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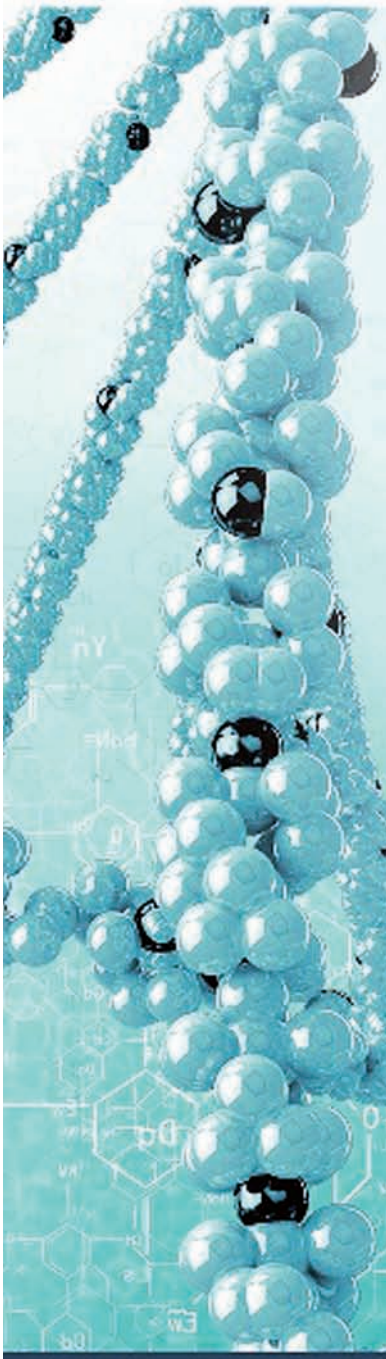

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- ОДНОНУКЛЕОТИДНЫЕ ПОЛИМОРФИЗМЫ: РОЛЬ В РАЗВИТИИ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ И ПЕРСПЕКТИВЫ КЛИНИЧЕСКОГО ПРИМЕНЕНИЯ
- ИММУНОТЕРАПИЯ ЗЛОКАЧЕСТВЕННЫХ ГЛИОМ: СОВРЕМЕННОЕ СОСТОЯНИЕ ПРОБЛЕМЫ И ПЕРСПЕКТИВНЫЕ НАПРАВЛЕНИЯ
- СТРАТЕГИЯ И ТАКТИКА КОМПЛЕКСНОГО ЛЕЧЕНИЯ БОЛЬНЫХ МЕТАСТАТИЧЕСКИМ КОЛОРЕКТАЛЬНЫМ РАКОМ

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ПОДДЕРЖИВАЮЩАЯ ТЕРАПИЯ В ОНКОЛОГИИ

Новые возможности в коррекции микронутриентной недостаточности у больных со злокачественными новообразованиями

Novel approaches for the correction of micronutrient deficiency in patients with malignant tumors

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Резюме

Метаболизм опухолевых клеток при онкологических заболеваниях является причиной дефицита микронутриентов, особенно при распространенном опухолевом процессе. На сегодняшний день доказано, что у пациентов со злокачественными новообразованиями имеется дефицит отдельных аминокислот (глицин, аргинин, цистеин, аспарагин, лизин, метионин), витаминов (C, E, D, группы B) и ряда микроэлементов (цинк, марганец, селен). К сожалению, проблеме микронутриентного дефицита и необходимости ее коррекции при онкологических заболеваниях не уделяется должного внимания. В современных исследованиях, в частности, проведенных у больных гепатоцеллюлярной карциномой в терминальной стадии, показано, что использование препаратов, влияющих на микронутриентный метаболизм (например, Онкоксин), позволяет увеличить аппетит, улучшить качество жизни, общее самочувствие и 2-месячную выживаемость. Таким образом, рациональная коррекция определенных микронутриентов может положительно влиять на общее состояние больных, результаты лечения и открывает новые перспективы в коррекции нарушений метаболизма у онкологических больных.

Abstract

The cancer cell metabolism leads to micronutrient deficiency of micronutrient deficiency, especially in patients with advanced disease. Various studies in patients with malignant tumors revealed the deficit of certain amino acids (glycine, arginine, cysteine, asparagine, lysine, methionine), vitamins (C, E, D, group B), and a number of trace elements (zinc, manganese, selenium). However, the problem of micronutrient deficiency, as well as the necessity of its correction in cancer patients are not widely recognized and poorly implemented by oncologists. The clinical studies in patients with terminal stage of hepatocellular carcinoma have shown that the use of food supplements affecting the micronutrient metabolism (e.g. Oncoxin) can improve appetite, quality of life and well-being. Furthermore, the ability to improve the 2 months overall survival in this group of patients by using of Oncoxin was demonstrated. Thus, the rational correction of micronutrient deficiency can have a positive effect on the general condition of patients and treatment results.

КЛЮЧЕВЫЕ СЛОВА

злокачественные новообразования, микронутриентная недостаточность, Онкоксин

KEY WORDS

malignant tumors, micronutrient deficiency, Oncoxin

КОНТАКТНАЯ ИНФОРМАЦИЯ

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English Translation

INTRODUCTION

Nutrient deficiency is a widespread problem in oncological diseases and an independent adverse factor influencing survival of oncological patients [1]. It is found that when the diagnosis is established 60% of patients with tumors of upper gastrointestinal tract and 45% of patients with lung cancer suffer from significant weight loss [2]. Nutrient deficiency is caused by many factors, such as anorexia, nausea, vomiting, diarrhea, intestinal obstruction, mucositis, dysphagia, taste perversion, systemic inflammation and others [1]. Energetic and plastic deficiency together with nutrient one lead to depression of immune system function, post-surgery infectious complications, mass atrophy, asthenia, and also increase toxicity and reduce the effectiveness of antitumor treatment. Besides, the progression of anorexia-cachexia syndrome causes about 20% of deaths in oncological patients [1]. Nutrient deficiency increases risk factors in oncological treatments period and leads to early developed Multiple Organ Dysfunction Syndrome, growth of drug administration and time which patients spend in hospitals, and as a consequence, direct and indirect costs for therapy [3]. Correction of nutritional status favors survival rates, reduces the risk of post-surgery complications and improves quality of life. It lets support positive nitrogen balance, reduce the quantity of infectious complications, gain body mass, and increase albumin level and the number of lymphocytes. According to Italian Society of Parenteral and Enteral Nutrition (2003) a domiciliary nutritive support treatment favors survival rates up to 2 years in 12-13% oncological patients with III-IV stages [1,4,5]. It is obvious that patients need all the nutrients but in some cases it is necessary some additional quantity of micronutrients which should be chosen considering the metabolic disorders, a type of tumor, its localization and the plan of treatment of the patient.

NOVEL APPROACHES FOR THE CORRECTION OF NUTRIENT DEFICIENCY IN PATIENTS WITH MALIGNANT TUMORS

Common aims of nutrient support in oncological patients include: correction of protein-energy deficiency, visceral protein pool support, reduction of quantity of adverse effects provoked by radio- and chemotherapy, preventive care and treatment of immunosuppression, improvement of life quality [6]. Currently to correct nutritive status deficiency they use: parenteral, enteral (including modular) and pharmacological feeding [3]. However the majority of medications do not respect special biochemical metabolic characteristics of oncological patients from the part of content of microelements and vitamins. Malignant tumors are often followed by micronutrient deficiency that differs from deficiency caused by alimentation as it has its own characteristics depending on the type/localization of the process and a chosen therapy. That let consider the aim of searching for new vitamin complexes and microelements for nutritive support an essential one.

THE IMPORTANCE OF VITAMINS FOR NUTRITIVE SUPPORT

According to numerous studies vitamins are essential not only as coenzymes in active centers of different ferments but also can have some antiproliferative activity [7]. The safety of using of complex vitamins including B,C,E,D groups in cancer cachexia in rats is experimentally proved as well as the deactivation of metastasis and improvement of general state [8]. Tumor cells synthesize collagenases and stromelysin as well as plasminogen activator; all that favors extracellular matrix sponginess, cytoarchitectonics anomalies and metastatic processes [9]. Vitamin C is involved in collagen synthesis and in collagen 'bridges' formation in connection tissue which allows its using during post-surgical period [10]. The same way the advantage of taking vitamins C and E by patients with cancer of kidney is a known fact [11]. The vitamins involved in metabolism of methyl groups (B12, B6, folic acid) which regulate processes of reparation and stabilization of the structure of nucleic acids are also very important. Their deficiency leads to single- or double-stranded tear of DNA molecule and chromosomal damage similar to the damages caused by ionizing radiation [12]. Number of studies determines that the deficiency of those vitamins is observed in cases of colon (with R53 overexpression) [13], pancreatic [14] and prostate cancer [15]. In other studies it was demonstrated that low levels of folic acid and vitamin B12 aggravate the progression of infection caused by human papilloma virus (HPV) and can provoke cervical cancer due to its influence on synthesis of core proteins of the virus as well as to transformation of the production of one of ribonucleoproteins [16]. The deficiency of folic acid and B12 accompanies the infection H.pylori, pernicious anemia and atrophic gastritis – the states that predispose stomach cancer [17]. Combined deficiency of vitamin B12 and folic acid provoked by abnormal folate metabolism can cause atherogenesis, venous thrombosis and malignant tumors progression [18]. It is found that folate deficiency in blood serum can increase risk of stomach cancer and possibility of its metastasis to lymph glands and liver [19]. Prescription of vitamin B12 to patients with prostate cancer with its deficiency improves their somatic condition and do not influences the tumor growth or metastasis [20]. The optimal intake of folic acid, vitamins B6 and B12 reduces risk of breast cancer [21]. An additional intake of nicotinamide favors 5-fluorouracil accumulation in colorectal metastases [22].

THE IMPORTANCE OF AMINO ACIDS FOR NUTRITIVE SUPPORT

One of the most important requirements to amino acid formulas is that they should contain essential amino acids. In modern preparations the percentage of essential amino acids to their total number is about 45-46%. Now it is obligatory to include nonessential amino acids into amino acid formulas as it favors more effective protein synthesis [3]. Cysteine influences fermentative antioxidant systems because its concentration is rate-limiting in reduced glutathione synthesis. The level of cysteine is connected with vitamins B12 and B6 as well as with methionine which is transformed after demethylation into homocysteine – cysteine progenitor. Together with B12 and folic acid it converses homocysteine to methionine which helps to keep body's methyl reserves (maintaining DNA stability). On the other hand the conversion of homocysteine to cysteine (B6 – co-factor) favors to maintain antioxidant activity. At first view it seems logical to use extra doses of essential amino acid methionine (as methyl reserves and a source of cysteine), however it is proved that it can lead to hyperhomocysteinemia and endothelial dysfunction [23]. Altogether methionine deficiency is followed by reduction of level of chemical toxicity effects and has a significant part in oncogenesis [23]. Thus, cysteine is an evident source of maintaining a desirable methylation intensity and antioxidant activity. Its administration in addition to vitamin B6 and folic acid increases availability of homocysteine for remethylation to methionine and favors an effective functioning of antioxidant systems which use reduced glutathione.

Arginine is a substrate for three isoenzymes of NO-synthases: endothelial, inducible and neuronal. Nitrogen oxide works as neurotransmitter, intercellular messenger and during peroxynitrite anion formation initiates a nitrosative stress [24]. It is necessary to mention that in Clinical Trials Registry of U.S. National Institute of Health there is a large quantity of trials about arginine as a medicine for such diseases as bronchial asthma, sickle-cell anemia, metabolic syndrome, preeclampsia, tuberculosis, malaria, gestational hypertension. Besides, arginine is actively studied as immunoactive nutrient in sepsis and in critically ill patients [25]. A possibility of administration of nutraceuticals rich in arginine in stomach (NCT01704664) and lever (NCT02041871) cancers, extensional abdominal surgeries (NCT00512213, NCT 01256034) and some other states are studied. Apart from immunomodulatory function L-arginine can also be important for preventive care of muscle atrophy in oncological diseases [26]. The possibility of prevention of mass atrophy in breast cancer with arginine administration nowadays is being studied in one of the largest universities of the USA (NCT004987380). There are also trials on the ability of arginine to improve quality of life and sexual function in men and women who had an

oncological disease (NCT004559134, NCT01105130).

Another known nutraceutical is glycine. Apart from immunomodulatory action this amino acid has also anti-inflammatory and cytoprotective effects [27]. Glycine is able to reduce the intensity of tissue damages of liver, kidneys, heart and colon in ischemia reperfusion injury and in circulation management after hypothermia [27]. Besides, glycine can reduce the intensity of a systemic inflammation, an important factor in developing malignant tumors and cancerous cachexia [28, 29]. It is demonstrated in sepsis model and in administration of endotoxin that glycine reduces the production of TNF, IL-6 – the main anti-inflammatory cytokines closely involved into pathophysiology of tumor growth and mass atrophy [30, 31]. In experimental studies it was discovered that this amino acid depresses the activation of a number of transcriptional factors including nuclear factor B that regulates gene expression of many anti-inflammatory cytokines and ferments involved into inflammatory reactions such as TNF alpha, IL-6, COX-2 [31]. The effect on the synthesis of lipid inflammatory mediators is followed by the reduction of phospholipase A2 activity [31]. It is important that glycine has ability to reduce nephro- and hepatotoxicity of medicines and a number of toxic combinations [32]. For example, glycine decreases nephrotoxicity of cyclosporine A. It is supposed that glycine due to depressing release of prostaglandin E2 out of Kupffer cells blokes liver damage caused by the preparation [33]. Anti-inflammatory effects of glycine are based on its ability to reduce the production of active oxygen forms (AOF) and oxidative stress intensity [34]. It is discovered that glycine in food minimizes depression of activity of Mg- and Cu-Zn-superoxide dismutase, glutathione peroxidase and catalase [34]. Because of its antioxidant action and reduction of producing TNF alpha glycine is an antagonist of proliferative effects of such stimulators of tumor growth as peroxisome proliferators and some fatty acids (corn oil, e.g.) [35]. Besides, glycine depresses melanoma B16 growth to 65% which reflects general antitumor properties of the amino acid [36]. It was shown in clinical studies that the administration of a diet rich in glycine in patients who had a surgery because of gastrointestinal cancer favors the reduction of intensity of inflammatory reaction and postoperative morbidity including infectious ones [28]. In patients with metabolic syndrome that type of a diet favors the reduction of oxidative stress and systolic arterial pressure [37]. Glycine and cysteine deficiency in HIV-positive people of older age is followed by reduced glutathione deficiency and as a consequence fatty acid oxidation disorder. An additional administration of those amino acids leads to sensitization of tissue cells to insulin, reduces body mass and fat, increases skeletal muscle [38].

THE IMPORTANCE OF MICROELEMENTS FOR NUTRITIVE SUPPORT

Among microelements the most important in oncology are selenium, zinc, manganese, chrome and cuprum which enter to the organism only from outside, with food. Zinc is an indispensable element; its deficiency can lead to severe immunodeficiency, reduction of testosterone level, oligospermia and muscle mass loss [39]. Its indispensability was discovered due to serious infections developing because of its deficiency [39]. Later zinc deficiency was recognized as a cause of a number of pathological conditions including stunted growth, sensorineural and cognitive disorders, and poor wound healing [39]. Nowadays is it known more than 300 ferments that have zinc as their cofactor and more than a 1000 of transcriptional factors that need the element for their functioning [39]. Zinc has a wide range of immune regulatory effects. Its intracellular level is a crucial factor of CD4+T-lymphosites activation when they interact with LPC activated dendritic cells [40]. Besides, intercellular zinc regulates the expression of molecules of the major histocompatibility complex class II [40, 41]. Thus, zinc is essential for the key stage of specific immune response – antigen presentation. Moreover zinc provides a correct maturation and function of neutrophils and NK-cells [42]. The influence of the microelement on macrophages is multidirectional. Zinc deficiency leads to phagocytic disorders, intracellular killing and dysregulation of nuclear factor kB activates synthesis of TNF alpha, IL-6, IL-8 and some other anti-inflammatory cytokines [41, 43]. It has been discovered recently that zinc has an antioxidant action. Firstly the microelement inhibits NADPH oxidase – an important source of active oxidation forms [44]. Secondly Zn is a cofactor of superoxide dismutase – a most important ferment of antioxidant systems and an inductor of synthesis of metallothioneins – low molecular weight proteins with a large quantity of cysteine which is able to bind heavy metals and hydroxyl radicals [44]. Zinc deficiency is very common. Up to 36% of elder people in developed countries suffer from it [39]. It is reported that about 80%of women do not consume a necessary quantity of zinc [45]. Its deficiency follows a number of oncological diseases such as prostate, lung and ovarian cancers [46]. It develops in patients who get long-term opioids therapy for chronic pain [47] or cisplatin chemotherapy [48]. It was discovered in animal model that a marginal zinc deficiency is connected with histopathological changes in female breast specific for malignant transformation [45]. Besides, it is supposed that zinc deficiency underlies in the growth of Hh ligand level and in the activation of Hh (Hedgehog) signaling pathway – one of the tumors growth activators in some types of cancer [46]. It is also set that in physiological conditions zinc works as a negative regulator of Hh signaling pathway [46]. Interesting results were

obtained while studying an additional administration of zinc with food (45mg/day) in elder people between 55-87 years old. It was discovered that such an intervention leads to the reduction of TNF production, oxidative stress markers. The most important thing though is that zinc administration is followed by 66% less frequency of infectious diseases during a year of monitoring [49]. An important zinc quality is its ability to correct taste perversion appearing as well in oncological diseases and also stimulate food consumption which is very important in anorexia-cachexia syndrome progression [50].

Manganese is a component of several ferments essential for a normal bone structure formation. In experimental manganese deficiency studies in people it was discovered that it is followed by dermatitis of miliaria type and lipid storage disease [51]. Manganese draws researchers' attention in the first place as a cofactor of one of the most important antioxidant ferments Mn isoferment superoxide dismutase (Mn SOD or SOD2) which expresses in mitochondria of mammals [52]. During long time SOD2 role in oncogenesis was just supposed and only in 2015 a study with direct demonstrations of its involvement into the process was published [52, 53]. The histologic pattern of liver in mice with SOD2 hepatocytes deficiency changed, the expression of tumor markers rose and the sensibility to carcinogens increased [53]. The absence of this ferment production by hepatoma cells was followed by their conversion to a more malignant phenotype and by appearance of all the cellular properties associating with tumor transformation [53]. In cases of SOD2 deficiency both in vivo and in vitro there were observed procarcinogen changes of two most important signaling pathways involved into tumor transformation: Wnt/β – catenin and connected with hypoxia [53].

THE IMPORTANCE OF INDIVIDUAL MACROMOLECULES FOR NUTRITIVE SUPPORT

Besides vitamins and microelements different macromolecules which compose nutritional supplements or medical preparations: glucosamine, glycyrrhizin, epigallocatechin gallate and others, have a definite positive effect on oncological diseases progression and quality of life of patients. During long time glucosamine was widely used in osteoarthrosis therapies. Its efficiency in that case is still a matter of discussion and research results are often contradictive. However according to the Cochrane review it can reduce pain and improve arthrosis functioning [54]. As glucosamine is non-prescription in the USA and a number of patients suffering from osteoarthrosis is very high it became possible to estimate the consequences of its use within a major epidemiological survey. It was discovered that glucosamine administration is followed by reduction of death risk: firstly by lungs diseases (risk ratio 0,59) and cancer (risk ratio 0,87) [55]. That research has brought interest back to glucosamine. It is assumed that its ability of reducing systemic inflammation activity underlies those effects. It was shown in clinical researches that use of glucosamine is followed by lowering of C-reactive protein and prostaglandin E2 levels while in experimental colitis model it was discovered that glucosamine depresses TNF alpha and IL-1 expression in colon mucosa provided that those effects are meditated by depression of nuclear factor B activity [57]. Glycyrrhizic acid (glycyrrhizin) is an immunomodulator, hepatoprotector and can be used in cirrhosis of liver therapy as well as in preventive care of many virus infections. In Japan glycyrrhizin is registered as a medicine which is traditionally used in allergic diseases treatments [58]. Antitumor properties of glycyrrhizin are being actively studied. Only for the latest several years dozens of articles that describe the mechanisms of this glycoside which bloke metabolism of tumor cells were published. Nowadays it is assumed that the main one is the ability to connect with HMGB1 protein and as a consequence to inhibit tumor microenvironment and angiogenesis [59]. Other effects of glycyrrhizin were discovered. Thus, in adenocarcinoma cell culture of lungs A549 and NCI-H23 glycyrrhizin depresses the expression and activity of thromboxane synthetase and provokes apoptosis of tumor cells [60]. Besides, it was shown that glycyrrhizin depresses cell growth of U251 human glioblastoma line (researchers explain the influence on proliferation and apoptosis by the reduction of nuclear factor B expression) [61]; prevents large-bowel carcinogenesis in model with dimethylhydrazine (in depression of nuclear factor B expression, COX-2, vascular endothelial growth factor, TNF alpha and increase of apoptosis signal molecules) [62]; causes leukemia cells death in mice with WEHI-3 (activating at once several signaling pathways of apoptosis and depressing proliferative impulses) [63, 64]. It is obvious that glycyrrhizin cannot be considered as a wholesome anticancer drug; however its effect can be used for modification of biological reactions in patients with oncological diseases [64]. There have been published already clinical trial data confirming a high preventive effectiveness of this substance in hepatocellular carcinoma in patients with chronic hepatitis C when they do not give response to interferon therapy [65, 66]. Glycyrrhizin has not only antitumor and anti-inflammatory action. It also has a wide range of hepatoprotective effects which were demonstrated in clinical trials. It was discovered that glycyrrhizin leads to a significant reduction of ALT and improvement of histologic pattern of liver in patients with chronic hepatitis C who did not response to the interferon + ribavirin therapy [67] and prevents autoimmune hepatitis progress when administrated early [68]. In infectious mononucleosis and in complicated liver dysfunction glycyrrhizin does not only favor to its quicker recuperation but also has an immunomodulating effect influencing positively on cellular immunity [69]. Hepatoprotective properties of glycyrrhizin

can be very important in toxic liver damage caused by chemotherapy. That quality was shown in patients with stomach cancer. It was found out that glycyrrhizin administration during FOLFOX and XELOX chemotherapy is much less followed by liver dysfunction cases (more than 2 times less in comparison with placebo group) [70]. Epigallocatechin gallate (EGCG) – is a natural polyphenol, one of the main components of green tea. Polyphenols have attracted researchers' attention for a long time because of their high antioxidant activity. As long as the activation of active oxygen forms production underlies carcinogenesis and neoplastic proliferation they started to study EGCG as a possible anticancer drug. Its ability to depress the activity of the heat shock protein Hsp90 is considered nowadays its main antitumor effect [71]. For the first 9 month of 2015 57 articles containing "epigallocatechin gallate" and "cancer" as key words were published (PubMed). Most of them are articles about model trials or experiments in vitro with positive results. Promising preliminary results in small groups of patients were obtained in chronic lymphocytic leukemia [72, 73 and 74] and in backsets after surgical treatment of colon cancer [75]. A most important property of green tea polyphenols might be their radio- and chemoprotective action. EGCG is known to be very effective in acute esophagitis management induced by radio- and chemotherapy because of its antioxidant and anti-inflammatory effects [76, 77]. EGCG administration can also be approved in different states connected with inflammation including a systemic one. EGCG can be very effective in interstitial cystitis, ulcerative colitis, acne and some other diseases caused by an inflammation [78, 79 and 80]. It is considered that an anti-inflammatory action is realized both by a direct depression of NF kappa B activity and by a mediated reduction of AOF production [81]. Thus, and importance and value of macro- and micronutrients for oncological patients is a subject of active scientific inquiry nowadays. Due to the obtained data it became possible to think of a scientifically proven practice of that approach.

NEW OPPORTUNITIES OF MICRONUTRIENT SUPPORT IN ONCOLOGICAL PATIENTS

In modern conditions of molecular-biological approach to antitumoral therapy it became clear that apart from blocking pathological pathways that provide proliferation and metastasis of malignant tumors it is possible as well as essential to affect macro and micro levels of metabolic process in oncological patients. One of such opportunities gives Oncoxin, a preparation that contains the following ingredients: 1) vitamins – folic acid, cyanocobalamin, pyridoxine and ascorbic acid; 2) amino acids – glycine, arginine and cysteine; 3) microelements – zinc and manganese; 4) biologically active substances – glucosamine, glycyrrhizin acid and green tea extract containing EGCG. Apart from nutritional status normalization in experimental trials Oncoxin has showed its ability to restrain colon cancer metastasis into liver [82], activation of apoptosis and potentiation of antiproliferative effect of sorafenib in culture of hepatocellular carcinoma [83]. Oncoxin reduces the proliferation of HER2-overexpressive breast cancer cells lines BT474 and SKBRS [84]. According to clinical trial data the administration of Oncoxin in patients with terminal hepatocellular carcinoma improves quality of life and possibly increases its expectancy (85). Thus, in that clinical group a positive improvement of 2-month survival rate after Oncoxin administration was demonstrated (9 out of 19 patients; 47%) in comparison with those patients who did not receive Oncoxin (0 out of 10 patients; $p<0,0001$). In the clinical trial there were not registered side effects of Oncoxin, 32% of patients noticed improvements of appetite and general state [85]. As a result Oncoxin administration can be considered as an additional corrective method for nutritive deficiency that influences positively quality of life and results of antitumor therapy.

CONCLUSSION

The problem of micronutrient deficiency as well as micronutrient support in oncological diseases does not often find a proper attention and comprehension in oncology specialist. At the same time a correct balanced diet with an additional administration of special micronutrients improves patients' state and increases chances for survival. An individually adjusted modern micronutrient support not only improves protein-energy status but also favors to decrease quantity of complications and concurrent diseases which reduces the costs of therapy and medical attendance. An example of a careful combination of vitamins, amino acids, microelements and biologically active substances in Oncoxin which administration is able to improve both somatic status of oncological patients and their after-history results.

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