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ORIGINAL ARTICLE

Effects of enteral nutrition intervention on immune and nutritional indexes of patients with gastric malignant cancer during postoperative chemotherapy

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Abstract

Objective The aim of this study was to investigate changes in nutritional status and related indexes in patients with Nutritional Risk Score (NRS) ≥ 3 gastric cancer after nutritional support treatment.

Methods A total of 50 patients with gastric cancer were divided into two groups according to the different nutritional support treatment they received during postoperative chemotherapy: immune-enhanced enteral nutrition group (n = 25) and conventional enteral nutrition group (n = 25). Changes in patient' body mass index (BMI), hemoglobin (HB), serum total protein (TP), serum albumin (ALB), and immune indexes (CD3+, CD4+/CD8+, CD3+/CD8+) were monitored before and after chemotherapy. At the same time, the incidence and classification of gastrointestinal adverse reactions after chemotherapy were assessed.

Results Compared with the conventional enteral nutrition group, the nutritional and immune indexes in the immune-enhanced enteral nutrition group were significantly improved. After chemotherapy, the incidence of adverse reactions in the digestive tract was relatively lower and the grade was reduced.

Conclusion Immune-enhanced enteral nutrition support can significantly improve the nutritional status of patients, improve immune function, increase the susceptibility of cancer patients to chemotherapy, reduce toxicity and adverse effects, and improve the quality of life of tumor patients compared with conventional enteral nutrition support.

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Key words: gastrointestinal malignancy; enteral nutrition; immune-enhanced nutrition support therapy

Cancer is a widespread disease with extremely high mortality, which seriously threatens human health. In recent years, the incidence of cancer has increased year by year. Gastrointestinal cancer is a common malignancy seen in clinics and surgery is the standard of radical treatment. However, the quality of life of patients after surgery is greatly affected. Surgery of gastrointestinal tumors is often accompanied by short-term and long-term complications. The five-year survival rate of these patients is no more than 61% [1–4]. Nutritional risk refers to the risk of adverse effects on a patients' clinical outcomes (hospitalization time, complications of infection, etc.) due to existing or potential nutritional factors [5]. Malignant tumor patients are prone to malnutrition and have a poor prognosis due to their unique stress state and high basal metabolic rate [6–7]. Gastrointestinal tumors involve the digestive tract, affect the digestion and absorption of food, and the risk of malnutrition is higher than that of other tumors [8]. Over 60% of patients with upper gastrointestinal cancer suffer from malnutrition while around 30% of patients with hepatobiliary and colorectal tumors have malnutrition [9]. More than 15% of patients with malignant tumor experience a 10% weight loss at the time of presentation [10] and around 40% of cancer patients die from malnutrition, rather than the cancer itself [11].

Tumor cells have the capacity of malignant uptake, even if no nutrition is provided, tumor cells can still absorb nutrients from the hosttissue and subsequently show increased tissue consumption, anorexia, skeletal muscle atrophy, fatigue, anemia, and hypoalbuminemia. This can eventually lead to the occurrence of cancer anorexia-cachexia syndrome (CACS), caused by both tumor metabolism and the host immune response. CACS

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manifests as malignant consumption of the body (10% body weight loss), reduced food intake (6.276 KJ/d), and systemic inflammation (c-reactive protein > 10 mg/L) as well as other malignant depletion manifestations [12]. More than 50% of patients with advanced tumors suffer from CACS. It is noteworthy that some patients with early tumors may also have CACS [13]. Early nutrition support therapy (NST) for cancer patients can meet the daily basic metabolic needs of the body, promote the recovery of intestinal barrier function in patients with digestive tract surgery, regulate intestinal flora, promote visceral protein synthesis, improve chemotherapy tolerance, and reduce adverse reactions caused by radiotherapy and chemotherapy [14–15].

In this study, 50 patients with gastrointestinal cancer with Nutritional Risk Score (NRS) ≥ 3 were collected and divided into the immune-enhanced enteral nutrition treatment group and the conventional enteral nutrition treatment group according to the different nutritional support treatments. The effects of nutritional support therapy on the nutrition-related laboratory indexes and immune function as well as the tolerance to chemotherapy and chemotherapy-related adverse reactions of the two groups were compared and analyzed.

Materials and methods

Patient population and data collection

A total of 50 patients [31 male and 19 female, aged 18–72 years, average age 51 years, Karnofsky Performance Status (KPS) score > 60, stable condition, and clinical stage II–III] with gastric malignant tumors after surgery were included in the study. All patients were treated with the XELOX regimen. All were diagnosed as poorly differentiated adenocarcinoma of the stomach by pathology and were receiving chemotherapy. Baseline examination showed no distant metastasis. Patients with cardiopulmonary, liver, and kidney disease were excluded from the study. Changes in nutritional status indicators, including body mass index (BMI), serum total protein (TP), serum albumin (ALB), and hemoglobin (Hb) were assessed as well as immune indicators, including CD3+, CD4+/CD8+, CD3+/CD8+. The incidence and grading of gastrointestinal adverse reactions after chemotherapy were also monitored and analyzed.

Methods

According to the NRS 2002, a total score ≥ 3 is classified as nutritional risk and < 3 as non-nutritional risk [16]. Focus on patients with nutritional risks. Patients were divided into the immune-enhanced enteral nutrition therapy group (receiving whey protein powder supplemented with glutamine, arginine, omega-3 fatty acid, and total nutrition formula powder) or the conventional enteral nutrition support group (receiving full nutrition formula powder rich in protein, fat, carbohydrate, vitamins and minerals) depending on the nutritional support treatment they received. Analysis was carried out of each subject's nutritional status and clinical outcomes before and after 3 weeks of chemotherapy. Body mass index (BMI) ranged from 18.5 to 23.9 kg/m^2 in the subjects, with a BMI of 17.0–18.4 kg/m^2 indicating mild malnutrition, moderate dystrophy at 16.0–16.9 kg/m^2, and severe malnutrition at < 16.0 kg/m^2 [17]. World Health Organization (WHO) criteria for toxicity and side effects of chemotherapeutic drugs are shown in Table 1. Changes in Hb, ALB, TP, and BMI before chemotherapy were compared with those after 3 cycles of chemotherapy. Immune indexes defined as the changes of T lymphocyte subsets CD3+, CD3+/CD8+, and CD4+/CD8+ before and after chemotherapy were also collected.

Statistical analysis

Data processing was performed using SPSS 20.0 statistical software. Count data was expressed as frequency and rate, and measurement data was expressed as mean ± standard deviation ($\bar{\chi} \pm s$). Comparisons between groups was performed using independent sample *t*-tests. Differences were considered significant at *P*-values < 0.05.

Results

After analysis, there were no significant differences in the patient characteristics, including age, sex, and duration of disease, between the two groups ($P > 0.05$; Table 2), suggesting that the two groups of patients were comparable. The absolute value of BMI in the immune-enhanced group increased more than that in the conventional enteral nutrition group, but there was no significant difference between the two groups. There

Table 1 WHO chemotherapeutic side reaction degree

Gastrointestinal reaction	Grade 0	Grade I	Grade II	Grade III	Grade IV
Oral cavity	None	Erythema, pain	Small ulcers, edible	Large ulcers, liquid food only	Inability to eat
Nausea and vomiting	None	Nausea	Temporary vomiting	Vomiting, need treatment	Uncontrolled vomiting
Diarrhea	None	Transience (< 2 h)	Tolerable (> 2 h)	Intolerance, treatment	Bloody diarrhea
Astriction	None	Occasionally or intermittently	Continuous constipation	Serious constipation, affecting daily life	Life-threatening conditions (such as intestinal obstruction, toxic megacolon)

Table 2 General information comparison between two groups

	Immune-enhanced group (n = 25)	Conventional group (n = 25)	P
Age (year)	51 (35–72)	51 (18–69)	0.540
Gender			
Male	15 (51.7%)	16 (55.2%)	0.574
Female	10 (34.5%)	9 (31.0%)	
BMI	19.08 ± 2.79	19.40 ± 2.31	0.206
ALB	35.04 ± 5.99	34.89 ± 5.37	0.344
TP	56.20 ± 5.32	55.54 ± 5.40	0.679
HB	120.12 ± 17.07	121.48 ± 19.10	0.638

Notes: By one-way ANOVA, $P > 0.05$, there is no significant differences among two groups

Table 3 Comparison of nutritional status in two groups before and after chemotherapy

	Before chemotherapy	After chemotherapy	P
BMI			
I	19.08 ± 2.79	20.43 ± 2.01	0.060
E	19.40 ± 2.31	19.21 ± 1.65	0.126
ALB			
I	35.04 ± 5.99	38.64 ± 2.04	0.000
E	34.89 ± 5.37	36.91 ± 3.89	0.188
TP			
I	56.20 ± 5.32	59.33 ± 1.75	0.000
E	55.54 ± 5.40	57.66 ± 2.94	0.015
HB			
I	120.12 ± 17.07	130.04 ± 10.13	0.007
E	121.48 ± 19.10	127.44 ± 16.70	0.348

Table 4 Comparison of immune related indexes in two groups before and after chemotherapy

	Before chemotherapy	After chemotherapy	P
CD3+			
I	52.4 ± 5.1	60.9 ± 3.5	0.021
E	51.7 ± 5.1	53.5 ± 5.1	0.932
CD3+/CD8+			
I	38.04 ± 3.83	44.77 ± 5.62	0.016
E	38.16 ± 4.96	41.39 ± 5.22	0.390
CD4+/CD8+			
I	26.56 ± 2.19	29.20 ± 3.43	0.027
E	25.21 ± 2.00	29.90 ± 2.54	0.373

were significant differences in Hb, TP, and ALB ($P < 0.05$; Table 3). The percentage of CD3+, CD3+/CD8+, and CD4+/CD8+ T cells in the peripheral blood of the two groups before chemotherapy was at a low level, and there was no significant difference between the two groups before treatment. After 3 cycles of chemotherapy and enteral nutrition support, the percentage of CD3+, CD3+/CD8+, and CD4+/CD8+ cells was higher in the immune-enhanced group than that in patients receiving conventional enteral nutrition support, and the difference was statistically significant ($P < 0.05$; Table 4), indicating an improvement inimmune status.

The incidence of adverse reactions, such as anorexia, nausea, vomiting, abdominal pain, and diarrhea, after chemotherapy in the two groups was analyzed and the incidence of adverse reactions of the digestive tract in the immune-enhanced group was significantly lower than that of the conventional enteral nutrition group. The incidence of grade I–II digestive tract adverse reactions in the immune-enhanced group was 80% and grade III–IV adverse reactions were present in 20% of participants, while the incidence of grade I–II adverse reactions in the conventional enteral nutrition group was 44% and grade III–IV was 56%, which was statistically significant ($P = 0.008$).

Discussion

The metabolism of various nutrients that provide energy in cancer patients is altered compared with that in a healthy human body. The energy supply needed by a healthy individual in daily living is mainly supplied by the aerobic decomposition of sugar. In the case of hypoxia, energy can be obtained by anaerobic glycolysis. When a tumor occurs in the body, anaerobic glycolysis is predominantly utilized, even under aerobic conditions. Approximately 50% of ATP in tumor cells is obtained by glycolysis. Most patients with tumors have changes such as the reduction of glycogen stores, increased gluconeogenesis, and insulin resistance. Most tumor patients have reduced fat reserves and body weight, resulting in increased endogenous fat hydrolysis and fatty acid oxidation, increased triglyceride conversion, and ultimately an increased plasma free fatty acid concentration [18]. Meanwhile, protein catabolism is increased, anabolism decreased, and protein conversion rate is increased. This leads to an abnormal plasma amino acid spectrum, skeletal muscle atrophy, hypoalbuminemia, and a negative nitrogen balance [19–20]. Malnutrition can lead to decreased active ability, reduced responsiveness to anti-tumor therapy, increased incidence of adverse reactions to treatment, and can affect the quality of life and survival time of patients.

As one of the primary treatment methods of cancer, chemotherapy kills tumor cells by inhibiting the growth and reproduction of tumor cells, so as to reduce the risk of tumor recurrence and metastasis and to prolong the survival time of patients. Chemotherapy drugs not only kill tumor tissue, but also have a certain effect on the growth of normal tissue cells, resulting in malnutrition. Long-term malnutrition leads to problems in the absorption, distribution, metabolism, and excretion of drugs in the body, which affects the pharmacokinetics of chemotherapeutic drugs, causing an accumulation

of chemotherapeutic drugs in the body, and increasing the toxicity and side effects. The incidence of adverse reactions, such as anorexia, fatigue, nausea, vomiting, diarrhea, and constipation, is significantly increased with malnutrition, which in turn increases the risk of malnutrition in patients and forms a vicious cycle. Ultimately this leads to reduced sensitivity and tolerance of patients to chemotherapy, affecting the quality of life and increasing the mortality rate [21].

Malnutrition is a very important factor affecting the prognosis of patients with gastrointestinal malignant tumors during the management and treatment of these tumors [22]. The common cause of malnutrition in these patients may be that for the tumor to grow, it competes with the healthy tissue to bind raw material, resulting in the normal metabolism of the body being affected [23]. Digestive tract tumors also directly compress or obstruct the digestive tract, hindering the digestion and absorption of nutrients, leading to an increased incidence of malnutrition [24]. In addition, a patients' own psychological factors and anorexia factors secreted by tumors themselves act on the hypothalamus, which can also lead to loss of appetite [25–26]. Therefore, early nutritional support therapy plays an important role in improving the prognosis and the tolerance of patients to treatment.

Current nutritional support therapy includes enteral nutritional support therapy and parenteral nutritional support therapy. In recent years, early enteral nutrition has been recommended for postoperative patients with gastrointestinal tumors [27]. Studies have shown that parenteral nutrition alone can lead to intestinal flora translocation, intestinal mucosal atrophy, decreased intestinal barrier function, and increase the incidence of infection and metabolic complications. Severe cases can lead to complications such as sepsis and multiple organ dysfunction [28–30]. Early detection of patients with nutritional risks and early nutritional support can reduce the intestinal inflammatory response, stimulate hormone and digestive fluid secretion, promote intestinal mucosal barrier repair, prevent intestinal flora translocation, improve immunity, shorten hospitalization time, and improve the quality of life of patients [10, 31–33]. Therefore, early enteral nutrition intervention is essential for patients with digestive tract tumors [34].

Current studies have found that soluble immunosuppressive factors can be secreted during the development and progression of malignant tumors, resulting in low cellular immune function, characterized by a reduction in CD3+, CD4+/CD8+, and CD3+/CD8+ T cells, leading to tumor development, metastasis, and ultimately, a poor prognosis [35–37]. It has been shown that T cell subsets are considered to be the main effect or cells of cancer treatment. A variety of immune cells play an important role in preventing tumor growth and metastasis, which is the theoretical basis of the clinical application of immunotherapy for a variety of tumors, including gastrointestinal tumors [36–37]. When the number and function of T cell subsets change, the ability to eliminate tumor cells is reduced, which directly affects tumor development and prognosis [38–39]. Dynamic detection of T cell subsets in the peripheral blood of digestive tract tumors before and after treatment can indirectly reflect the immune status of the body and have a certain suggestive significance for the evaluation of disease prognosis.

The main role of nutritional support is to meet the needs of patients to recover metabolism and immune responses on the basis of daily necessary energy for the body [40]. The timely addition of immune-enhanced nutrition therapy in the clinic can play a significant role in treatment. Nutritional therapy, adding a full-nutrition formula to immune-enhanced whey protein, can fully supplement the body's energy supply, improve immunity, maintain organ function, and reduce the occurrence of complications and adverse reactions [41]. Immune nutrients such as arginine, glutamine, and omega-3 fatty acid are immunomodulators and intestinal mucosal nutrient substrates, which can remove toxic substances and promote intestinal mucosal growth [42–43].

Glutamine is an essential amino acid, which can be obtained by healthy individuals by eating a normal diet. It plays a role in promoting cell growth and protein synthesis [44]. Some researchers have also shown that glutamine plays an indispensable role in the treatment of digestive tract tumors [45], acting on the intestinal mucosa, reducing the patient's inflammatory response, and reducing the incidence of infection [46–47]. It has been reported that glutamine supplementation can reduce the incidence of vomiting and gastrointestinal discomfort after surgery by improving intestinal immune function, reducing the stimulation and damage of treatment to the gastrointestinal mucosa, and is conducive to the recovery of gastrointestinal function. Moreover, glutamine has no obvious promoting effects on the growth of tumors, nor does it increase the incidence of metastasis of tumors [48–49].

Arginine can promote the progression of tumor cells from the G0 phase to the S phase and can be combined with chemotherapy drugs that specifically act on the S phase to improve the sensitivity of chemotherapy [50]. Arginine can also promote the release of growth hormone, prolactin, and insulin as well as stimulating the differentiation and proliferation of T cells, enhancing the function of T cells, and modulating immune regulation by effecting macrophages, NK cells and monocytes [51–52].

Omega-3 fatty acids, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and flax oil, are polyunsaturated fatty acids. They are important

components of biofilms and can play a role as anti-inflammatory agents as well as regulating immunity, modulating the bodies energy, thereby enhancing the ability to eliminate bacteria and inhibit tumor growth. These acids also have a certain anti-tumor effect and can inhibit the growth of a variety of tumor cells. Domestic scholars have suggested that EPA and DHA can inhibit the growth of gastric cancer cell lines [53] in a dose and time dependent manner. EPA has a synergistic effect on epirubicin, improving the therapeutic effect and reducing the side effects of chemotherapy. Comprehensive research has found that exogenous glutamine, arginine, and omega-3 fatty acids may reduce macrophage phagocytosis and superoxide production by reducing prostaglandin E2 synthesis [54–55], thus reducing the incidence of mucositis and diarrhea as well as other adverse effects of chemotherapy and increase the uptake of chemotherapeutic agents by tumor tissues, increasing the local concentration of chemotherapeutic drugs, which can inhibit tumor and synergistic chemotherapy [41].

This study found that early enteral nutrition support can prolong progression-free survival (PFS), and immune-enhanced enteral nutrition support therapy may be a valuable method to improve a patient's long-term quality of life [56]. Research has shown that gastrointestinal symptoms and protein reduction can reflect the nutritional status of cancer patients after chemotherapy, and this plays an important role in detecting early malnutrition and can guide the evaluation of therapeutic effects after intervention [57]. In this study, by screening patients with NRS ≥ 3 after gastrointestinal tumor surgery, the effects of early immune enhanced enteral nutrition support after adding the above-mentioned immuno-nutrients on nutritional indicators (BMI, TP, ALB, and Hb), immune indicators, and digestive tract reactions after chemotherapy were compared with that of conventional enteral nutrition support. It was found that compared with conventional enteral nutrition support, early enteral nutrition support with immune enhancement significantly increased the nutrition related and immune indexes, and the difference was statistically significant. The incidence of adverse gastrointestinal reactions was also lower after chemotherapy in this group. This indicates that for patients undergoing gastrointestinal tumor surgery, early immune-enhanced enteral nutrition not only promotes the recovery of nutritional status and immunity post-surgery, but also plays a role in improving a patients' tolerance to chemotherapy and reducing the related side effects. In turn, the quality of life of patients and overall prognosis will be improved. This provides a theoretical basis for the recovery of early nutritional status and the improvement of tolerance and sensitivity of subsequent adjuvant chemotherapy in patients with gastrointestinal cancer.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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