

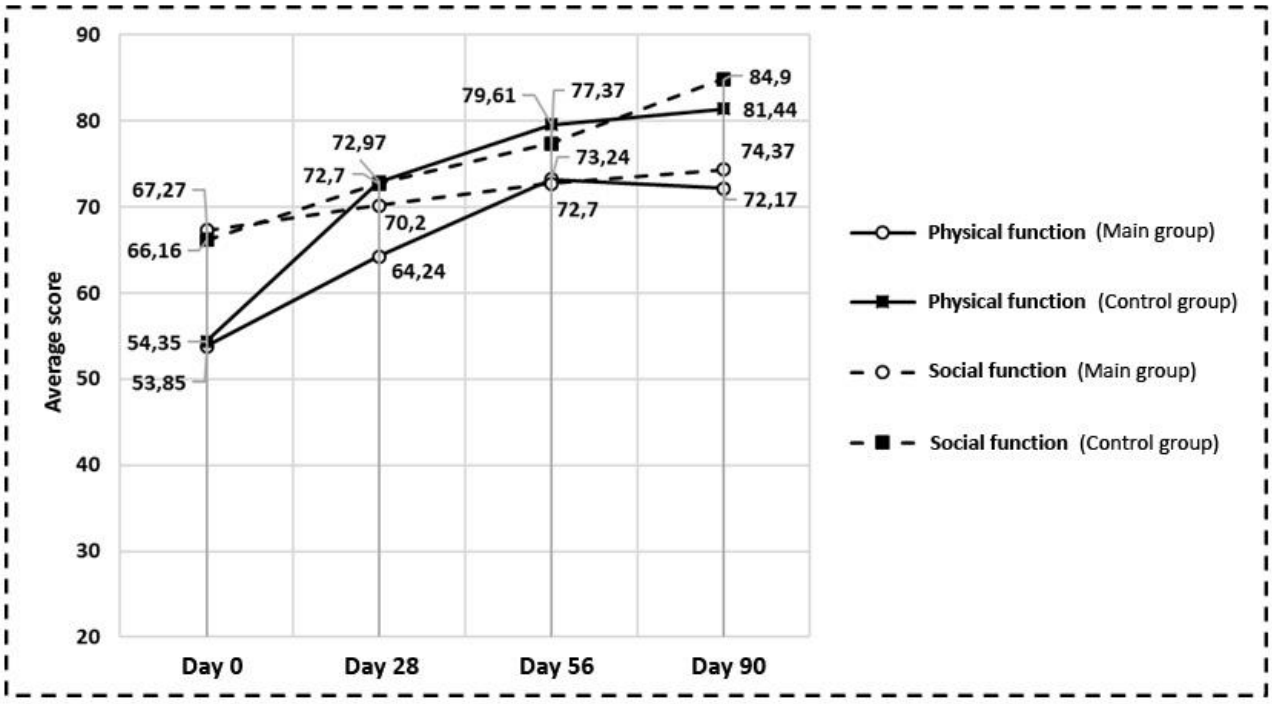

Fig. 17. Dynamics of "Physical function" and "Social function" indicators

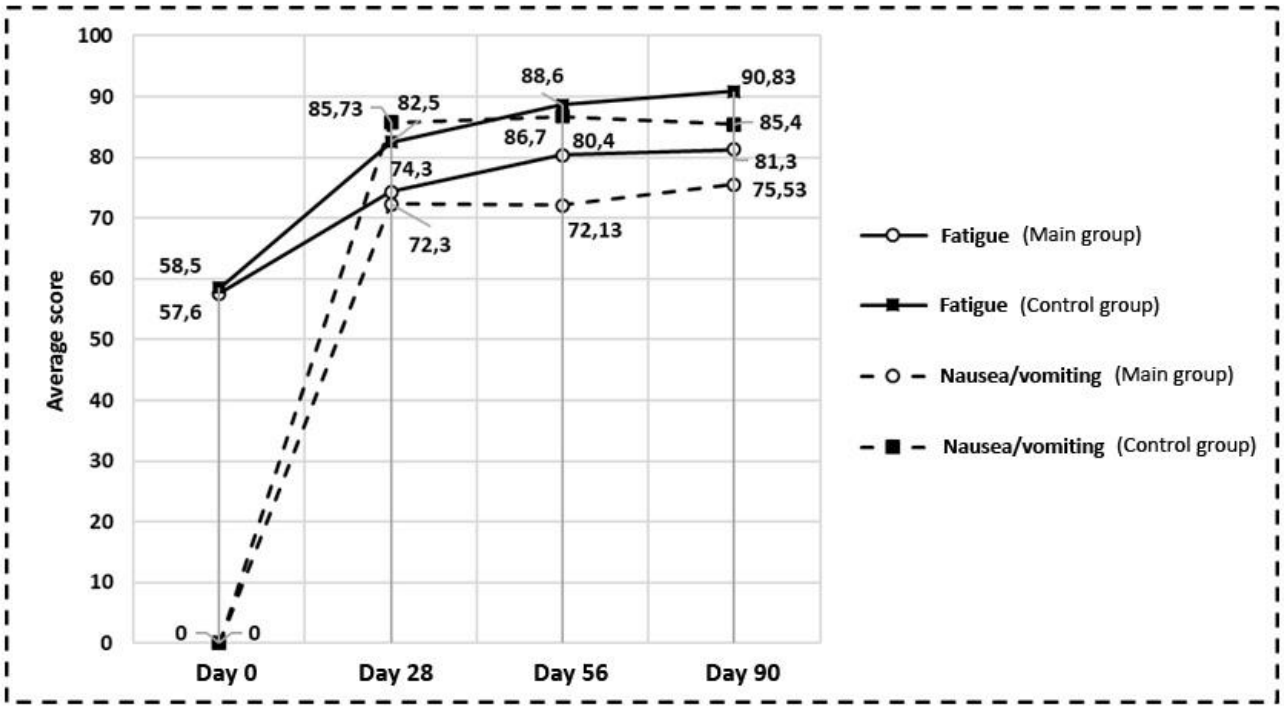

Fig. 18. Dynamics of indicators "Fatigue", "Nausea/vomiting"

To assess the statistical significance of the dynamics of quality of life 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 (D0, D28, D56, D90) and the "subjects" factor is random). The results of VA are shown in the **table. 58 - 59**.

A comparison of the following levels of the "visit" factor with the initial data (D0) was also performed using the contrast analysis of the **table. 60 - 61**.

Table 58 - The main results of DA quality of life in the main group

Dependent variable	Factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
General health status	Visit	503,000	3	167,667	30,076	0.000
	Patients	859,467	29	29,637	5,316	0.000
General assessment of quality of life	Visit	1121,167	3	373,722	31,819	0.000
	Patients	792,967	29	27,344	2,328	0.001
Physical function	Visit	7318,467	3	2439,489	12,128	0.000
	Patients	9153.467	29	315,637	1,569	0.067
Role function	Visit	108,225	3	36,075	1,725	0.094
	Patients	1619,242	29	55,836	6,076	0.000
Emotional function	Visit	174,292	3	58,097	0.993	0.400
	Patients	4819,742	29	166,198	2,841	0.000
Cognitive function	Visit	77,600	3	25,867	1,510	0.122
	Patients	1890,667	29	65,195	13,888	0.000
Social function	Visit	861,933	3	287,311	2,674	0.052
	Patients	60417,367	29	2083,357	19,392	0.000
Fatigue	Visit	10855,800	3	3618,600	14,401	0.000
	Patients	46951,800	29	1619,028	6,443	0.000
Nausea/vomiting	Visit	121183.758	3	40394,586	629,245	0.000
	Patients	10430,242	29	359,664	5,603	0.000
Pain	Visit	49988.703	3	16662.901	73,481	0.000
	Patients	50515,828	28	1804,137	7,956	0.000
Sleep disorders	Visit	7577,539	3	2525,846	8,002	0.000
	Patients	30992.835	29	1068,718	3,386	0.000
Loss of appetite	Visit	10830,833	3	3610,278	24,905	0.000
	Patients	5441.867	29	187,651	1,294	0.180
Constipation	Visit	13,867	3	4,622	1,896	0.136
	Patients	1421,467	29	49,016	20,102	0.000
Diarrhea	Visit	42412.825	3	14137.608	106,695	0.000
	Patients	34104,842	29	1176,029	8,875	0.000
Financial difficulties	Visit	45,200	3	15,067	2,176	0.097
	Patients	483,967	29	16,689	2,411	0.001

Table 59 - The main results of VA quality of life in the control group

Dependent variable	Factor	Sum of squares	Number of degrees of freedom	Average square	F	Meaning.
General health status	Visit	2906,225	3	968,742	28,315	0.000
	Patients	2905,042	29	100,174	2,928	0.000
General assessment of quality of life	Visit	2558,758	3	852,919	38,279	0.000
	Patients	1740,342	29	60,012	2,693	0.000
Physical function	Visit	13864.067	3	4621,356	17,594	0.000
	Patients	13620.367	29	469,668	1,788	0.021
Role function	Visit	66,758	3	22,253	1,525	0.111
	Patients	1091,242	29	37,629	10,527	0.000
Emotional function	Visit	263,767	3	87,922	1,651	0.183
	Patients	2920,367	29	100,702	1,891	0.012
Cognitive function	Visit	95,600	3	31,867	1,242	0.242
	Patients	2124,700	29	73,266	12,052	0.000
Social function	Visit	5598.233	3	1866,078	9,047	0.000
	Patients	45293.867	29	1561,857	7,572	0.000
Fatigue	Visit	19793.225	3	6597,742	28,057	0.000
	Patients	34199.842	29	1179,305	5,015	0.000
Nausea/vomiting	Visit	159383.612	3	53127.871	706,562	0.000
	Patients	16684.690	28	595,882	7,925	0.000
Pain	Visit	50637.975	3	16879.325	69,239	0.000
	Patients	52638.608	29	1815,124	7,446	0.000
Sleep disorders	Visit	9680.508	3	3226,836	10,875	0.000
	Patients	24792.367	29	854,909	2,881	0.000
Loss of appetite	Visit	10670.425	3	3556,808	35,245	0.000
	Patients	2902,342	29	100,081	0.992	0.491
Constipation	Visit	29,367	3	9,789	0.587	0.625
	Patients	980,867	29	33,823	2,029	0.006
Diarrhea	Visit	41880.225	3	13960.075	95,851	0.000
	Patients	28149,342	29	970,667	6,665	0.000
Financial difficulties	Visit	44,092	3	14,697	1,186	0.320
	Patients	703,742	29	24,267	1,958	0.009

Table 60 - Results of a contrast analysis of quality of life indicators in the main group

Dependent variable	Contrasts	Estimated contrast	Stand. mistake	p-value*
General health status	D28 - Dsc	-3,433	0.610	0.000*
	D56 - Dsc	-5,533		0.000*
	D90 - Dsc	-4,233		0.000*
General assessment of quality of life	D28 - Dsc	-3,467	0.885	0.000*
	D56 - Dsc	-7,733		0.000*
	D90 - Dsc	-6,867		0.000*
Physical function	D28 - Dsc	10,467	3,662	0.005*
	D56 - Dsc	19,500		0.000*
	D90 - Dsc	18,433		0.000*
Role function	D28 - Dsc	-1,600	0.783	0.244
	D56 - Dsc	-2,200		0.106
	D90 - Dsc	-2,433		0.063
Emotional function	D28 - Dsc	-3,233	1,975	0.105
	D56 - Dsc	-2.033		0.306
	D90 - Dsc	-0.967		0.626
Cognitive function	D28 - Dsc	-0.600	0.559	0.286
	D56 - Dsc	-0.867		0.104
	D90 - Dsc	-1,000		0.058
Social function	D28 - Dsc	2,933	2,767	0.276
	D56 - Dsc	5,433		0.055
	D90 - Dsc	7,100		0.009*
Fatigue	D28 - Dsc	16,700	4,093	0.000*
	D56 - Dsc	22,800		0.000*
	D90 - Dsc	23,700		0.000*
Nausea/vomiting	D28 - Dsc	72,300	2,069	0.000*
	D56 - Dsc	72,133		0.000*
	D90 - Dsc	75,533		0.000*
Pain	D28 - Dsc	49,952	3,955	0.000*
	D56 - Dsc	47,634		0.000*
	D90 - Dsc	45,890		0.000*
Sleep disorders	D28 - Dsc	15,127	4,587	0.001*
	D56 - Dsc	17,173		0.000*
	D90 - Dsc	20,873		0.000*
Loss of appetite	D28 - Dsc	17,800	3,109	0.000*
	D56 - Dsc	23,033		0.000*
	D90 - Dsc	23,233		0.000*
Constipation	D28 - Dsc	-0.533	0.403	0.189
	D56 - Dsc	-0.667		0.202
	D90 - Dsc	-0.733		0.077
Diarrhea	D28 - Dsc	43,100	2,972	0.000*
	D56 - Dsc	43,233		0.000*
	D90 - Dsc	43,900		0.000*

Financial difficulties	D28 - Dsc	-0.267	0.679	0.696
	D56 - Dsc	-0.400		0.558
	D90 - Dsc	-1,400		0.071
**Statistically significant differences are observed* *The conclusion is made at a significance level of 0.05*				

Table 61 - Results of contrast analysis of quality of life indicators in the control group

Dependent variable	Contrasts	Estimated contrast	Stand. mistake	p-value*
General health status	D28 - Dsc	-7,567	1,510	0.000*
	D56 - Dsc	-11,167		0.000*
	D90 - Dsc	-12,767		0.000*
General assessment of quality of life	D28 - Dsc	-6,067	1,219	0.000*
	D56 - Dsc	-10,700		0.000*
	D90 - Dsc	-11,667		0.000*
Physical function	D28 - Dsc	18,700	4,185	0.000*
	D56 - Dsc	25,333		0.000*
	D90 - Dsc	27,167		0.000*
Role function	D28 - Dsc	-1.333	0.488	0.386
	D56 - Dsc	-1.533		0.226
	D90 - Dsc	0.100		0.902
Emotional function	D28 - Dsc	-1.633	1,884	0.388
	D56 - Dsc	-3.067		0.107
	D90 - Dsc	0.767		0.685
Cognitive function	D28 - Dsc	-0.650	0.637	0.243
	D56 - Dsc	-0.870		0.110
	D90 - Dsc	-1.030		0.058
Social function	D28 - Dsc	6,533	3,308	0.082
	D56 - Dsc	11,200		0.003*
	D90 - Dsc	18,733		0.000*
Fatigue	D28 - Dsc	24,000	3,959	0.000*
	D56 - Dsc	30,100		0.000*
	D90 - Dsc	32,333		0.000*
Nausea/vomiting	D28 - Dsc	85,241	2,277	0.000*
	D56 - Dsc	86,310		0.000*
	D90 - Dsc	85,241		0.000*
Pain	D28 - Dsc	50,100	4,031	0.000*
	D56 - Dsc	47,113		0.000*
	D90 - Dsc	44,427		0.000*
Sleep disorders	D28 - Dsc	15,107	4,448	0.001*
	D56 - Dsc	21,707		0.000*
	D90 - Dsc	22,273		0.000*

Loss of appetite	D28 - Dsc	18,933	2,594	0.000*
	D56 - Dsc	21,500		0.000*
	D90 - Dsc	23,800		0.000*
Constipation	D28 - Dsc	-0.767	1,054	0.469
	D56 - Dsc	-1.333		0.209
	D90 - Dsc	-0.667		0.729
Diarrhea	D28 - Dsc	45,500	3,116	0.000*
	D56 - Dsc	43,100		0.000*
	D90 - Dsc	40,167		0.000*
Financial difficulties	D28 - Dsc	-1.567	0.909	0.088
	D56 - Dsc	-0.733		0.422
	D90 - Dsc	-0.200		0.909
**Statistically significant differences are observed* *The conclusion is made at a significance level of 0.05*				

Conclusions .

1. In both groups, a statistically significant decrease in the quality of life was established on the scale of "general state of health" and the scale of "assessment of the quality of life".
2. In both groups, a statistically significant decrease in the quality of life on the scales of physical and social function was established.
3. In both groups, a statistically significant decrease in the quality of life was established according to symptomatic scales: fatigue, nausea/vomiting, diarrhea, loss of appetite, sleep disorders, pain.
4. According to other scales and indicators, no statistically significant changes in the course of treatment were revealed.

15.7. Analysis of comparison of dynamics of quality of life between groups

Since in the initial state the groups did not differ statistically significantly in terms of quality of life, the comparison between the groups was performed by dT_i differences with the help of the Mann-Whitney test, i.e. individual differences dT_i were not normally distributed in both groups.

The results of the analysis of the comparison of the dynamics of the quality of life indicators between the groups are shown in **Table 62.**

Table 62 - Comparison of groups using the Mann-Whitney criterion on the dynamics of quality of life indicators

Indicator	dTi	U of Mann-Whitney	Wilcoxon W	Z-statistics	p-value (double-sided)	Differences between groups*
General health status	d28	355,000	820,000	-1,760	0.048	Significant
	d56	382,000	847,000	-1.824	0.026	Significant
	d90	109,500	574,500	-5.049	0.000	Significant
General assessment of quality of life	d28	328,000	793,000	-1.993	0.011	Significant
	d56	336,500	801,500	-2,113	0.006	Significant
	d90	268,000	733,000	-2,740	0.000	Significant
Physical function	d28	420,000	885,000	-1,770	0.038	Significant
	d56	354,000	819,000	-2,439	0.000	Significant
	d90	264,500	729,500	-2.773	0.000	Significant
Role function	d28	426,000	891,000	-0.456	0.648	Not significant
	d56	397,500	862,500	-0.977	0.329	Not significant
	d90	413,000	878,000	-0.675	0.500	Not significant
Emotional function	d28	372,500	837,500	-1,190	0.234	Not significant
	d56	328,000	793,000	-1.837	0.066	Not significant
	d90	406,500	871,500	-0.655	0.513	Not significant
Cognitive function	d28	377,500	842,500	-1,411	0.158	Not significant
	d56	413,000	878,000	-0.689	0.491	Not significant
	d90	425,000	890,000	-0.457	0.648	Not significant
Social function	d28	230,000	505,000	-5,113	0.000	Significant
	d56	203,000	561,000	-5,246	0.000	Significant
	d90	225,500	562,500	-5,221	0.000	Significant
Fatigue	d28	128,000	593,000	-4,788	0.000	Significant
	d56	254,500	719,500	-2,908	0.004	Significant
	d90	211,500	676,500	-3.546	0.000	Significant
Nausea/vomiting	d28	215,000	465,000	-6,917	0.000	Significant
	d56	235,000	465,000	-6,833	0.000	Significant
	d90	211,000	465,000	-6,749	0.000	Significant
Pain	d28	179,000	644,000	-1.755	0.085	Not significant
	d56	277,000	742,000	-1.853	0.058	Not significant
	d90	441,500	906,500	-0.131	0.896	Not significant
Sleep disorders	d28	440,500	905,500	-0.142	0.887	Not significant
	d56	428,500	893,500	-0.319	0.749	Not significant
	d90	376,500	841,500	-1.094	0.274	Not significant
Loss of appetite	d28	343,500	808,500	-1,602	0.109	Not significant
	d56	372,500	837,500	-1.181	0.238	Not significant
	d90	358,000	823,000	-1.375	0.169	Not significant
Constipation	d28	443,500	908,500	-0.104	0.917	Not significant
	d56	383,000	848,000	-1.041	0.298	Not significant
	d90	428,500	893,500	-0.386	0.700	Not significant
Diarrhea	d28	311,000	776,000	-1,216	0.185	Not significant
	d56	324,500	789,500	-1.942	0.052	Not significant

	d90	345,000	810,000	-1.633	0.103	Not significant
Financial difficulties	d28	439,000	904,000	-0.226	0.821	Not significant
	d56	448,000	913,000	-0.037	0.971	Not significant
	d90	408,500	873,500	-0.649	0.516	Not significant
**The conclusion is made at a significance level of 0.05*						

Conclusions .

1. During the analysis, it was established that the patients of the control group had a significantly more significant decrease in quality of life according to the EORTC QLQ-C30 scale, compared to the patients of the main group according to the following scales:

- on the scale of the general state of health;
- according to the quality of life rating scale;
- on the physical function scale;
- on the social function scale;
- according to symptomatic scales: fatigue, nausea/vomiting.

2. On the other scales, no statistically significant changes between the groups were revealed.

15.8. Evaluation of the general condition of patients on the ECOG scale

When assessing the general condition of patients on the ECOG scale, it was revealed that the general condition of 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 63**.

Table 63 - Characteristics of the general condition of patients according to the ECOG scale during treatment (abs. number, %)

General condition (points)	The main group n = 30	Control group n = 30	p-value*
0	-	-	0.030 * *
1	15 (50.0%)	6 (20.0%)	
2	15 (50.0%)	24 (80.0%)	
3	-	-	
4	-	-	

**The analysis was performed using the Pearson chi-square test*
Conclusion at the significance level of 0.05
***Statistically significant differences are observed*

Conclusion According to the results of the analysis of the data presented in **table 63**, it is possible to state 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.

15.9. Evaluation of the effectiveness of adjuvant chemotherapy

The assessment of the direct therapeutic effect of adjuvant chemotherapy was carried out in accordance with standard criteria based on the data of MRI or CT scans conducted after 6 courses of chemotherapy.

Analyzing the results of the distribution of patients according to the reaction of tumor growth to the treatment, it should be noted that in the main group, the absence of tumor growth was observed in 28 patients, in the control group - in 22 patients. Resumption of the tumor growth process was noted in 2 patients of the main group and in 8 patients of the control group. During the analysis, the absence of significant differences between these indicators was noted (p>0.05).

Table 64 - Analysis of patients according to the reaction of tumor growth to the treatment

Category	The main group n = 30	Control group n = 30	p-value*
There is tumor growth	2	8	0.080
There is no tumor growth	28	22	
**The conclusion is made at a significance level of 0.05* *The comparison was made using Fisher's exact test*			

15.10. Conclusion about the exceeding efficiency.

A conclusion about the greater effectiveness of therapy including the drug under study (main group) compared to therapy without the drug under study (control group) should be made on the basis of statistically significant differences when comparing the groups on the main variables assessing the degree of toxicity. It was assumed that any reduction in the level of toxicity in any of the variables is clinically important.

Based on the results of the analysis, it can be concluded that there are statistically significant differences between the groups, proving a greater positive effect in the prevention of toxic reactions of chemotherapy and a reduction in the degree of their severity in patients who received, against the background of antitumor

chemotherapy, the study drug Donovit-VS®, according to compared to the group of patients who received only chemotherapy.

A significantly more pronounced decrease in the level of leukocytes, hemoglobin and platelets was revealed in patients of the control group, compared to the main group (Table 35), ($p < 0.05$). Also, in the control group there was a statistically significant greater number of patients who developed leukopenia (Table 36.51), ($p = 0.015$).

In the control group, a statistically significant higher number of patients who experienced nausea/vomiting as a result of chemotherapy was registered (Table 53), ($p = 0.0003$).

It was established that in patients who took the research drug Donovit-VS®, a higher quality of life was observed during treatment with chemotherapeutic drugs, according to the EORTC QLQ-C30 questionnaire, compared to patients who did not take Donovit-VS® (table 62). Differences between groups on the scales of general health, quality of life assessment, physical and social function, and symptomatic scales such as fatigue and nausea/vomiting are statistically significant ($p < 0.05$).

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

15.11. Tolerability analysis

In the course of the study, AE/AR were registered in 100% of the main and control groups. None of the AE/AR fell under the category of serious. All AE/AR were directly related to chemotherapy and corresponded to the toxicity profile of the chemotherapeutic 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/AE: 95 in the main group and 166 in the control room).

In the process of research, in the group of patients taking the study drug, no allergic and anaphylactic reactions, significant fluctuating hemodynamic parameters

were recorded. 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.

On the basis of 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 the **table. 65.** Final statistics of AE/AR **- in the table. 66.**

Table 65 - List of registered AE/AR

Parameter	**The main group n=30**		**Control group n=30**	
	n	**%**	**n**	**%**
Nausea/vomiting	13	43.3	30	100.0
Diarrhea	12	40.0	16	53.3
Constipation	3	10.0	5	16.7
Skin manifestations	4	13.3	6	20.0
Alopecia	30	100.0	30	100.0
Peripheral neuropathy	13	43,3,3	17	56.7
Leukopenia	6	20.0	16	53.3
Anemia	2	6,7	7	23.3
Thrombocytopenia	3	10.0	10	33.3
ALT elevation	3	10.0	8	26.7
Elevation of AST	4	13.3	8	26.7
Elevation of bilirubin	0	0	3	10.0

Table 66 — Final statistics of AE/AR

Analyzed indicators	**The main group**		**Control group**	
	n	**%**	**n**	**%**
Subjects evaluated for AE/AR	30	100.0	30	100.0
The number of AE/AR	93	-	156	-
Patients with AE/AR	30	100.0	30	100.0
Number of serious AE/AR	0	0	0	0
Patients with serious 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 of the drug due to AE/AR	0	0	2	10.0

15.12. Discussion of research results

This study to study the effectiveness and tolerability of the drug Donovit-VS®, a tablet produced by Astrapharm LLC, was conducted in accordance with the ethical principles of the Helsinki Declaration, the current regulatory documents and legislation of Ukraine, as well as the clinical research protocol.

The research was conducted as open, comparative, randomized, in parallel groups.

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

The aim of the study was to study the influence of the research drug on the degree of toxicity of chemotherapy and on the quality of life of patients taking chemotherapeutic drugs. Then, a comparison of the treatment results obtained in the main and control groups, with the aim of establishing a higher efficiency in the group of patients receiving chemotherapy + Donovit-VS® in comparison with the group of patients receiving only chemotherapy. It was assumed that the use of the research drug Donovit-VS ® will reduce the toxicity of the chemotherapy and improve the quality of life of patients.

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

The study included patients of both sexes aged from 18 to 70 years with a diagnosis of colorectal cancer (rectal cancer T_{2-4} N_{0-2} $M_{0,}$ colon cancer T_{2-4} N_{1-2} M_0) after radical surgical removal of the tumor.

Patients in the main and control groups received polychemotherapy in accordance with international standards for the treatment of colorectal cancer according to the FOLFOX scheme - 4, 6 courses with an interval of 14 days. In addition, the patients of the main group received the research drug Donovit-VS®, tablets produced by Astrapharm LLC, 1 tablet 3 times a day for 3 months. The average number of chemotherapy courses received by patients during this study was 5.93 in the main group and 5.87 in the control group. Reducing the duration of treatment to 4 courses in 2 patients of the control group was due to the toxicity of chemotherapy, and in 1 patient, the main reason was the refusal to continue treatment after the 4th course of chemotherapy.

During 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 study according to the protocol. 60 patients were included in the analysis of efficacy and tolerability.

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

The secondary variable is the quality of life of the patient during treatment according to the EORTC - QLQ - C 30 questionnaire.

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

Toxic reactions to chemotherapy were assessed after each course of chemotherapy using the CTC *NCIC* toxicity scale . Out of 60 patients who received postoperative chemotherapy according to the FOLFOX-4 scheme, complications developed in 100.0% of patients. Toxic reactions of the applied chemotherapy regimen were predictable, manageable and corresponded mainly to the 1st and 2nd degrees of toxicity on the CTC *NCIC scale.* Grade 3 toxicity was observed only in 2 patients (3.3%) of the control group.

Gastrointestinal toxicity was noted most often in patients, its manifestations were noted in 45 (75.0%) patients, of which grade 3 toxicity was observed in 1 (1.7%). Neurotoxicity was the second most frequent complication and was observed in 32 patients (53.3%), but only in 2 (3.3%) patients it reached the 2nd degree. Hematological toxicity of the 1st degree was revealed in 26 patients (43.3%), 2nd degree - in 6 (10.0%) - and 3rd degree - in 1 patient. Hepatotoxicity of the 1st degree developed in 7 patients (23.3%), in 5 (16.7%) patients this complication had the 2nd degree of severity. Cutaneous manifestations were observed in 10 patients. Reduction of courses of adjuvant treatment due to the development of toxic effects - in 2 patients (5.0%).

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

1). In the main and control groups, a statistically significant decrease in the level of leukocytes after the first course of chemotherapy, platelets, after the third course of chemotherapy, and hemoglobin, after the fourth course of chemotherapy compared to the initial data was revealed.

Changes in other hematological indicators in both groups were not statistically and clinically significant throughout the study.

2). A significantly more pronounced decrease was revealed:

- level of leukocytes, after the first course of chemotherapy, in patients of the control group, compared to the baseline;
- hemoglobin level, after the fourth course of chemotherapy, in patients of the control group, in comparison with the main one;
- level of platelets, after the third course of chemotherapy, in patients of the control group, compared to the baseline.

The groups did not differ significantly in other hematological indicators.

3). A significantly higher frequency of leukopenia was revealed in patients of the control group compared to the main group ($p = 0.015$). A decrease in the number of leukocytes ($<4.0x10^9$ cells/l) was observed in 6 (20.0%) patients of the main group and in 16 (53.3%) patients of the control group.

4). A higher frequency of anemia and thrombocytopenia was noted in patients of the control group, compared to the main group. Thus, a decrease in the level of hemoglobin (<110 g/l) was observed in 2 (6.7%) patients of the main group and in 7 (23.3%) patients of the control group. A decrease in the number of platelets (< 100 x 10^9 cells/l) was observed in 3 (10.0%) patients of the main group and in 10 (33.3%) patients of the control group. However, the difference between the groups on these indicators is not reliable.

5). In the main and control groups, a statistically significant increase in the level of ALT and AST was revealed starting from the 42nd day of therapy (after the third course).

Changes in other biochemical indicators in both groups were within the physiological norm and were not statistically and clinically significant.

6). A higher number of patients with increased levels of ALT, AST and bilirubin in the control group was noted, compared to the main group, however, the difference between the groups in terms of these indicators is not significant.

7). A significantly higher number of patients with nausea/vomiting was found in the control group compared to the main group ($p = 0.0003$).

8). A significantly more significant decrease in the quality of life according to the EORTC QLQ-C30 scale was established in patients of the control group compared to patients of the main group according to the following scales:

- on the scale of the general state of health
- according to the quality of life rating scale
- on the physical function scale
- on the social function scale
- according to symptomatic scales: fatigue, nausea/vomiting.

The above testifies in favor of higher efficiency in the group of patients who received the drug Donovit-VS® on the background of antitumor chemotherapy compared to the group of patients who received only chemotherapy.

The data obtained in the course of the study also allow us to draw a conclusion about the good tolerability of the drug under study. In the process of research, in the group of patients taking the study drug, no allergic and anaphylactic reactions, significant fluctuating hemodynamic parameters were recorded. 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 chemotherapeutic 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: 93 in the main group and 156 in the control room).

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

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

16.**CONCLUSIONS AND RECOMMENDATIONS**

1. On the basis of clinical research data, it was proven that the treatment of patients with colorectal cancer was more effective in the group of patients who received, against the background of antitumor chemotherapy, the research drug Donovit-VS®, tablets manufactured by Astrapharm LLC, compared to the group of patients who received only chemotherapy according to the main variable This was manifested in a decrease in the severity of such complications of chemotherapy as: leukopenia, anemia, and thrombocytopenia, as well as in a decrease in the severity and frequency of occurrence and frequency of nausea and vomiting.

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

3. The study drug Donovit-VS®, tablets manufactured by Astrapharm LLC, was well tolerated by all 100% of patients. In the course of the study, in the group of patients

taking the drug Donovit-VS®, no allergic and anaphylactic reactions, significant fluctuating hemodynamic parameters were recorded. 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 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: 93 in the main group and 156 in control).

4. Based on the data obtained during the clinical study, the research drug Donovit-VS®, tablets produced by Astrapharm LLC, can be recommended for medical use in patients with colorectal cancer as an accompanying drug during a course of chemotherapy, with the aim of preventing and reducing the degree of severity toxic reactions and improving the quality of life of patients taking chemotherapeutic drugs.

Recommended regimen: 1 tablet 3 times a day for 3 months.

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Appendix A
Randomization
scheme and additional results of statistical data processing

Table A.1. Simple randomization scheme for 60 patients in a ratio of 1:1

Randomization number	Random number	Group
001	0.729717	Control
002	0.210914	Control
003	0.297048	The main
004	0.886975	The main
005	0.259712	Control
006	0.651449	Control
007	0.133891	The main
008	0.151104	Control
009	0.393347	The main
010	0.722466	Control
011	0.75507	The main
012	0.034882	Control
013	0.750071	The main
014	0.878127	Control
015	0.860597	Control
016	0.250772	The main
017	0.754991	Control
018	0.155602	Control
019	0.401461	Control
020	0.758306	The main
021	0.092007	The main
022	0.815696	The main
023	0.657753	Control
024	0.529714	The main
025	0.406933	The main
026	0.233468	Control
027	0.566788	The main

Randomization number	Random number	Group
028	0.565546	Control
029	0.260619	The main
030	0.038864	The main
031	0.301237	Control
032	0.160295	Control
033	0.332083	Control
034	0.507333	The main
035	0.097244	The main
036	0.418028	The main
037	0.871629	The main
038	0.200462	Control
039	0.332554	The main
040	0.018004	The main
041	0.403977	Control
042	0.856592	The main
043	0.854643	Control
044	0.230304	The main
045	0.681385	The main
046	0.531449	Control
047	0.558833	The main
048	0.181453	The main
049	0.886775	Control
050	0.988764	Control
051	0.216427	The main
052	0.370048	Control
053	0.086859	Control
054	0.340905	Control
055	0.552827	The main
056	0.43238	The main
057	0.935262	Control
058	0.939494	Control
059	0.575663	The main
060	0.158062	Control

Table A.2. Results of checking the normality of data distribution for the indicators "Age" and "Body mass" in groups

Group	Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
The main	age, years	0.968	30	0.477	Normal
Control		0.927	30	0.041	Normal
The main	Body mass, kg	0.963	30	0.377	Normal
Control		0.922	30	0.030	Normal
* *The conclusion is made at a 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	heart rate	0.986	30	0.949	Normal
Control		0.977	30	0.734	Normal
The main	SBR	0.974	30	0.651	Normal
Control		0.971	30	0.560	Normal
The main	DBR	0.968	30	0.474	Normal
Control		0.974	30	0.658	Normal
The main	t bodies	0.979	30	0.795	Normal
Control		0.959	30	0.298	Normal
**At a significance level of 0.01*					

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

Group	Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
The main	Leukocytes, $x10^9$ cells/l	0.946	30	0.130	Normal
Control		0.920	30	0.027	Normal
The main	Erythrocytes, $x10^{12}$ /l	0.979	30	0.793	Normal
Control		0.972	30	0.593	Normal
The main	Hematocrit, %	0.976	30	0.725	Normal
Control		0.981	30	0.849	Normal
The main	Hemoglobin, g/l	0.946	30	0.131	Normal
Control		0.976	30	0.707	Normal
The main	Platelets, $\times 10^9$	0.981	30	0.849	Normal

Control	cells/l	0.976	30	0.715	Normal
The main	Neutrophils, %	0.929	30	0.045	Normal
Control		0.979	30	0.799	Normal
The main	Lymphocytes, %	0.955	30	0.223	Normal
Control		0.987	30	0.966	Normal
The main	Monocytes, %	0.978	30	0.783	Normal
Control		0.972	30	0.590	Normal
The main	Eosinophils, %	0.976	30	0.707	Normal
Control		0.955	30	0.231	Normal
The main	Basophils, %	0.973	30	0.616	Normal
Control		0.973	30	0.621	Normal
The main	ESR, mm/h	0.964	30	0.395	Normal
Control		0.924	30	0.035	Normal
The main	ALT, Un/l	0.956	30	0.244	Normal
Control		0.970	30	0.538	Normal
The main	AST, Un/l	0.978	30	0.762	Normal
Control		0.968	30	0.476	Normal
The main	Total bilirubin,	0.950	30	0.165	Normal
Control	μmol/l	0.927	30	0.040	Normal
The main	Creatinine,	0.981	30	0.856	Normal
Control	μmol/l	0.950	30	0.169	Normal
The main	Glucose, mmol/l	0.957	30	0.263	Normal
Control		0.981	30	0.861	Normal
The main	Specific weight	0.960	30	,315	Normal
Control		0.970	30	0.541	Normal
The main	pH	0.975	30	0.678	Normal
Control		0.969	30	0.512	Normal
The main	Leukocytes, cells	0.977	30	0.754	Normal
Control	in sight	0.963	30	0.370	Normal
The main	Erythrocytes,	0.946	30	0.130	Normal
Control	cells in sight	0.920	30	0.027	Normal
**At a significance level of 0.01*					

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*
The main group				
SBR	0.993	210	0.450	Normal
DBR	0.995	210	0.742	Normal
heart rate	0.991	210	0.229	Normal
Body temperature	0.993	210	0.477	Normal

Control group				
SBR	0.993	210	0.368	Normal
DBR	0.995	210	0.651	Normal
heart rate	0.991	210	0.188	Normal
Body temperature	0.995	210	0.700	Normal
**The conclusion is made at a significance level of 0.01*				

Table A.6. The results of checking the normality of the distribution of the residuals of the dispersion analysis for the indicators of the general blood analysis

Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
The main group				
Leukocytes	0.993	210	0.449	Normal
Erythrocytes	0.993	210	0.473	Normal
Hematocrit	0.995	210	0.769	Normal
Hemoglobin	0.995	210	0.697	Normal
Platelets	0.991	210	0.239	Normal
Neutrophils	0.994	210	0.435	Normal
Lymphocytes	0.990	210	0.177	Normal
Monocytes	0.995	210	0.789	Normal
Eosinophils	0.996	210	0.886	Normal
Basophils	0.993	210	0.396	Normal
ESR	0.992	210	0.281	Normal
Control group				
Leukocytes	0.996	210	0.809	Normal
Erythrocytes	0.989	210	0.119	Normal
Hematocrit	0.995	210	0.768	Normal
Hemoglobin	0.983	210	0.013	Normal
Platelets	0.992	210	0.286	Normal
Neutrophils	0.994	210	0.514	Normal
Lymphocytes	0.992	210	0.308	Normal
Monocytes	0.993	210	0.459	Normal
Eosinophils	0.989	210	0.108	Normal
Basophils	0.991	210	0.243	Normal
ESR	0.997	210	0.930	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 parameters in the main group

Indicator	dTi	Statistics	Number of degrees of freedom	p-value	Conclusion*
Leukocytes	dT14	0.416	30	0.000	Not normal
	dT28	0.405	30	0.000	Not normal
	dT42	0.434	30	0.000	Not normal
	dT56	0.516	30	0.000	Not normal
	dT70	0.576	30	0.000	Not normal
	dT90	0.579	30	0.000	Not normal
Erythrocytes	dT14	0.427	30	0.000	Not normal
	dT28	0.426	30	0.000	Not normal
	dT42	0.687	30	0.000	Not normal
	dT56	0.586	30	0.000	Not normal
	dT70	0.607	30	0.000	Not normal
	dT90	0.507	30	0.000	Not normal
Hematocrit	dT14	0.425	30	0.000	Not normal
	dT28	0.473	30	0.000	Not normal
	dT42	0.528	30	0.000	Not normal
	dT56	0.580	30	0.000	Not normal
	dT70	0.702	30	0.000	Not normal
	dT90	0.565	30	0.000	Not normal
Hemoglobin	dT14	0.479	30	0.000	Not normal
	dT28	0.482	30	0.000	Not normal
	dT42	0.532	30	0.000	Not normal
	dT56	0.661	30	0.000	Not normal
	dT70	0.605	30	0.000	Not normal
	dT90	0.644	30	0.000	Not normal
Platelets	dT14	0.435	30	0.000	Not normal
	dT28	0.581	30	0.000	Not normal
	dT42	0.602	30	0.000	Not normal
	dT56	0.671	30	0.000	Not normal
	dT70	0.773	30	0.000	Not normal
	dT90	0.805	30	0.000	Not normal
Neutrophils	dT14	0.528	30	0.000	Not normal
	dT28	0.677	30	0.000	Not normal
	dT42	0.665	30	0.000	Not normal
	dT56	0.703	30	0.000	Not normal
	dT70	0.787	30	0.000	Not normal
	dT90	0.820	30	0.000	Not normal

Lymphocytes	dT14	0.464	30	0.000	Not normal
	dT28	0.466	30	0.000	Not normal
	dT42	0.553	30	0.000	Not normal
	dT56	0.556	30	0.000	Not normal
	dT70	0.842	30	0.000	Not normal
	dT90	0.849	30	0.001	Not normal
Monocytes	dT14	0.414	30	0.000	Not normal
	dT28	0.453	30	0.000	Not normal
	dT42	0.844	30	0.000	Not normal
	dT56	0.870	30	0.002	Not normal
	dT70	0.902	30	0.009	Not normal
	dT90	0.896	30	0.007	Not normal
Eosinophils	dT14	0.598	30	0.000	Not normal
	dT28	0.793	30	0.000	Not normal
	dT42	0.832	30	0.000	Not normal
	dT56	0.873	30	0.002	Not normal
	dT70	0.902	30	0.009	Not normal
	dT90	0.888	30	0.004	Not normal
Basophils	dT14	0.792	30	0.000	Not normal
	dT28	0.838	30	0.000	Not normal
	dT42	0.858	30	0.001	Not normal
	dT56	0.883	30	0.003	Not normal
	dT70	0.870	30	0.002	Not normal
	dT90	0.704	30	0.000	Not normal
ESR	dT14	0.356	30	0.000	Not normal
	dT28	0.470	30	0.000	Not normal
	dT42	0.346	30	0.000	Not normal
	dT56	0.456	30	0.000	Not normal
	dT70	0.737	30	0.000	Not normal
	dT90	0.790	30	0.000	Not normal

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

Indicator	dTi	Statistics	Number of degrees of freedom	p-value	Conclusion*
Leukocytes	dT14	0.234	30	0.000	Not normal
	dT28	0.681	30	0.000	Not normal
	dT42	0.747	30	0.000	Not normal
	dT56	0.273	30	0.000	Not normal
	dT70	0.802	30	0.000	Not normal
	dT90	0.746	30	0.000	Not normal
Erythrocytes	dT14	0.245	30	0.000	Not normal

	dT28	0.496	30	0.000	Not normal
	dT42	0.245	30	0.000	Not normal
	dT56	0.371	30	0.000	Not normal
	dT70	0.642	30	0.000	Not normal
	dT90	0.476	30	0.000	Not normal
Hematocrit	dT14	0.799	30	0.000	Not normal
	dT28	0.882	30	0.003	Not normal
	dT42	0.860	30	0.001	Not normal
	dT56	0.881	30	0.003	Not normal
	dT70	0.867	30	0.001	Not normal
	dT90	0.891	30	0.005	Not normal
Hemoglobin	dT14	0.450	30	0.000	Not normal
	dT28	0.828	30	0.000	Not normal
	dT42	0.881	30	0.003	Not normal
	dT56	0.493	30	0.000	Not normal
	dT70	0.608	30	0.000	Not normal
	dT90	0.673	30	0.000	Not normal
Platelets	dT14	0.535	30	0.000	Not normal
	dT28	0.806	30	0.000	Not normal
	dT42	0.875	30	0.002	Not normal
	dT56	0.584	30	0.000	Not normal
	dT70	0.772	30	0.000	Not normal
	dT90	0.830	30	0.000	Not normal
Neutrophils	dT14	0.360	30	0.000	Not normal
	dT28	0.436	30	0.000	Not normal
	dT42	0.569	30	0.000	Not normal
	dT56	0.616	30	0.000	Not normal
	dT70	0.606	30	0.000	Not normal
	dT90	0.627	30	0.000	Not normal
Lymphocytes	dT14	0.501	30	0.000	Not normal
	dT28	0.347	30	0.000	Not normal
	dT42	0.455	30	0.000	Not normal
	dT56	0.505	30	0.000	Not normal
	dT70	0.503	30	0.000	Not normal
	dT90	0.347	30	0.000	Not normal
Monocytes	dT14	0.273	30	0.000	Not normal
	dT28	0.513	30	0.000	Not normal
	dT42	0.404	30	0.000	Not normal
	dT56	0.718	30	0.000	Not normal
	dT70	0.546	30	0.000	Not normal
	dT90	0.742	30	0.000	Not normal
Eosinophils	dT14	0.587	30	0.000	Not normal
	dT28	0.587	30	0.000	Not normal

	dT42	0.388	30	0.000	Not normal
	dT56	0.467	30	0.000	Not normal
	dT70	0.489	30	0.000	Not normal
	dT90	0.399	30	0.000	Not normal
Basophils	dT14	0.234	30	0.000	Not normal
	dT28	0.681	30	0.000	Not normal
	dT42	0.747	30	0.000	Not normal
	dT56	0.273	30	0.000	Not normal
	dT70	0.802	30	0.000	Not normal
	dT90	0.746	30	0.000	Not normal
ESR	dT14	0.245	30	0.000	Not normal
	dT28	0.496	30	0.000	Not normal
	dT42	0.245	30	0.000	Not normal
	dT56	0.371	30	0.000	Not normal
	dT70	0.642	30	0.000	Not normal
	dT90	0.476	30	0.000	Not normal

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

Indicator	Statistics	Number of degrees of freedom	p-value	Conclusion*
The main group				
ALT	0.996	210	0.866	Normal
AST	0.995	210	0.781	Normal
Total bilirubin	0.994	210	0.544	Normal
Creatinine	0.990	210	0.167	Normal
Glucose	0.992	210	0.315	Normal
Control group				
ALT	0.993	210	0.486	Normal
AST	0.991	210	0.203	Normal
Total bilirubin	0.989	210	0.104	Normal
Creatinine	0.995	210	0.748	Normal
Glucose	0.992	210	0.325	Normal
**The conclusion is made at a significance level of 0.01*				

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

Indicator	dTi	Statistics	Number of degrees of freedom	p-value	Conclusion*
ALT	dT14	0.458	30	0.000	Not normal
	dT28	0.587	30	0.000	Not normal

	dT42	0.695	30	0.000	Not normal
	dT56	0.414	30	0.000	Not normal
	dT70	0.776	30	0.000	Not normal
	dT90	0.824	30	0.000	Not normal
AST	dT14	0.679	30	0.000	Not normal
	dT28	0.641	30	0.000	Not normal
	dT42	0.702	30	0.000	Not normal
	dT56	0.776	30	0.000	Not normal
	dT70	0.821	30	0.000	Not normal
	dT90	0.769	30	0.000	Not normal
Total bilirubin	dT14	0.366	30	0.000	Not normal
	dT28	0.681	30	0.000	Not normal
	dT42	0.717	30	0.000	Not normal
	dT56	0.840	30	0.000	Not normal
	dT70	0.741	30	0.000	Not normal
	dT90	0.774	30	0.000	Not normal
Creatinine	dT14	0.433	30	0.000	Not normal
	dT28	0.645	30	0.000	Not normal
	dT42	0.743	30	0.000	Not normal
	dT56	0.750	30	0.000	Not normal
	dT70	0.738	30	0.000	Not normal
	dT90	0.764	30	0.000	Not normal
Glucose	dT14	0.490	30	0.000	Not normal
	dT28	0.682	30	0.000	Not normal
	dT42	0.752	30	0.000	Not normal
	dT56	0.759	30	0.000	Not normal
	dT70	0.797	30	0.000	Not normal
	dT90	0.810	30	0.000	Not normal

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

Indicator	dTi	Statistics	Number of degrees of freedom	p-value	Conclusion*
ALT	dT14	0.787	30	0.000	Not normal
	dT28	0.822	30	0.000	Not normal
	dT42	0.803	30	0.000	Not normal
	dT56	0.838	30	0.000	Not normal
	dT70	0.840	30	0.000	Not normal
	dT90	0.859	30	0.001	Not normal
AST	dT14	0.273	30	0.000	Not normal
	dT28	0.544	30	0.000	Not normal
	dT42	0.743	30	0.000	Not normal

	dT56	0.318	30	0.000	Not normal
	dT70	0.314	30	0.000	Not normal
	dT90	0.369	30	0.000	Not normal
Total bilirubin	dT14	0.246	30	0.000	Not normal
	dT28	0.590	30	0.000	Not normal
	dT42	0.756	30	0.000	Not normal
	dT56	0.746	30	0.000	Not normal
	dT70	0.740	30	0.000	Not normal
	dT90	0.769	30	0.000	Not normal
Creatinine	dT14	0.616	30	0.000	Not normal
	dT28	0.575	30	0.000	Not normal
	dT42	0.879	30	0.003	Not normal
	dT56	0.889	30	0.005	Not normal
	dT70	0.371	30	0.000	Not normal
	dT90	0.655	30	0.000	Not normal
Glucose	dT14	0.576	30	0.000	Not normal
	dT28	0.635	30	0.000	Not normal
	dT42	0.590	30	0.000	Not normal
	dT56	0.588	30	0.000	Not normal
	dT70	0.669	30	0.000	Not normal
	dT90	0.768	30	0.000	Not normal

Table A.12. The results of checking the normality of the distribution of dispersion analysis residues for indicators of the general analysis of urine

Indicator	**Statistics**	**Number of degrees of freedom**	**p-value**	**Conclusion***
The main group				
Specific weight	0.991	210	0.210	Normal
pH	0.990	210	0.155	Normal
Leukocytes, cells in sight	0.992	210	0.287	Normal
Erythrocytes, cells in sight	0.990	210	0.160	Normal
Control group				
Specific weight	0.991	210	0.214	Normal
pH	0.988	210	0.096	Normal
Leukocytes, cells in sight	0.989	210	0.101	Normal
Erythrocytes, cells in sight	0.986	210	0.067	Normal
**The conclusion is made at a significance level of 0.01*				

Table A.13. The results of checking the normality of the distribution of quality of life assessment indicators according to the EORTC QLQ-C30 scale before the beginning of the study

Indicator	Group	Statistics	Number of degrees of freedom	p-value	Conclusion*
General health status	The main	0.761	30	0.000	Not normal
	Control	0.809	30	0.000	Not normal
General assessment of quality of life	The main	0.733	30	0.000	Not normal
	Control	0.760	30	0.000	Not normal
Physical function	The main	0.776	30	0.000	Not normal
	Control	0.807	30	0.000	Not normal
Role function	The main	0.822	30	0.000	Not normal
	Control	0.792	30	0.000	Not normal
Emotional function	The main	0.780	30	0.000	Not normal
	Control	0.752	30	0.000	Not normal
Cognitive function	The main	0.775	30	0.000	Not normal
	Control	0.734	30	0.000	Not normal
Social function	The main	0.791	30	0.000	Not normal
	Control	0.830	30	0.000	Not normal
Fatigue	The main	0.826	30	0.001	Not normal
	Control	0.834	30	0.001	Not normal
Nausea/vomiting	The main	0.782	30	0.000	Not normal
	Control	0.740	30	0.000	Not normal
Pain	The main	0.731	30	0.000	Not normal
	Control	0.748	30	0.000	Not normal
Sleep disorders	The main	0.779	30	0.000	Not normal
	Control	0.795	30	0.000	Not normal
Loss of appetite	The main	0.820	30	0.000	Not normal
	Control	0.811	30	0.000	Not normal
Constipation	The main	0.782	30	0.000	Not normal
	Control	0.753	30	0.000	Not normal
Diarrhea	The main	0.728	30	0.000	Not normal
	Control	0.783	30	0.000	Not normal
Financial difficulties	The main	0.764	30	0.000	Not normal
	Control	0.745	30	0.000	Not normal
**The conclusion is made at a significance level of 0.01*					

Appendix B

Questionnaire for evaluating the quality of life of the European organization for cancer research and treatment
EORTC QLQ-C30 (version 3.0)

We want to ask you a few questions about you and your health. Please answer all the questions yourself, circling the number of the answer 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 (the first letters of your first name)_____

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

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

		No	Rather no than yes	Rather yes than no	Yes
1	Do you experience any difficulties when performing work that requires significant physical effort, for example, when you carry a heavy utility bag or suitcase?	1	2	3	4
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 on the street?	1	2	3	4
4	Do you have to 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	Rather yes than no	Yes
6	Did anything limit you in one way or another when you performed your work or other daily tasks?	1	2	3	4
7	Has anything limited you in one way or another while doing your favorite business or other leisure activities?	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 vacation?	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	Have you had a loss of 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	Was it difficult for you to concentrate on something, for example, reading a newspaper or watching TV?	1	2	3	4
21	Have you experienced a feeling of tension?	1	2	3	4
22	Have you experienced a feeling of anxiety?	1	2	3	4
23	Have you experienced a feeling of irritation?	1	2	3	4
24	Have you experienced a feeling of depression?	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 the treatment you were undergoing 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 from 1 to 7 that most accurately reflects your situation.

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

1 2 3 4 5 6 7

Very bad Excellent

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

1 2 3 4 5 6 7

Very bad Excellent