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Влияние нутритивной поддержки на питательный статус, качество жизни и выживаемость у онкологических больных, получающих системное лекарственное противоопухолевое лечение

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АННОТАЦИЯ

Недостаточность питания — распространённая проблема среди онкологических пациентов, обусловленная непосредственным влиянием опухоли и последствиями специфической терапии, — отрицательно сказывается на качестве жизни и ухудшает результаты противоопухолевого лечения. Нутритивная поддержка играет важную роль при проведении системной лекарственной противоопухолевой терапии, однако недостаточность питания, развивающаяся на фоне злокачественных новообразований, остаётся недооценённой, и в клинической практике ей уделяется мало внимания.

Для оценки необходимости и безопасности нутритивной поддержки на фоне системного лекарственного противоопухолевого лечения злокачественных новообразований проведён анализ публикаций в медицинских базах eLibrary, PubMed, Medline с акцентом на оценку безопасности и эффективности нутритивной поддержки на фоне проведения системного лекарственного противоопухолевого лечения за период 2003-2022 гг. по следующим ключевым словам: онкология, химиотерапия, нутритивная поддержка, омега-3 жирные кислоты, глутамин.

Согласно полученным данным, характерный для больных злокачественными новообразованиями синдром анорексии-кахексии приводит к развитию саркопении, отрицательно влияющей на результаты специфической терапии. Своевременное назначение нутритивной поддержки достоверно улучшает результаты лечения, качество жизни, а также увеличивает выживаемость у пациентов, получающих нехирургическую противоопухолевую терапию, и нутритивная поддержка, проводимая параллельно с противоопухолевым лекарственным лечением, способствует улучшению его результатов.

Ключевые слова: онкология; химиотерапия; нутритивная поддержка; омега-3 жирные кислоты; глутамин.

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ЭКО•ВЕКТОР

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The effect of nutritional support on nutritional status, quality of life, and survival in cancer patients receiving systemic anticancer therapy

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ABSTRACT

Malnutrition, a common problem among cancer patients, due to the direct influence of the tumor and the consequences of specific therapy, negatively affects the patient's quality of life and is detrimental to the results of anticancer treatment. Nutritional support plays a vital role in systemic drug anticancer therapy; however, malnutrition that develops against a background of malignant neoplasms remains underestimated and receives little attention in clinical practice.

To assess the need for and safety of nutritional support in this context, an analysis of publications in the medical databases e-Library, PubMed, and Medline was performed with an emphasis on assessing the safety and efficacy of NP in the presence of systemic drug antitumor treatment for the period 2003–2022 using the keywords oncology, chemotherapy, nutritional support, omega-3 fatty acids, and glutamine.

The obtained data show that patients with cancer have anorexia-cachexia syndrome, leading to the development of sarcopenia, which negatively affects the results of specific therapy. Timely appointment of nutritional support significantly improves the results of treatment, as well as quality of life, and increases the survival rate in patients receiving non-surgical anticancer therapy; moreover, nutritional support administered in parallel with anticancer drug therapy improves treatment results.

Keywords: oncology; chemotherapy; nutritional support; omega-3 fatty acids; glutamine.

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INTRODUCTION

Weight loss in cancer patients is a complex multicomponent process. There are three groups of factors responsible for weight loss: tumor-related, anticancer treatment-related, and patient-specific factors.

The paraneoplastic effects of a tumor result in chronic inflammation associated with high levels of pro-inflammatory cytokines. This leads to appetite disorders (both due to a direct effect on satiation centers of the brain and indirectly through dysregulation of the satiation hormones leptin and ghrelin) and a significant inhibition of structural protein synthesis. Together, these factors cause anorexia. In addition, the tumor produces specific agents such as protein- and lipid-mobilizing factors that accelerate self-protein degradation and lipolysis, resulting in sarcopenia and increased weight loss [1]. Moreover, the tumor can directly impair gastrointestinal function, and the resulting nutritional disorder accelerates weight loss.

Active anticancer treatment has mainly an adverse immediate effect on the nutritional status. In particular, disorders develop rapidly in the presence of severe systemic toxicity or systemic infection.

When evaluating individual patient characteristics contributing to malnutrition, attention should be given to psychological distress that develops when a patient becomes aware of the malignancy, followed by apathy and depression, which also increase the severity of anorexia. In addition, decreased physical activity results in muscle weakness.

MAIN SYNDROMES ASSOCIATED WITH WEIGHT LOSS IN CANCER PATIENTS

Anorexia-cachexia syndrome

Weight loss that persists despite seemingly sufficient amount and caloric content of food may be suggestive of the anorexia-cachexia syndrome, a complex disorder characterized by chronic, progressive, unintentional weight loss, with low (if any) efficacy of conventional nutritional support [2]. Malnutrition typical for the syndrome can be easily detected. The minimum set of diagnostic tools for the detection of malnutrition (the Global Leadership Initiative on Malnutrition criteria) includes phenotypic and etiologic factors. Phenotypic criteria include weight loss, low body mass index, and muscle mass loss confirmed by validated methods [3]. Etiologic criteria include reduced food consumption and digestion, as well as inflammation (which is *a priori* present in cancer patients) (Table 1). Malnutrition is confirmed when at least one phenotypic and one etiologic criterion is met.

Sarcopenia

Uncontrolled anorexia-cachexia syndrome results in apathy, weakness, iron deficiency anemia, and anemia of chronic disease [4], as well as sarcopenia, a syndrome characterized by progressive and generalized loss of weight and strength in skeletal muscles. The European Working Group on Sarcopenia in Older People recommends using two criteria for diagnosing sarcopenia: low muscle mass together with low muscle strength and/or low physical performance (Table 2) [5].

Three objective visualization methods can be used to evaluate the muscle mass: computed tomography (CT), magnetic resonance imaging (MRI), and dual-energy X-ray absorptiometry (DXA). CT and MRI are considered precise methods, a diagnostic gold standard that helps distinguish adipose tissue from other soft tissues in the body. However, high research cost, limited availability of the equipment, and concerns about radiation exposure limit their use in routine clinical practice.

DXA is a promising alternative method for both research and clinical use that helps distinguish bone, adipose, and

Table 1. Phenotypic and etiological criteria for diagnosing malnutrition (adapted from [3])

Phenotypic criteria			Etiologic criteria	
Weight loss, %	**Body mass index, kg/m^2**	**Muscle mass loss**	**Reduced food consumption and/or digestion**	**Inflammation**
>5% in the last 6 months or >10% in more than 6 months	<20, if <70 years old; <22, if >70 years old; Asia: <18.5, if <70 years old; <20, if >70 years old	Confirmed using validated diagnostic techniques	⩽50% of the nutritional requirement for >1 week, or any reduction for >2 weeks, or any chronic gastrointestinal disorder negatively affecting digestion or absorption	Acute condition/ injury or inflammation associated with a chronic disease

Table 2. Diagnostic criteria for sarcopenia (adapted from [5])

The diagnosis is based on one mandatory criterion plus at least one additional criterion
Low muscle mass (mandatory criterion)
Low muscle strength (additional criterion)
Low physical performance (additional criterion)

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muscle tissue. This type of full-body scan is associated with minimum radiation exposure of patients. The main disadvantage of this method is the need for a bulky equipment, which prevents its use in large-scale epidemiological studies.

Validated methods also include bioelectrical impedance analysis, which allows the evaluation of fat and lean body mass. The test is inexpensive, easy to use, easily reproducible, and suitable for both outpatients and inpatients. Bioelectrical impedance analysis methods used in routine clinical practice have been studied for over 10 years, and the results correlate well with MRI data.

Anthropometric measurements are still relevant as well. Calculations based on mid-upper arm circumference and skin fold thickness are used for muscle mass evaluation. However, age-related changes, edema, and loss of skin elasticity affect the reliability of the method, especially in elderly patients. These and other factors undermine the reliability of anthropometric measurements; therefore, they are not recommended for the routine diagnosis of sarcopenia.

Dynamometry is used for the evaluation of muscle strength, whereas physical performance can be evaluated using various tests (e.g., the six-minute walk test) [6].

THE EFFECT OF WEIGHT LOSS ON ANTICANCER THERAPY OUTCOMES

Most cytostatic agents are distributed in the lean body mass, and a loss of muscle volume can change their predicted pharmacokinetics, negatively affecting the outcomes of anticancer treatment and increasing its toxicity [7]. It has been shown that sarcopenia is a predictor of chemotherapy-induced toxicity and affects the probability of survival in cancer patients receiving anticancer drug treatment. The correlation between the toxicity of taxane-based regimens and survival rates in advanced breast cancer has been observed, for example, by S.S. Shachar et al. [8]. The study included patients with metastatic breast cancer who received first-line taxane-based chemotherapy (*n*=40). During the routine CT for the TNM cancer staging, skeletal muscle areas at the L3 lumbar vertebral body level were measured. Sarcopenia, defined as skeletal muscle area (cm^2) / height (m^2) <41, was diagnosed in 58 patients. It has also been found that chemotherapy dose reduction or delay was twice more common in patients with sarcopenia compared to patients with normal muscle mass. In the sarcopenia group, grade 3/4 toxicity was observed in 57% of patients, whereas this value was as low as 18% in the control group. Only patients with low muscle mass (39% of patients vs. 0% of controls) required hospitalization due to chemotherapy-induced toxicity. Moreover, relapse-free survival was lower in patients with sarcopenia. Thus, there was a direct correlation between the toxicity of taxane-based regimens, relapse-free survival rate, and sarcopenia.

Similar results were obtained by M.J. Sealy et al., [9] who investigated the relationship between low muscle mass and early discontinuation of chemotherapy due to toxicity in patients with head and neck tumors.The authors found a positive correlation between sarcopenia and early discontinuation of chemotherapy in 213 patients in a unidimensional (p=0.007; OR=0.96 [0.94–0.99]) and multidimensional analysis (p=0.021; OR=0.96 [0.92–0.99]), which resulted in lower relapse-free and overall survival rates.

Sarcopenia had a similar effect on the outcomes of radiotherapy. J.A. Langius et al. [10] measured the body weight before and during curative adjuvant radiotherapy. A weight loss of >5% of the baseline value while on radiotherapy or 7.5% during the following 12 weeks was considered significant. Overall, 1,340 patients with head and neck tumors were included in the study. The differences in 5-year overall and tumor-specific survival between the groups with different weight loss were analyzed by Cox regression adjusted for sociodemographic and tumor-specific factors. It was found that there was no weight loss in 70% of patients before radiotherapy, 16% had weight loss below 5%, 9% had lost 5–10% of the baseline body weight, and 5% had lost >10% of body weight. Five-year overall and tumor-specific survival in these groups were 71%, 59%, 47%, and 42% (p <0.001) and 86%, 86%, 81%, and 71%, respectively (p <0.001). Considering the multivariate analysis, weight loss of >10% before radiotherapy was associated with lower overall (HR=1.7; 95% CI 1.2–2.5; p=0.002) and tumor-specific survival (HR=2.1; 95% CI 1.2–3.5; p=0.007). Five-year overall and tumor-specific survival in patients with significant weight loss while on radiotherapy was 62% and 82% (p=0.01) *vs.* 70% and 89% in patients without weight loss (p=0.001). Thus, weight loss both before and during radiotherapy is an important predictor for 5-year overall and tumor-specific survival in patients with head and neck tumors [10].

These results were supported by data of a meta-analysis by M. Findlay et al., [11] which studied the prognostic effect of sarcopenia on overall survival in patients with head and neck tumors receiving radiotherapy alone or in combination with another treatment. Of 6,211 reviewed studies, 7 were included in the analysis (a total of 1,059 patients). According to the data provided, the prevalence of sarcopenia was 6.6%–64.4% before treatment and 12.4%–65.8% after treatment. Sarcopenia at baseline was associated with lower overall survival (HR=2.07; 95% CI 1.47–2.92; p <0.0001; I^2=49%). Similar results were obtained in patients with sarcopenia after treatment (HR=2.93; 95% CI 2.00–4.29; p <0.00001; I^2=0%), with confirmed moderate or low heterogeneity. The level of evidence for overall survival according to the GRADE (Grading of Recommendation Assessment, Development, and Evaluation) system in patients with sarcopenia was low before treatment and moderate after treatment. Thus, sarcopenia determined based on CT findings correlates with a lower overall survival in patients with head and neck tumors and has a clinically significant prognostic value [11].

EARLY CLINICAL DIAGNOSIS OF MALNUTRITION AND ITS MANAGEMENT

Various questionnaires can be used for the early diagnosis of malnutrition in routine clinical practice (e.g., Nutrition Risk Screening 2002 (NRS-2002)). The testing is short but makes it possible to suspect malnutrition at the health screening stage [12]. According to the recommendations of the European Society for Clinical Nutrition and Metabolism (ESPEN), as amended in 2021, early detection of malnutrition requires regular evaluation of food consumption and changes in body weight and body mass index, starting from the diagnosis stage. The screening should be repeated as necessary, depending on the stability of the clinical setting. In cases where malnutrition is detected, objective and quantitative evaluation of the diet, symptoms of dyspepsia, muscle mass, physical performance, and systemic inflammation degree are recommended in patients with abnormalities. Where there are no changes in body weight, the caloric content should be similar to that in healthy people, i.e., 25–30 kcal/kg of body weight per day, provided that the caloric requirement is not calculated on a case-by-case basis, for example, by indirect calorimetry. The recommended protein intake should be >1 g/kg/day (1.5 g/kg/day, where possible). The doses of vitamins and minerals should correspond to the recommended daily value. Excessive intake of micronutrients in the absence of a specific deficiency is impractical. In cancer patients with weight loss and insulin resistance, it is recommended to increase the dietary fat-to-carbohydrate ratio in order to improve the caloric value of the diet and decrease the glycemic load [13].

When nutritional support is prescribed, a dietary adjustment is required at the first stage to improve the alimentary support in patients who can feed themselves but are malnourished or at risk of malnutrition. Dietary consultations, management of dyspepsia, and sip feeding are also recommended [13]. In cases where malnutrition due to chemotherapy persists despite the dietary consultations and sip feeding, it is recommended to start with enteral nutrition (EN) when making a decision on nutritional support. If EN is insufficient or unfeasible, parenteral nutrition (PN) can be prescribed. In cases of long-term malnutrition, the nutritional support (oral, EN, or PN) shall be gradually intensified during several days, together with measures to prevent a refeeding syndrome. In cases of chronic malnutrition and/or uncontrolled malabsorption, EN or PN are provided at home, where possible [13].

In patients on chemotherapy, it is recommended to ensure adequate diet and physical activity to maintain the muscle mass, strength, endurance, and metabolism; moderate-intensity aerobic exercises (50–70% of the baseline peak pulse rate or aerobic capacity), three trainings per week, 10–60 min each are recommended, as well as individual weight-bearing exercises to maintain the muscle strength and muscle mass [13].

During high-dose chemotherapy and after stem cell transplantation, it is recommended to maintain physical activity and ensure adequate diet with EN and/or PN. EN is preferable, except for severe mucositis, uncontrollable vomiting, intestinal obstruction, severe malabsorption, persistent diarrhea, or graft-versus-host disease. After allogeneic transplantation, low-bacteria diet for >30 days is not recommended [13].

Adequate nutrient intake is important for both tolerance to anticancer treatment and survival of patients. For example, A. van der Werf et al. [14] investigated the effect of adequate diet on treatment outcomes in patients with advanced colorectal cancer. This randomized controlled trial focused on the effect of dietary recommendations on changes in muscle mass and treatment outcomes in patients with metastatic colorectal cancer receiving first-line chemotherapy. The study included patients on first-line chemotherapy (n=107) who were randomized into two groups: the first group was supervised by a nutrition specialist, whereas the second group did not receive dietary consultations. The recommendations of the nutrition specialist were aimed at nutrient intake according to clinical practice guidelines, using sip feeding or EN as indicated. Physical activity was also recommended. Evaluation based on CT findings was performed before treatment and after 9 weeks of CAPOX/capecitabine chemotherapy or 12 weeks of FOLFOX chemotherapy. The primary endpoint was the percentage of patients with a clinically significant reduction in skeletal muscle area by 6.0 cm^2, measured by CT. Secondary endpoints included body weight, quality of life, treatment-related toxicity, absence of disease progression, and overall and relapse-free survival. At the second stage of the examination, there were no intergroup differences in the mean change in skeletal muscle area (2.5±9.5 cm^2; p=0.891), as well as in the number of patients with a clinically significant reduction in skeletal muscle area by 6.0 cm^2 (30% in the treatment group vs. 31% in the control group; p=0.467). However, there was a significant increase in body weight (p=0.045), progression-free survival (p=0.039), and overall survival (p=0.046) in the treatment group. Thus, nutritional support in accordance with clinical practice guidelines in patients receiving first-line chemotherapy for the treatment of metastatic colorectal cancer did not affect the change in body weight. However, adequate nutrient intake contributed to an increase in the body weight and improved both progression-free survival and overall survival in the study patients.

Notably, most patients are ready to adjust their diet and use feeding formulas daily to improve the caloric and nutritional value of the diet. According to our data, 80% of patients hold this opinion. Due to the lack of information, most patients (approximately 74% of the respondents) do not use special diets, and only a small number of patients (7.5%) additionally receive conventional feeding formulas. For example, only 1 of 80 respondents in our study used

sip feeding daily [15]. Similar results were obtained by other authors [16].

Additional nutritional support while on nonsurgical treatment significantly improves its outcomes [14, 17–19]. T. Li et al. [20] have demonstrated that EN while on chemoradiotherapy for the treatment of esophageal cancer improves overall survival. This prospective, randomized, controlled, multicenter study included 158 patients with unresectable esophageal cancer who received chemoradiotherapy; 106 patients received additional EN (EN group), while the remaining patients had conventional diet (control group). Weight loss on chemoradiotherapy was 0.72±3.27 kg in the EN group and 2.10±2.89 kg in the control group (p <0.001). In the EN group, there was a less remarkable decrease in albumin and hemoglobin levels compared to the control group (2.66±5.05 vs. 4.75±4.94 g/L; p <0.001, and 10.29±15.78 vs. 18.48±14.66 g/L; p <0.001, respectively). Grade 3/4 leukopenia was 1.5 times more common in the control group compared to the EN group (33.3 vs. 20.0%; p=0.011). Moreover, the completion rate of chemoradiotherapy in the EN group was 30% higher compared to the control group (92.5 vs. 67.3%; p=0.001). The incidence of infectious complications in the EN group was 1.5 times lower compared to the control group (18.8 vs. 31.7%; p=0.021). Moreover, the treatment group also showed better tumor response to chemoradiotherapy (81.1 vs. 67.3%; p=0.004). Survival rates in 1 and 2 years were significantly higher in the EN group (89.6 and 75.4%, respectively) compared to the control group (78.5 and 57.9%, respectively). Thus, EN was efficient in terms of improvement of the nutritional status, treatment tolerance, and long-term outcomes in patients with esophageal cancer who received chemoradiotherapy [20].

The prescription of PN during anticancer drug treatment is still debatable. However, between chemotherapy cycles, additional PN is not contraindicated and helps compensate for the lack of energy and plastic substrates. In cases where the dietary calories together with additional EN are less than 60% of the estimated value, additional PN is prescribed to compensate for the missing 40%. A well-balanced three-in-one regimen including amino acids, glucose, and fat emulsion is a first choice therapy in such cases [13].

It is impossible to overestimate the importance of fatty acids, the main component of fat emulsions, in metabolism. Fatty acids are hormone precursors; they affect cell signaling pathways and can regulate gene expression by acting as ligands for nuclear receptors. They are one of the main energy sources and are responsible for the transport of fat-soluble vitamins. Moreover, they act as key determinants of the structural integrity of cell membranes. The structure of fatty acids (in particular, the chain length and degree of unsaturation) is crucial for the interaction between ligands and immune cells driven by various biological mechanisms associated with the structure and function of cell membranes. It has been shown that fatty acids affect the lymphocyte membrane fluidity in a structure-dependent manner (due to the structure of fatty acids). Medium-chain triglycerides increase the fluidity of the cell membranes of neutrophils. Within a cell membrane, microdomains of the phospholipid bilayer, the so-called lipid rafts, with a unique lipid environment facilitate cell-to-cell signaling. Numerous receptors and signal proteins are localized in these rafts. It has been shown that omega-3 polyunsaturated fatty acids can change the cell function by displacing acylated proteins from rafts [21].

Arachidonic, eicosapentaenoic, and docosahexaenoic acids are sources of biologically active lipid mediators, [22] of which the best known are eicosanoids, including prostaglandins, thromboxanes, and leukotrienes. Arachidonic acid (omega-6 fatty acids) is a known precursor of pro-inflammatory thromboxanes 2-series, pro-inflammatory leukotrienes 4-series, and prostaglandins 4-series with bronchoconstriction properties. On the contrary, eicosapentaenoic acid is used for the synthesis of anti-inflammatory thromboxanes 3-series, leukotrienes 5-series, and prostaglandins 3-series with bronchorelaxation properties. The functional significance of this process is revealed by the anti-inflammatory effect of the metabolic products of eicosapentaenoic acid. Increased levels of eicosapentaenoic acid in the diet or PN solution leads to partial replacement of arachidonic acid by eicosapentaenoic acid in cell membrane phospholipids, which reduces the synthesis of pro-inflammatory eicosanoids from arachidonic acid and increases the synthesis of anti-inflammatory eicosanoids from eicosapentaenoic acid (see Figure). Therefore, considering the biological value of fatty acids, they shall never be excluded from the diet or nutritional support.

According to the ESPEN guidelines, additional use of omega-3 fatty acids or fish oil is recommended in patients with advanced or metastatic cancer and a risk of weight

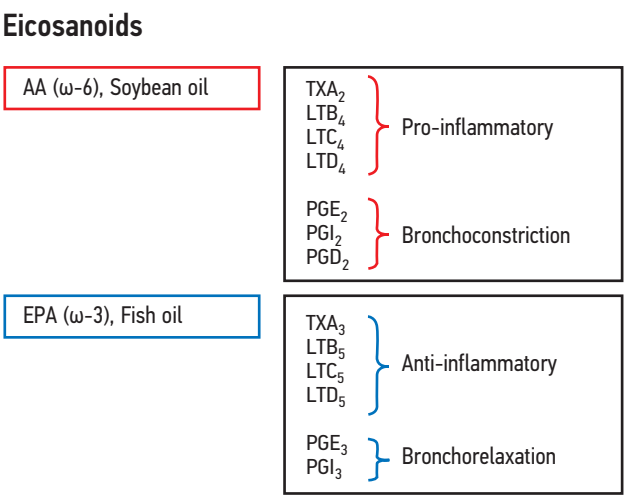

Figure. Synthesis of eicosanoids from fatty acids.
Note: AA — arachidonic acid; EPA — eicosapentaenoic acid.

loss and malnutrition to stabilize or improve their appetite, diet, and lean and overall body mass. Nutritional support with omega-3 fatty acids improves the nutritional and performance status of patients. R. Fietkau et al. [23] conducted a controlled, randomized, prospective, double-blind, multicenter study involving 111 patients with head and neck tumors and esophageal cancer on chemoradiotherapy to evaluate the effect of EN with omega-3 fatty acids on the nutritional and performance status. Some patients had a conventional diet, whereas others additionally received nutritional support with omega-3 fatty acids through a gastrostomy tube. The primary endpoint was a change in the lean body mass from baseline after chemoradiotherapy (weeks 7 and 14), measured by bioelectrical impedance analysis. Secondary endpoints were additional parameters including body composition, anthropometric measurements, handgrip test (hand dynamometry), quality of life (QLQ-C30 questionnaire of the European Organization for Research and Treatment of Cancer (EORTC)), and ECOG performance status (ECOG score, Eastern Cooperative Oncology Group). Borderline significance was achieved for the primary endpoint (an increase in the lean body mass). After chemoradiotherapy, the patients receiving nutritional support with omega-3 fatty acids lost only 0.82±0.64 kg of lean body mass compared to 2.82±0.77 kg in patients with conventional diet (p=0.055). There was an improvement in the body weight and lean body mass, which was however not significant. Subjective parameters, including the Kondrup score (p=0.0165) and SGA score (p=0.0065), improved significantly in the treatment group compared to the control group. The handgrip test score, ECOG score, and quality of life score after chemoradiotherapy were also higher in the treatment group. Thus, the authors concluded that special-purpose EN rich in omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids) significantly improves the nutritional status and has a positive effect on the performance status of patients with head and neck tumors [23].

The same trend was observed in the study by K. Sánchez-Lara et al. [24], which evaluated the effect of nutritional support with eicosapentaenoic acid on nutritional status and clinical outcomes in patients with advanced non-small cell lung cancer. All patients received paclitaxel and cisplatin/carboplatin. The body weight, body composition, diet, inflammation parameters, and quality of life were evaluated at baseline and after the first and second cycle of chemotherapy. The randomized trial included 92 patients, half of which (EN group) received eicosapentaenoic acid (2.2 g/day). During the two treatment cycles, the caloric value and protein intake with a regular diet decreased progressively (p=0.08 and p=0.04, respectively) in the control group, whereas there was an increase in these parameters in the treatment group (receiving EN with omega-3 fatty acids). Moreover, the muscle mass gain in the treatment group was 1.6±5.0 kg compared to the muscle mass loss of 2.0±6 kg in the control group (p=0.01). There was a significant decrease in the levels of C-reactive protein and tumor necrosis factor α (–1.31 mg/dL; p=0.02, and –11.1 pg/mL; p=0.05, respectively) in the treatment group, while these parameters remained unchanged in the control group (+0.19 mg/dL; p=0.305, and +0.16 pg/mL; p=0.93, respectively). The quality of life analysis showed a decrease in the severity of fatigue, anorexia, and polyneuropathy in the treatment group ($p \leqslant 0.05$). The authors concluded that EN rich in eicosapentaenoic acid improves the nutritional status (including an increase in the muscle mass), promotes self-increased protein and energy intake by patients in the regular diet, and reduces the severity of fatigue, anorexia, and polyneuropathy in patients with non-small cell lung cancer receiving chemotherapy [24].

The possibility and necessity of glutamine administration as part of drug treatment are still debatable. Glutamine is a conditionally essential amino acid. Its levels decrease significantly under catabolic stress (postoperatively or due to injury or sepsis), when glutamine uptake by the kidneys, gastrointestinal tract, and immune system increases dramatically. The cells of the intestinal mucosa are particularly dependent on glutamine, and its depletion leads to rapid necrosis. Circulating glutamine is the most abundant amino acid, accounting for over 20% of the free amino acid pool in blood and 40% in muscles. This amino acid is food-derived and accumulates in the small intestine, the endothelium of which absorbs up to 30% of this glutamine. Its blood level is relatively constant, presumably due to *de novo* synthesis and release from skeletal muscles, lungs, and adipose tissue. In rapidly dividing cells, such as lymphocytes and enterocytes of the small intestine, glutamine is actively absorbed and used for both energy production and as a source of carbon and nitrogen for synthesis. Thus, it is important for protection against infections and helps the gastrointestinal mucosa act as a barrier to bacterial translocation in the gastrointestinal tract [25].

The requirement for glutamine increases significantly with the acceleration of catabolic processes, including the development of a universal metabolic response to acute injury. For example, the requirement for glutamine after chemotherapy increases up to 20–40 g/day. However, in the case of malnutrition in mucositis, muscle tissue, which reduces in volume due to sarcopenia, becomes the main source of glutamine. Thus, additional oral or parenteral glutamine administration is necessary [25]. In 2003, N. Piccirillo et al. [26] studied the ability of glutamine to stimulate the reproduction of gastrointestinal cells in 58 patients who received high-dose chemotherapy and underwent autologous stem cell transplantation. All patients received total PN for 14 days; 12 patients additionally received glutamine at a dose of 200 g/day, 10 patients at a dose of 13.5 g/day, and 26 patients did not receive glutamine. In the glutamine groups, the recovery

rate of leukocytes was higher, mucositis was less severe, and its duration was shorter compared to patients who did not receive glutamine [26].

Subsequent studies confirmed the positive effect of glutamine in the prevention and treatment of mucositis. In 2014, the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) published clinical practice guidelines derived from evidence-based studies [27]. For example, in patients with head and neck tumors receiving chemoradiotherapy, oral glutamine for rinsing the mouth or swallowing is recommended for the prevention of mucositis. These recommendations were based on level II evidence obtained from several randomized controlled trials. According to the presented data, oral glutamine significantly reduces the severity and duration of oral mucositis, as well as the intensity of the associated pain syndrome [28–30]. The results of a meta-analysis published by T. Peng et al. [31] in 2021 support these findings. The meta-analysis evaluated the efficacy of glutamine for the prevention and treatment of moderate-to-severe chemotherapy-induced or radiation-induced oral mucositis in cancer patients. Based on the analysis of 16 randomized trials, the authors concluded that oral glutamine significantly reduces the incidence of stomatitis during chemotherapy and radiotherapy [31]. Thus, glutamine administration is justified in cancer patients for the prevention and treatment of severe complications associated with systemic treatment.

GENERAL PRINCIPLES OF NUTRITIONAL SUPPORT

Nutritional support is an important part of adjuvant therapy in oncology. It is indicated in cases of insufficient natural oral nutrition (energy intake <60% of the estimated requirement for >1–2 weeks). Physiological EN, which starts with an attempt to initiate sip feeding, is the first choice method of nutritional support. When oral feeding is impossible, nutrients are administered using feeding or gastrostomy tubes. The target value of protein intake is 1.0–1.5 g/kg of body weight per day. The daily caloric intake (dietary or PN) is 25–30 kcal/kg of body weight per day (in the absence of infectious complications, hyperthermia, etc.). The qualitative composition must comprise fats and daily doses of vitamins and micronutrients. In cancer patients with weight loss and insulin resistance, it is necessary to increase the dietary fat-to-carbohydrate ratio to improve the caloric value of the diet and decrease the glycemic load.

When enteral feeding is impossible or ineffective, additional or total PN is recommended. In this case, preliminary improvement of the water-salt balance, administration of thiamine at a dose of 200–300 mg/day, and a balanced mixture of micronutrients before and during an increase in the caloric intake is necessary for the prevention of refeeding syndrome. Monitoring of the following electrolytes is recommended, with their oral, enteral, or parenteral replacement, where necessary: potassium (daily requirement approximately 24 mmol/kg), phosphorus (daily requirement approximately 0.3–0.6 mmol/kg), and magnesium (daily requirement approximately 0.2 mmol/kg IV or 0.4 mmol/kg orally) [13].

When planning nutritional support in patients receiving nonsurgical anticancer treatment, it is necessary to reduce the proportion of omega-6 fatty acids (soybean oil) and increase the proportion of omega-3 fatty acids to 1.5–2 g/day (for example, oral fish oil in a normal diet, Supportan Drink for sip feeding, Supportan for enteral feeding, and SMOFKabiven for PN, or additional Omegaven 10% during conventional EN/PN) and omega-9 fatty acids (for example, olive oil orally, and SMOFKabiven for PN) [13]. The principles of infusion therapy are the same as in the general population.

With adequate nutritional support, glutamine is needed to reduce the severity of mucositis: oral dosage forms (Glutamine Plus 20–30 g/day × 3); if oral administration is impossible, enteral feeding with Intestamine (glutamine 30 g/500 mL) or parenteral Dipeptiven 20% (1.5–2.5 mL/kg/day, which is equivalent to 0.3–0.5 g/kg N(2)-L-alanyl-L-glutamine) [13]. In cases of mucositis or postoperatively in patients receiving neoadjuvant chemotherapy, Dipeptiven 20% is prescribed at a dose of 150–200 mL.

CONCLUSION

Therefore, timely evaluation of the nutritional status and monitoring of the risk of anorexia-cachexia syndrome are of great importance, as they allow preventing its progression and transition to the refractory stage. Timely initiation of nutritional support can be performed in parallel with anticancer drug treatment, which improves its outcomes. This innovative approach will help improve the tolerability of anticancer therapy and increase patients' survival.

ADDITIONAL INFORMATION

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