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ORIGINAL ARTICLE

A randomized trial of the role of neutrophil mitochondrial dysfunction in the medical rehabilitation of patients receiving palliative chemotherapy for metastatic colorectal cancer

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ABSTRACT

BACKGROUND: Of the 7.3 billion people inhabiting our planet, there are nearly 20 million new cases of cancer and 9.7 million cancer deaths worldwide each year. World Health Organization (WHO) expects cancer incidence to increase by 77% by 2050, with more than 75% of cancer-related deaths occurring in low- and middle-income countries over the next decade. Therefore, one of the current prospectus challenges is to address the problem of finding a cheap and affordable way to restore health in humans during and after cancer treatment.

METHODS: The study was planned to include 200 patients with colorectal cancer (CRC) from 19 regions of Kazakhstan. The efficacy of palliative therapy during four courses of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) chemotherapy in combination with sodium nucleinate in patients with metastatic CRC was evaluated in the main group. The efficacy of four courses of standard FOLFOX chemotherapy was evaluated in the control group. The results were evaluated with comparison of quality of life, dynamics of laboratory tests and overall survival in the main and control groups. potential correlations between the dynamics of mitochondrial dysfunction, patients' quality of life.

RESULTS: We confirmed the assumption that the use of sodium nucleonate increased the patient's adaptation and probably improved the tumor microenvironment, which led to an improvement in the quality of life and will reduce the incidence of adverse effects. We also proposed a model of dynamic monitoring of the patient's well-being, which consists of measuring the level of immunity, the proportion of cells with active mitochondria and the QLQ-CR29 questionnaire.

CONCLUSIONS: Monitoring mitochondrial dysfunction during palliative therapy for CRC is a promising direction for improving quality of life and reducing 1-year mortality.

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KEY WORDS: Colorectal neoplasms; Drug therapy; Rehabilitation; Mitochondria; Sodium nucleinate.

An analysis of mortality causes among oncological patients revealed that hematological and infectious complications, arising from reduced immunity, accounted for one-third of the deaths in patients receiving high-dose chemotherapy. Additionally, in 39.2% of the patients, these complications led to complete or partial cessation of antineoplastic treatments. Aggressive, high-dose antineoplastic chemotherapy almost universally leads to severe complications such as cardiac insufficiency, intestinal dysbiosis, reduced cellular and humoral immunity, and a significant deterioration in the overall condition of patients.[1] Increasingly, literature discusses the effective use of checkpoint inhibitors combined with standard chemotherapy[2, 3] and the concept of "immunosurveillance" in the clinical treatment of cancer. According to this concept, specific antitumor therapy is only effective when the immune system is balanced and fully functional.[4] In 1971, the USA recognized a new interdisciplinary field of "oncological patient rehabilitation" aimed at the physical and social adaptation of individuals undergoing cancer treatment. It is known that all tumors are associated with 2-8 cumulative mutations and gene polymorphism of cancer cells in the tumor,[5] and attempts are even being made to create a genetic classification of tumors. However, numerous studies indicate that achieving an oncogenic burden capable of causing cancer requires a series of somatic mutations, potentially transforming initially benign tumor cells and enabling metastasis of highly proliferative tumors. From this, it becomes virtually impossible to create a unified genetic map of tumors, and the role of epigenetic causes related to the cancer microenvironment significantly increases.[6] The condition of the microenvironment depends on the state of immunity and the quality of metabolic processes, including the state of mitochondria.[7] Also, the level of mitochondrial deoxyribonucleic acid (DNA) in mononuclear lymphocytes of peripheral blood (PBMCs) decreases gradually with aging and is associated with health status among the elderly population.[8, 9] Since 2007, the trial of the natural oligodinucleotide – sodium adenosine nucleonate in oncological practice, in joint Italian-Kazakh pilot studies conducted from 2007 to 2010, has yielded promising results using the Italian immunological agent, sodium nucleinate, for the prevention of leukopenia and infectious complications in medical antitumor therapy for breast cancer, skin melanoma, cervical cancer, non-small cell lung cancer, and cancers of the colon and rectum.[10] This scientific work later formed the basis for a multicentered controlled study under the auspices of the Eurasian Association of Oncologists (EAO) titled "Immunological Medical Rehabilitation in Socially Significant Diseases, including Tuberculosis, Hepatitis B Virus, and Malignant Neoplasms," funded by a grant from the Kazakh National Medical University.[11] This article presents a segment of the research focused on palliative care and medical, immunological rehabilitation in the chemotherapy of metastatic and locally advanced colorectal cancer (CRC), with additional use of mitochondrial DNA and sodium adenosine nucleonate. The aim of the study was to improve quality of life and reduce 1-year mortality in the palliative treatment of metastatic forms of CRC.

Materials and methods

This is Phase II clinical trials a parallel multicenter randomized controlled trial in 19 clinics from different regions of Kazakhstan. The object of the study were 200 patients with histologically verified diagnosis of CRC. Thirteen people were excluded from the study due to a change in the treatment protocol. The study is listed at www.clinicaltrials.gov (NCI identifier #NCT06209229) (Table I). The main group included 89 patients with metastatic CRC (stages T3-4 N1-2 M), receiving four courses of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) chemotherapy (days 1-2: Oxaliplatin 100 mg/m^2 IV infusion, given as a 120 min IV infusion in 500 mL D5W, concurrent with leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2) IV infusion, followed by 5-FU 400 mg/m^2 IV bolus, followed by 46-h 5-FU infusion (2400 mg/m^2 for first two cycles, and may be increased to 3000 mg/m^2 if tolerated by patient (no toxicity>grade 1 during the first two cycles), days 3-14: rest days) combined with mitochondrial immunotherapy using sodium nucleinate. The medical

TABLE I.—*Distribution of CRC patients by type of treatment.*

N.	Types of treatment	N. of patients
1	Main group – chemotherapy according to the FOLFOX regimen in combination with sodium nucleonate	89
2	Control group chemotherapy according to the FOLFOX regimen	98
	Total	187

CRC: colorectal cancer; FOLFOX: folinic acid, 5-fluorouracil, and oxaliplatin.

rehabilitation protocol involved administering sodium nucleinate at 50 mg per day: 25 mg in the morning and 25 mg at lunch before meals, daily for 4 months. The control group consisted of 98 patients with metastatic CRC (stages T3-4 N1-2 M), who received only four courses of FOLFOX chemotherapy. In both groups, general and biochemical blood analyses were conducted monthly.

Additionally, before the start of treatment and 1 month after the end of treatment, PET-CT scans were performed, levels of tumor markers carcinoembryonic antigen (CEA) and CA-19-9 were determined, immunological status CD4/CD8 and mitochondrial activity of neutrophils were assessed, and echocardiography was conducted to determine the left ventricular ejection fraction. A well-being questionnaire (the European Organization for Research and Treatment of Cancer [EORTC] QLQ-CR29) was also administered.
In the main group, the effectiveness of palliative care during four courses of FOLFOX chemotherapy combined with correction of mitochondrial dysfunction sodium nucleinate was evaluated in patients with metastatic CRC and patient education in the principles of metabolic rehabilitation. In the control group, the effectiveness of four courses of standard FOLFOX chemotherapy administered independently was assessed for metastatic CRC. An evaluation of the results was conducted, comparing quality of life, dynamics of laboratory studies, and overall survival in the main and control groups. The impact of quantitative and qualitative indicators of mitochondrial activity in the blood of patients in both the main and control groups was assessed, as well as potential correlations between the dynamics of mitochondrial dysfunction, patients' quality of life, tolerance to the toxic effects of chemotherapy, and the reduction of 1-year mortality in patients with CRC.

Critical points

The critical points are:

- reduction in treatment interruptions due to leukopenia, neutropenia, and infectious complications during chemotherapy for metastatic CRC;
- improved quality of life (assessed by the EORTC QLQ-CR29 questionnaire);
- reduction in 1-year mortality during palliative treatment of metastatic CRC.

Statistical analysis

Statistical analysis of the study results was performed using the application program package "Statistica 7.0" (StatSoft, Tulsa, OK, USA) for Windows (Microsoft Corp., Redmond, WA, USA). The Mann-Whitney U-criterion was used to compare the studied samples by qualitative indicators. Patients admitted within short time intervals were randomized independently and sequentially into treatment groups. Each patient included in the study would be assigned a serial number in accordance with a table of random sequences of numbers that are uniformly distributed in the interval 0-99,999. Block randomization would be conducted in a 1:1 ratio. To ensure blinding, the number was assigned by the automatic registrar of the medical information system of the admission department and was not disclosed to the researcher. The researcher was unaware of the meaning of the table of random numbers. The nurse responsible for the intake, the laboratory technician conducting the tests, and the researcher performing the measurements are unaware of the patient's chart, with the exception of the assigned number. The physician overseeing the examination and prescribing the therapy will not have access to the results of the functional evaluation of blood and other measurements, nor will they be privy to the results of the questionnaire. The results were entered into the subject's chart at the conclusion of the treatment course and will be supplemented by a follow-up examination conducted 12 months later.

A survival analysis was conducted, employing the χ^2 test, Mann-Whitney U Test, and Kaplan-Meier analysis. For the QLQ-CR29 comparison, changes were deemed statistically significant when the observed change exceeded 10 points or 7.5%. To ascertain the statistical significance of the test, an ANOVA analysis was performed.

Study participants will be recruited as patients present to the clinic, up to a maximum of 12 patients per week. Each patient included in the study will be assigned an ordinal number sequentially according to a table of a random sequence. For the purpose of blinding, the number will be assigned by the registrar of the admission department and will not be further involved in the study. The intake nurse and the researcher will not know the patient's chart except for the assigned number.

Results

A total of 200 patients were enrolled, of whom 187 with histologically verified diagnoses of CRC completed the Qualiti of Life (QOL) questionnaires at all three time points and therefore served as our study population. All cancers had central pathology review. The distribution of patients in groups based on age, sex, tumor stage, location of the primary focus, and distant metastases was comparable. The average age of patients in the main and control groups was 61.8 and 61.7 years, respectively. Gender distribution in the groups showed that in the main group, women accounted for 48.1%, and in the control group, 56.6%; men constituted 51.9% in the main group and 43.4% in the control group. Locally advanced cancer T4N1M0 was identified in 22.8% of the main group and 24.0% of the control group. Metastatic CRC with liver involvement at stage T3-4N1M1 was found in 36.1% of the main group and 33.7% of the control group; metastatic CRC with lung involvement at stage T3-4N1M1 comprised 20.4% of the main group and 21.6% of the control group; metastatic CRC with carcinomatosis of abdominal organs at stage T3-4N1M1 was identified in 6.0% of the main group and 8.4% of the control group; CRC affecting mediastinal, cervical, and retroperitoneal lymph nodes T3-4N3M1 accounted for 18.1% in the main group and 13.2% in the control group (Table II).

In analyzing the results of the study, which evaluated the effectiveness of FOLFOX chemotherapy combined with mitochondrial immunotherapy using sodium nucleinate in 187 patients with metastatic CRC (stages T3-4 N1-2 M1), the following outcomes were observed (Table III, Figure 1):

- treatment interruptions in the control group, which only received FOLFOX chemotherapy, were noted in 53.01% of cases, whereas in the use of additional mitochondrial therapy with sodium nucleinate (mitochondrial DNA), treatment interruptions were noted in only 6.7%, $P<0.001$;
- tumor process stabilization in the control group, which only received FOLFOX chemotherapy, was observed in 21.4% of cases, whereas in the main group, with the addition of sodium nucleinate (mitochondrial DNA) to chemotherapy, stabilization occurred in 84% of cases, $P<0.05$;

TABLE II.—*Distribution of CRC patients by age, sex, treatment type, and metastasis localization.*

N.	Prognostic factors	Main group	Control group
1.	Average patient age	61.8 years	61.7 years
2.	Male gender	51.8%	43.37%
3.	Female gender	48.1%	56,6%
4.	Localization of primary focus in the colon	53.0%	45.7%
5.	Localization of primary focus in the rectum	46.9%	54.2%
6.	Locally advanced CRC T4 N0M0, T4 N1-2M0, T3N1-2M0	22.8%	24.0%
7.	Metastatic CRC with liver involvement	36.1%	33.7%
8.	Metastatic CRC with lung involvement	20.4%	21.6%
9.	Metastatic CRC affecting both lungs and liver	8.4%	9.6 %
10.	Metastatic CRC with involvement of mediastinal, cervical, and retroperitoneal lymph nodes	18.1%	13.2%
11.	Metastatic CRC with carcinomatosis of abdominal organs	6.0%	8.4%

CRC: colorectal cancer.

TABLE III.—*Treatment outcomes using accompanying palliative therapy during FOLFOX chemotherapy for locally advanced and metastatic CRC.*

N.	Treatment results	Main group	Control group	Statistical significance of differences
1	Stabilization of the tumor process	64.0% 57 out of 89	12.2% 12 out of 98	P<0.001
2	Partial regression of the tumor process	1.1% 1 out of 89	0	P<0.05
3	Deterioration of condition leading to cessation of treatment	13.5% 12 out of 89	77.6% 76 out of 98	P<0.001
4	Fatalities during treatment.	6.7% 6 out of 89	27.6% 27 out of 98	P<0.001

CRC: colorectal cancer; FOLFOX: folinic acid, 5-fluorouracil, and oxaliplatin.

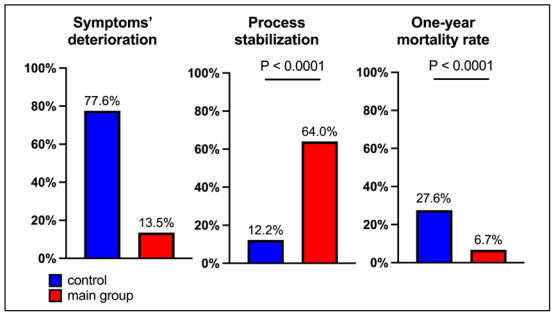

Figure 1.—Treatment outcomes using accompanying medical rehabilitation during FOLFOX chemotherapy for locally advanced and metastatic CRC.
CRC: colorectal cancer; FOLFOX: folinic acid, 5-fluorouracil, and oxaliplatin.

- lethal outcomes during the conduct of palliative chemotherapy in combination with mitochondrial therapy in advanced stages of CRC were noted in 7.8% of cases, whereas in the control group, which only received chemotherapy, lethal outcomes were observed in 26.6% of cases, P<0.05.

The combination of adenosine sodium nulenonate and chemotherapy in the treatment of metastatic CRC resulted in an improvement in general well-being, as evidenced by an increase in general vitality, appetite and performance, which became evident by the end of the 1st week of therapy. As indicated by the EORTC QLQ-C29 quality-of-life questionnaire, the control group exhibited a decrease or change in Quality of Life Score of less than 10 points, whereas the main group demonstrated an improvement in quality of life in over half of the cases. The observed difference was greater than 10 points. However, the repeated-measures ANOVA Test using F-distribution indicated that the mean values of all groups were assumed to be equal, and no statistical differences between the groups were identified in the follow-up tests. The results were found to follow a normal distribution based on the Shapiro-Wilk Test (α=0.05), P=0.062. However, it was observed that an improvement in quality of life was consistently associated with elevated mitochondrial activity in neutrophils among patients, with a higher prevalence in the group receiving sodium nucleinate (Figure 1).

Furthermore, during dynamic monitoring of tumor marker levels, it was observed that in some patients, the level of carbohydrate antigen 19-9 (CA 19-9) increased after the end of medical rehabilitation therapy (Figure 2, 3). Analysis of medical histories and patient complaints revealed that the peak increase in tumor markers coincided with the discontinuation of sodium nucleinate and the occurrence of seasonal acute respiratory viral infections (Figure 4). Additionally, this period also saw an increase in the level of the nonspecific marker of cell destruction – lactate dehydrogenase (Figure 5),[12] which has proven to be a very reliable dynamic marker in monitoring the progression of the oncological process in our practice.

The horizontal axis indicates the sequential number of the patient's visits to the doctor and lab test sessions, while the vertical axis shows the CA 19-9 level in blood in U/L. The increase coincides with the period following the discontinuation of sodium nucleinate and the occurrence of seasonal colds.

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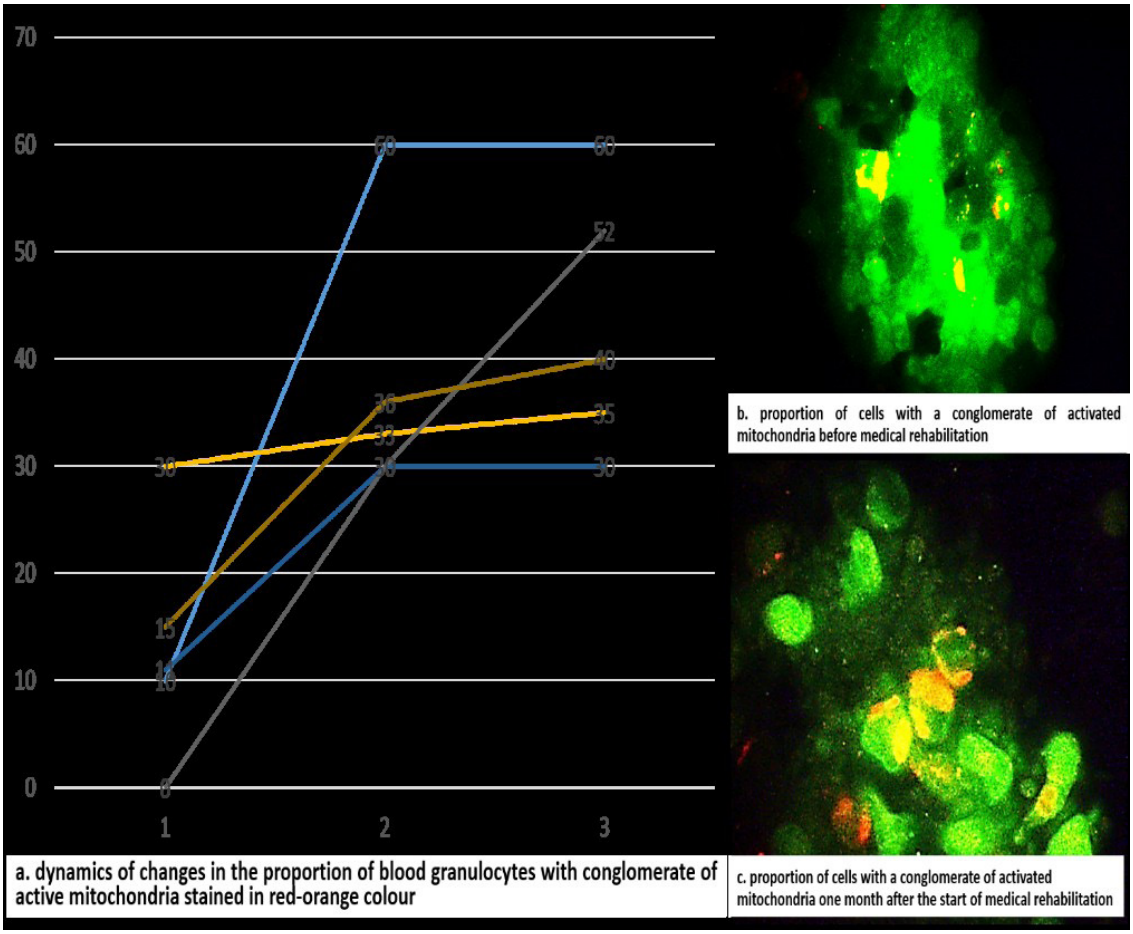

Figure 2.—It can be observed that the number of active mitochondria capturing oxygen (red-orange fluorescence) is minimal before treatment, but after receiving sodium nucleinate (mitochondrial DNA), there is a significant increase, enhancing the oxygen capture by neutrophil mitochondria (yellow fluorescence). This is accompanied by an improvement in quality of life, a decrease in lethargy and fatigue, and improved cardiovascular function as evidenced by an increase in the left ventricular ejection fraction of more than 7.5% according to echocardiography data in the main group. The increase in mitochondrial activity in neutrophils correlates with a significant reduction in the levels of oncological markers CEA and CA-19-9 and tumor activity during the 4-month control study in 64% of patients receiving palliative chemotherapy according to the "FOLFOX" scheme and mitochondrial immunotherapy.
CA 19-9: carbohydrate antigen 19-9; CRC: colorectal cancer; DNA: deoxyribonucleic acid; CEA: carcinoembryonic antigen; FOLFOX: folinic acid, 5-fluorouracil, and oxaliplatin.

lab test sessions, while the vertical axis should indicate the level of lactate dehydrogenase in blood in U/L (please note an error in the original text, which mistakenly states the vertical axis as CA 19-09). The increase occurs during the period after the discontinuation of sodium nucleinate and the occurrence of seasonal colds.

During the same period, there was a decrease in the neutrophil-to-lymphocyte ratio combined with a slight increase in white blood cell count, likely related to the reduced reserves of the body, insufficient for a full immune response to the emerging infectious challenge. Upon analyzing the qualitative state of neutrophil function, it was found that the Nitroblue Tetrazolium (NTB) Test[13] indicated a decrease in the proportion of leukocytes containing vacuoles with hydrogen peroxide, which points to a qualitative deficiency in nonspecific immunity (Figure 6).

While receiving accompanying therapy, stable lysosome contents within granulocytes are

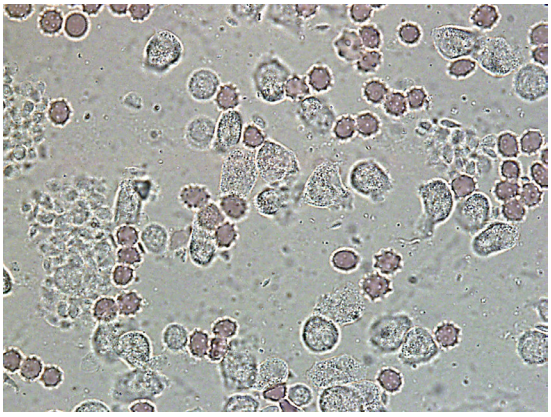

Figure 3.—It is apparent that most neutrophils contain active intracellular inclusions – "mitochondria: cellular power plants," "vacuoles" for defence against viruses and bacteria. The percentage of such "active" cells in the field of view is substantial. Patients with such high functional activity of neutrophils generally have a significantly lower likelihood of infectious complications.

observed, but a month after discontinuing sodium nucleinate therapy, there is a decrease in these indicators, leading to agranulocytosis. An interesting feature is the combination of a decrease in the qualitative composition of granulocytes with an increase in CA 19-09 and LDH levels in the patient's blood. It is possible that neutrophils significantly contribute to the formation of the tumor microenvironment and that immunological monitoring should not be limited to just CD4/CD8 control.

Discussion

Analysis of the current situation in palliative care for oncological patients shows a lack of unified approaches in this area. For instance, according to ASCO and NCCN protocols from 2021 in the USA, primary palliative care should combine anticancer treatment (chemotherapy, radiation) and non-specific, accompanying medical rehabilitation, specifically: eliminating unwanted life-threatening symptoms resulting from both the oncological process and adverse effects of chemotherapy or radiation.[14] Unfortunately, using only standalone chemotherapy in advanced-stage patients, ASCO and NCCN experts did not find improvement in outcomes after palliative chemotherapy in patients with medium and low functional status and, on the contrary, noted further deterioration in those who initially had a good status.[15] A similar study in Poland was dedicated to palliative chemotherapy in patients with advanced CRC.[16] It concluded that standalone palliative chemotherapy is not relevant and may lead to worse outcomes for patients than mere observation. Matsumoto *et al.*[17] show that standalone palliative chemotherapy does not always prolong life and may increase the likelihood of patient death, as life extension is not always possible with such treatment due to the combination of toxic effects from the tumor process and deterioration due to decreased immunity, infectious complications,

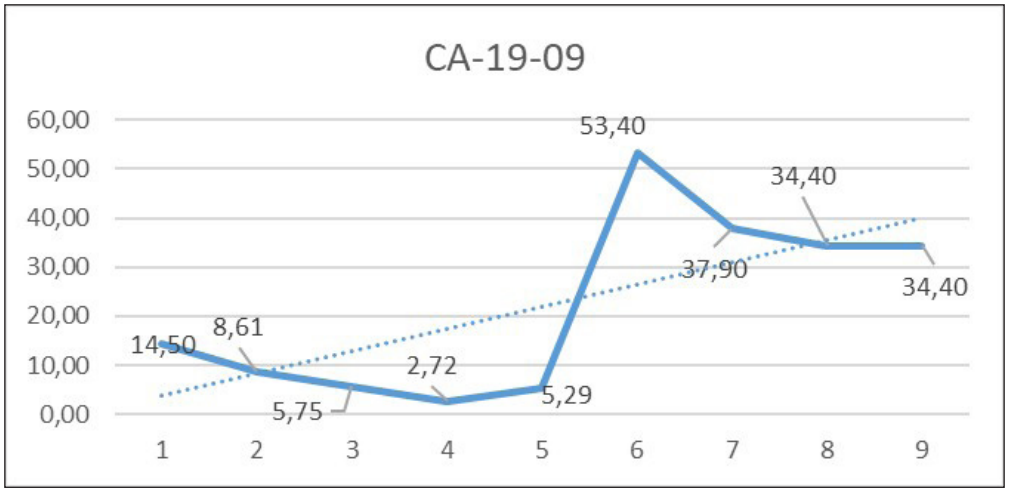

Figure 4.—Changes in the dynamics of CA 19-9 levels over a year of patient monitoring.
CA 19-9: carbohydrate antigen 19-9.

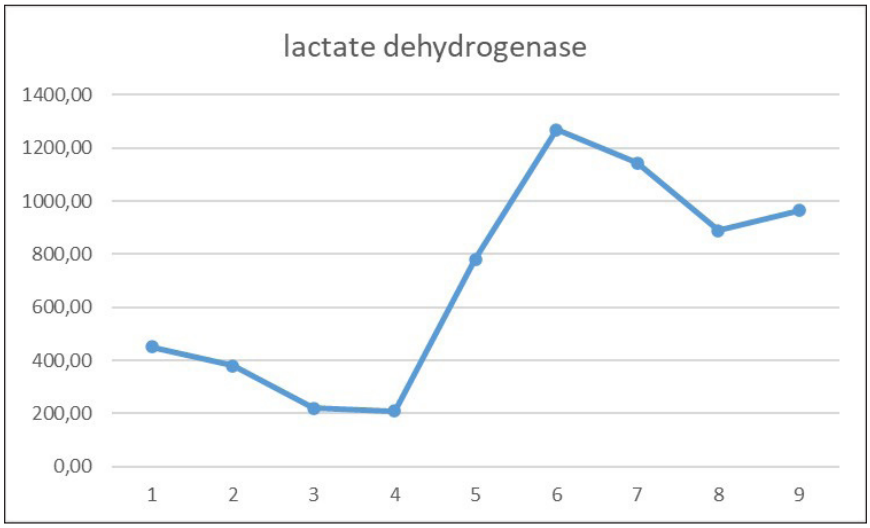

Figure 5.—Dynamics of lactate dehydrogenase levels in blood over a year of patient monitoring.

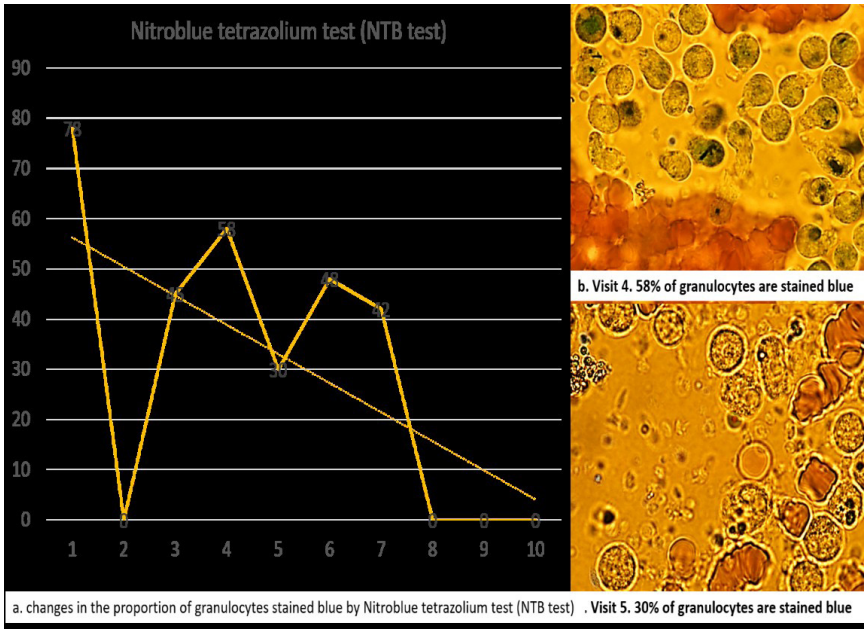

Figure 6.—Dynamics of the proportion of neutrophils stained by the NTB Test in blue relative to the total number of blood leukocytes over a year.
NTB: nitroblue tetrazolium.

and worsening of the cardiovascular and hepatic systems.[17] In terms of palliative effect and improving quality of life, the use of additional, accompanying mitochondrial therapy in chemotherapy for metastatic CRC has been shown to improve overall well-being in terms of increased general tone, appetite, and work capacity after the 1st week of therapy, correlating with an increase in mitochondrial activity in neutrophils (Patent RK).[18]

Moreover, an important direction, in our view, is the monitoring of mitochondrial dysfunction in the body before, during, and after chemotherapy in patients with CRC. This allows for the personalization of palliative accompanying therapy,

medical rehabilitation, and improvement in the quality of life of patients, and reduction in 1-year mortality.

Conclusions

In chemotherapy of metastatic CRC using the FOLFOX regimen combined with sodium nucleinate, there is an improvement in quality of life and a reduction in chemotherapy stoppage rates from 53.01% in the control group receiving standalone chemotherapy, to 6.7% in the main group, P<0.001. Tumor process stabilization in the control group, undergoing only FOLFOX chemotherapy, was observed in 21.4% of cases, while in the main group, supplemented with sodium nucleinate (mitochondrial DNA), it was 64%, P<0.001. Lethal outcomes during the period of palliative chemotherapy combined with mitochondrial therapy in advanced forms of CRC were noted in 6.7% of cases, compared to 27.6% in the control group, P<0.001. Monitoring mitochondrial dysfunction during palliative therapy for CRC is a promising direction for improving quality of life and reducing 1-year mortality. The entire human body should be considered as the tumor microenvironment, and even stress should be viewed as a component of immunological control.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Nurlan T. Baltabekov have given substantial contributions to the conception or the design of the manuscript; Stanislav A. Panov and Khadisha Kashikova contributed to acquisition, analysis and interpretation of the data. All authors have participated to the manuscript draft; Nurlan T. Baltabekov revised it critically. All authors read and approved the final version of the manuscript.

History

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