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Original Article

Early enteral immunonutrition support protects the cellular and humoral immune functions of patients with pancreatic cancer after chemotherapy

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Abstract: Objective: This paper aimed to investigate the effects of early enteral immunonutrition support (EINS) on improving chemotherapy efficacy and immune and gastrointestinal functions in patients with pancreatic cancer. Methods: From August 2014 to April 2016, 78 patients with pancreatic cancer admitted to Weihai Central Hospital were selected and were randomly divided into a control group and an observation group (n=39 in each group). After chemotherapy, patients in the control group were given conventional nutrition support (CNS), whereas those in the observation group were given EINS. Their adverse reactions and survival rates were evaluated. The recovery time of gastrointestinal function after chemotherapy, CD4+ and CD8+ in whole blood, levels of IgG, IgA, IgM, serum gastrointestinal hormone gastrin (GAS), motilin (MTL), vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP) were detected before and one week after chemotherapy. Results: The total incidence of adverse reactions in the observation group was significantly lower than that in the control group ($P<0.05$). The 3-year survival rate in the control group was significantly lower than that in the observation group ($P<0.05$). One week after chemotherapy, anal exhaust time, defecation time, and the recovery time of bowel sounds in the observation group were significantly shorter than those in the control group ($P<0.05$). One week after chemotherapy, the levels of CD4+ and CD8+ in the two groups significantly reduced, and levels in the observation group were significantly higher than those in the control group ($P<0.05$). Conclusion: Early EINS can protect the cellular and humoral immune functions of patients with pancreatic cancer after chemotherapy and promote their gastrointestinal functional recovery, significantly better than conventional nutrition.

Keywords: Early enteral immunonutrition support, pancreatic cancer, chemotherapy, immune function, gastrointestinal function

Introduction

Pancreatic cancer is a malignant tumor disease with a high incidence and malignancy, and its mortality is extremely high in China [1, 2]. Although the disease is unapparent at its early stage, it progresses very rapidly. Therefore, most patients with the disease are in advanced stages when they are initially diagnosed, with local and distant metastases. Due to limited medical access, most patients are unable to undergo operation after the disease is confirmed, which results in poor prognosis [3, 4]. At this time, only non-surgical chemotherapy and radiotherapy can inhibit disease conditions and prolong life [5]. However, toxic side effects caused by chemotherapeutic drugs lead to great adverse reactions, of which postoperative gastrointestinal peristalsis, nutrition function and immune responses are most significantly affected [6-8].

Recent studies have shown that early enteral nutrition therapy promotes the recovery of gastrointestinal peristalsis and improves immune and intestinal mucosal barrier functions after the treatment of patients with pancreatic cancer [9, 10]. As a newly developed supporting therapy, enteral immunonutrition preparations are rich in arginine, ω-3 polyunsaturated fatty acids and dietary fiber. These substances stimulate immune cells and enhance their responses in various ways, regulate the release and production of cytokines, and improve immuno-

regulatory and anti-oxidative stress activities, as well as enhance intestinal mucosal barrier and reduce infectious complications [11, 12].

Therefore, an intervention experiment of early enteral immunonutrition was conducted in this study, to specifically discuss the effects of early enteral immunonutrition support (EINS) on chemotherapy recovery and immune and gastrointestinal functions in patients with pancreatic cancer.

Materials and methods

General information

From August 2014 to April 2016, 78 patients with pancreatic cancer admitted to Weihai Central Hospital were selected and were randomly divided into the control and observation group (n=39 in each group). After chemotherapy, patients in the control group were given conventional nutrition support (CNS), whereas those in the observation group were given EINS. There were 43 males and 35 females, with an average age of 61.7±5.7 years.

Inclusion and exclusion criteria

The inclusion criterion is as follows: patients with pancreatic cancer that was confirmed by histopathological features.

The exclusion criteria are as follows: (1) patients with a contraindication to chemotherapy for pancreatic cancer; (2) patients complicated with other solid organ lesions; (3) patients complicated with other malignant tumors and tumor metastases; (4) patients with cognitive impairment or communication disorders; (5) patients with poor compliance. All patients and their relatives were aware of the research and signed an informed consent form. This study has been approved by the Medical Ethics Committee.

Experimental reagents and materials

Duodenal nutrition tubes were purchased from Jinan Chensheng Medical Silicone Rubber Product Co., Ltd. Enteral Nutritional Emulsion was purchased from Sino-Swed Pharmaceutical Corp., Ltd. CD4+ and CD8+ monoclonal antibodies were purchased from Santa Cruz Biotechnology, Inc. Flow cytometer was purchased from Shanghai SUCE Medical Technology Development Co., Ltd. A fully automatic biochemical analyzer was purchased from Anbio (Xiamen) Products Inc. Enzyme-linked immunosorbent assay (ELISA) kits were purchased from Beijing WDWK Biotechnology Co., Ltd.

Experimental methods

Enteral nutrition intervention: Two days after chemotherapy, patients in the observation group were given normal saline (about 300 mL) through a nasal feeding tube, and they had no significant discomfort. After that, a duodenal nutrition tube was inserted through the nose, and Enteral Nutritional Emulsion, a commonly used drug for immune support therapy, was selected as a nutrition preparation. On the 1st day of treatment, the dosage was one third of the total dosage, and then it was increased according to the patients' symptoms, with an infusion rate controlled at 30 ml/h to 80 ml/h. The patients were treated for 1 course of treatment. Patients in the control group were given only CNS, and the method, rate, and dosage of the infusion were the same as those in the observation group.

Detection of immune cell content in the peripheral blood: Before and one week after chemotherapy, peripheral venous blood (3 mL) was extracted from patients in the two groups. Then, anticoagulated whole blood (50 μL) was mixed with CD4+ and CD8+ monoclonal antibodies. After that, CD4+ and CD8+ cells were detected by the flow cytometer. The number of CD4+ and CD8+ lymphocytes was statistically analyzed by software. IgG, IgA, and IgM were detected by immunoturbidimetry. The steps were carried out in accordance with the product specifications.

Detection of serum hormone contents: Before and one week after chemotherapy, peripheral venous blood (5 mL) was collected from patients in the two groups, and centrifuged to separate the serum. After that, the levels of gastrin (GAS), motilin (MTL), vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP) were detected using ELISA kits.

Outcome measures

(1) Comparison of adverse reactions.

(2) Comparison of the 3-year survival rate.

(3) Comparison of the recovery time of gastrointestinal function after chemotherapy.

Table 1. General information

Indices	Control group n=39	Observation group n=39	x^2/t	P
Gender (People)			0.052	0.820
Male	22 (56.41)	21 (53.85)		
Female	17 (43.59)	18 (46.15)		
Age (Years)	61.2±5.9	61.4±5.5	0.155	0.877
BMI	21.6±2.3	22.0±2.1	0.802	0.425
TNM staging			0.495	0.920
Stage I	13 (33.33)	15 (38.46)		
Stage II	15 (38.46)	13 (33.33)		
Stage III	7 (17.95)	8 (20.51)		
Stage IV	4 (10.26)	3 (7.69)		
Differentiation			0.232	0.890
Highly differentiated	15 (38.46)	17 (43.59)		
Moderately differentiated	17 (43.59)	16 (41.03)		
Poorly differentiated	7 (17.95)	6 (15.38)		
Lymph node metastasis			0.473	0.492
No	24 (61.54)	21 (53.85)		
Yes	15 (38.46)	18 (46.15)		
Nerve transfer			0.206	0.650
No	22 (56.41)	20 (51.28)		
Yes	17 (43.59)	19 (48.72)		

(4) Comparison of the levels of CD4+ and CD8+ in whole blood before and one week after chemotherapy.

(5) Comparison of the levels of IgG, IgA, and IgM before and one week after chemotherapy.

(6) Comparison of the levels of GAS, MTL, VIP, and CGRP before and one week after chemotherapy.

Statistical methods

In this study, SPSS 19.0 (Beijing NDTimes Technology Co., Ltd.) was used for statistical analysis. Count data were analyzed by chi-square test. Measurement data were expressed by mean ± standard deviation, and t test was used for comparison between two groups, one-way analysis of variance for comparison between multiple groups, paired t test for comparison between two groups before and after treatment. Kaplan-Meier was used to analyze survival curves. Graphpad Prism8 was used to plot figures. When $P<0.05$, the difference is statistically significant.

Results

Comparison of general information

There was no significant difference between the control and observation groups in gender, age, pathological staging and differentiation before treatment ($P>0.05$). More details are shown in **Table 1**.

Comparison of incidence of adverse reactions

The observation group had 1 case of nausea, 2 cases of vomiting, 1 case of hemorrhaging, and 1 case of intestinal obstruction; while the control group had 3 cases of nausea, 4 cases of vomiting, 3 cases of hemorrhaging, and 3 cases of intestinal obstruction. The total incidence of adverse reactions was 12.82% (5 cases) in the observation group, significantly lower than 33.33% (13 cases) in the control group ($P<0.05$). More details are shown in **Table 2** and **Figure 1**.

Comparison of 3-year survival rates

The 3-year survival rate in the control group (58.97%) was significantly lower than that in

Table 2. Comparison of postoperative adverse reactions (%)

Groups	Nausea	Vomiting	Hemorrhage	Intestinal obstruction	Total incidence of adverse reactions
Control group n=39	3 (7.69)	4 (10.26)	3 (7.69)	3 (7.69)	13 (33.33)
Observation group n=39	1 (2.56)	2 (5.13)	1 (2.56)	1 (2.56)	5 (12.82)
x^2	-	-	-	-	4.622
P	-	-	-	-	0.032

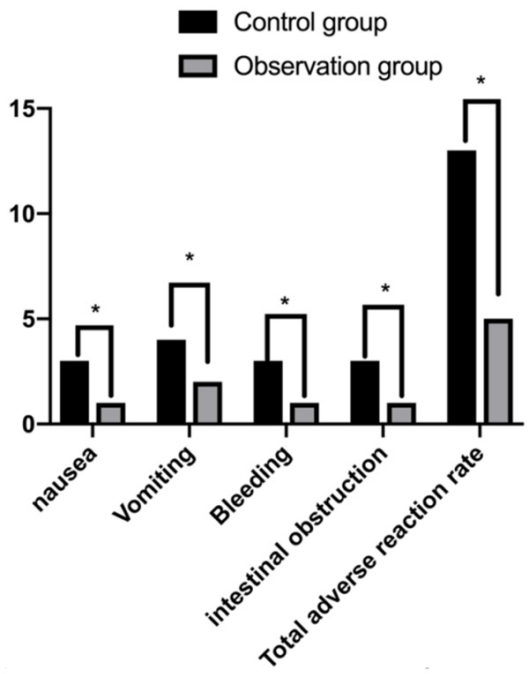

Figure 1. Comparison of postoperative adverse reactions. The observation group had 1 case of nausea, 2 cases of vomiting, 1 case of hemorrhaging, and 1 case of intestinal obstruction; while the control group had 3 cases of nausea, 4 cases of vomiting, 3 cases of hemorrhaging, and 3 cases of intestinal obstruction. The total incidence of adverse reactions was 12.82% (5 cases) in the observation group, significantly lower than 33.33% (13 cases) in the control group (P<0.05). Note: * indicates P<0.05.

the observation group (79.49%) (P<0.05). More details are shown in **Table 3** and **Figure 2**.

Comparison of recovery time of gastrointestinal function one week after chemotherapy

One week after chemotherapy, anal exhaust time, defecation time, and the recovery time of bowel sounds in the observation group were significantly shorter than those in the control group (P<0.05). More details are shown in **Table 4**.

Comparison of levels of CD4+ and CD8+ in whole blood between the time before and one week after chemotherapy

Before chemotherapy, there was no significant difference in the levels of serum CD4+ and CD8+ between the two groups (P>0.05). One week after chemotherapy, the levels in the two groups significantly reduced, and the levels in the observation group were significantly higher than those in the control group (P<0.05). More details are shown in **Table 5** and **Figure 3**.

Comparison of levels of IgG, IgA, and IgM between the time before and one week after chemotherapy

Before chemotherapy, there was no significant difference in the levels of serum IgG, IgA, and IgM between the two groups (P>0.05). One week after chemotherapy, the levels in the two groups significantly reduced, and the levels in the observation group were significantly higher than those in the control group (P<0.05). More details are shown in **Table 6**.

Comparison of contents of serum GAS, MTL, VIP, and CGRP between the time before and one week after chemotherapy

Before chemotherapy, there was no significant difference in the levels of serum GAS, MTL, VIP, and CGRP between the two groups (P>0.05). One week after chemotherapy, the levels in the two groups significantly reduced, and the levels in the observation group were significantly higher than those in the control group (P<0.05). More details are shown in **Table 7**.

Discussion

Pancreatic cancer, which is a clinically known tumor type with the highest malignancy, usually has pathological symptoms of gastrointestinal diseases [13]. A survey has shown that the inci-

Table 3. Comparison of 3-year survival rate (%)

Groups	Three-year survival rate	X^2	P
Control group n=39	23 (58.97)	3.852	0.049
Observation group n=39	31 (79.49)		

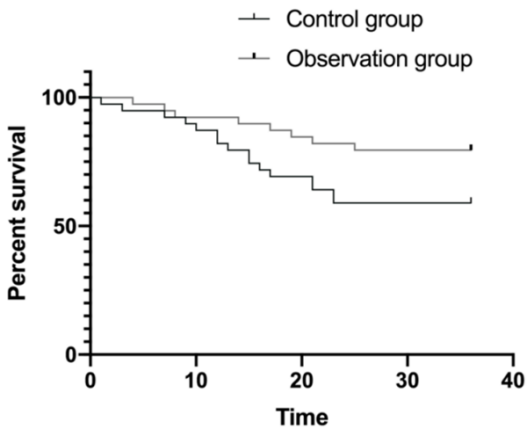

Figure 2. Comparison of 3-year survival rate. The 3-year survival rate in the control group was significantly lower than that in the observation group (P<0.05).

dence of this disease in China rapidly increased with changes in Chinese life and eating habits [14]. Pancreatic cancer is usually confirmed in its advanced stages, and the anatomical structure of the pancreatic tissue is complex, so surgical treatment easily damages peripheral organs and blood vessels, and the postoperative recurrence rate is high. Therefore, radiotherapy and chemotherapy are usually used for the treatment of pancreatic cancer [15, 16]. Shortly after chemotherapy patients experience dysfunction of eating, digestion and absorption, which has an adverse effect on their prognosis and rehabilitation. Malnutrition and disease-caused consumption of the body also weaken their immune and gastrointestinal functions [17, 18]. Therefore, early enteral nutrition support shortly after chemotherapy for pancreatic cancer has been widely recognized scholars. It provides energy substrates for the body, regulates immune cells and inflammatory cytokines through specific nutritional modes, and inhibits hypersensitivity, as well as maintains the immune and anti-inflammatory functions of the body, so as to protect the gastrointestinal tract [19, 20].

The incidence of adverse reactions and 3-year survival rate were compared between the control and observation groups. The results showed that the total incidence of adverse reactions in the observation group was significantly lower than that in the control group (P<0.05); and the 3-year survival rate in the control group (58.97%) was significantly lower than that in the observation group (79.49%) (P<0.05). These findings suggest that early EINS as an adjuvant therapy is markedly effective for patients with pancreatic cancer after chemotherapy, and it reduces the overall incidence of complications and death toll. The specific effects of early EINS on the patients' gastrointestinal function were further studied. The results showed that one week after chemotherapy, anal exhaust time, defecation time, and the recovery time of bowel sounds in the observation group were significantly shorter than those in the control group (P<0.05); the levels of serum GAS, MTL, VIP, and CGRP reduced, and the levels in the observation group were significantly higher than those in the control group (P<0.05). These findings indicate that changes in the gastrointestinal function after chemotherapy are related to the abnormal expressions of MTL, GAS, VIP, and CGRP. Chemotherapy inhibits the secretion of gastrointestinal hormones. According to the recovery time of gastrointestinal hormones and functions, early EINS is beneficial to gastrointestinal functional recovery. MTL secreted by small intestinal cells promotes the cyclic activity of small intestine, and GAS secreted by antral cells promotes the secretion of gastric acids and protease and strengthens gastrointestinal peristalsis [21, 22]. VIP secretes a large amount of water and bicarbonate by inhibiting the secretion of gastric acids and pepsin, so as to restore gastric mucosal barrier function [23]. CGRP, which is an important sensory neurotransmitter, reduces pain threshold and increases visceral sensitivity [24]. These studies have shown that early nutritional support is effective for patients with pancreatic cancer after chemotherapy, which is consistent with the results of this study. The expression of gastrointestinal hormones increases after treatment with early EINS, which indicates that early EINS can protect the gastrointestinal function of patients with pancreatic cancer after chemotherapy. According to relevant studies, severe nutritional deficiency causes reduced immune

Table 4. Comparison of recovery time of gastrointestinal function one week after chemotherapy (s)

Groups	Anal exhaust time	Defecation time	Recovery time of bowel sounds
Control group n=39	2.32±0.84	3.94±1.42	2.43±0.73
Observation group n=39	1.46±0.56	2.84±1.13	2.13±0.45
t	5.320	3.785	2.185
P	<0.001	<0.001	0.032

Table 5. Comparison of levels of CD4+ and CD8+ in whole blood between time before and one week after chemotherapy

Groups	Control group n=39	Observation group n=39	t	P
CD4+ Before chemotherapy	34.53±3.53	34.64±3.58	0.137	0.892
CD4+ One week after chemotherapy	27.43±3.35	30.34±3.45	3.779	<0.001
t	9.111	5.401		
P	<0.001	<0.001		
CD8+ Before chemotherapy	36.34±3.32	36.31±3.36	0.040	0.969
CD8+ One week after chemotherapy	29.44±3.14	31.43±3.25	2.750	0.007
t	9.430	6.519		
P	<0.001	<0.001		

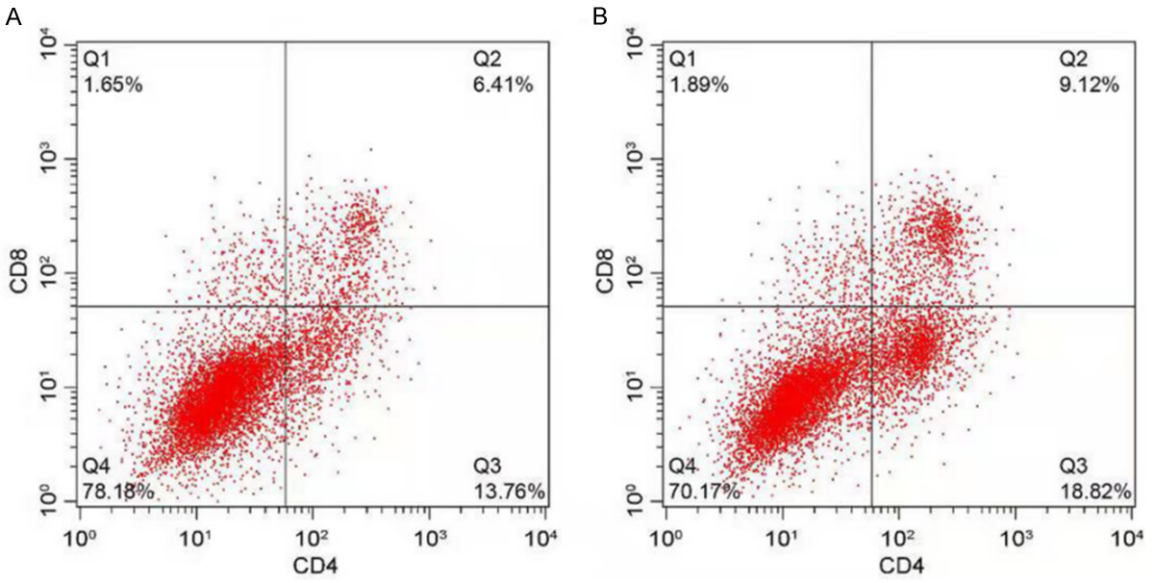

Figure 3. Flow cytometry of CD4+ and CD8+ in the two groups of patients after one week of chemotherapy in the observation group (A) and control group (B).

function, which increases the risks of infections and inflammation after surgery and chemotherapy [25, 26]. Therefore, the immune function of patients was studied. The results showed that one week after chemotherapy, the levels of CD4+, CD8+, IgG, IgA, and IgM in the two groups significantly reduced, and the levels in the observation group were significantly higher than those in the control group (P<0.05). This suggests that chemotherapy inhibits the immune responses of the body and EINS strengthens the immunity of the body. EINS affects the mitosis of T cells. CD4+T and CD8+T cells belong to T lymphocytes and they are involved in cellular immune responses, so the decreased ratio of CD4+ to CD8+ is a common manifestation of T lymphocyte dysfunction [27-29]. Malnutrition aggravates immune dysfunc-

Table 6. Comparison of levels of IgG, IgA, and IgM between time before and one week after chemotherapy (g/L)

Groups	Control group n=39	Observation group n=39	t	P
IgG before chemotherapy	12.53±3.13	12.59±3.09	0.085	0.932
IgG one week after chemotherapy	9.12±2.93	10.64±3.02	2.256	0.027
t	4.967	2.818		
P	<0.001	0.006		
IgA before chemotherapy	2.28±0.67	2.26±0.64	0.135	0.893
IgA one week after chemotherapy	1.40±0.59	1.70±0.63	2.171	0.033
t	6.156	3.894		
P	<0.001	<0.001		
IgM before chemotherapy	0.87±0.17	0.89±0.18	0.505	0.615
IgM one week after chemotherapy	0.62±0.11	0.72±0.15		
t	7.710	4.531		
P	<0.001	<0.001		

Table 7. Comparison of levels of GAS, MTL, VIP, and CGRP between time before and one week after chemotherapy

Groups	Control group n=39	Observation group n=39	t	P
GAS before chemotherapy	56.25±7.21	56.45±7.17	0.123	0.903
GAS one week after chemotherapy	33.34±5.48	44.34±6.10	8.377	<0.001
t	15.800	8.034		
P	<0.001	<0.001		
MTL before chemotherapy	157.43±27.43	157.25±27.53	0.029	0.977
MTL one week after chemotherapy	113.53±23.63	141.45±25.53	5.012	<0.001
t	7.572	2.628		
P	<0.001	0.010		
VIP before chemotherapy	69.65±18.35	69.93±18.73	0.067	0.947
VIP one week after chemotherapy	43.63±14.34	52.34±15.45	2.580	0.012
t	6.977	4.524		
P	<0.001	<0.001		
CGRP before chemotherapy	103.45±13.53	104.53±13.24	0.356	0.723
CGRP one week after chemotherapy	67.34±7.53	87.43±8.34	11.170	<0.001
t	14.560	6.825		
P	<0.001	<0.001		

tion and then inhibits the functions of lymphocytes and B cells. The reduced function of B cells and the insufficient secretion of autoantibodies reduce immunoglobulin synthesis, and IgG, IgM, and IgA in the peripheral blood [30]. These studies are consistent with our findings, which show that early EINS can regulate part of the immune responses by strengthening body nutrition and restoring the levels of immune function.

In summary, for patients with pancreatic cancer, early EINS after chemotherapy can regulate their gastrointestinal hormone secretion, enhance their sensitivity to immune responses and improve their gastrointestinal and immune functions, so it is worthy of promotion and application in clinical practice.

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Disclosure of conflict of interest

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