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ORIGINAL ARTICLE

Efficacy of irreversible electroporation ablation combined with natural killer cells in treating locally advanced pancreatic cancer

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Summary

Purpose: *To explore the efficacy and safety of irreversible electroporation (IRE) ablation combined with natural killer (NK) cells in the treatment of locally advanced pancreatic cancer (LAPC).*

Methods: *A total of 92 LAPC patients treated in our hospital from January 2016 to January 2017 were enrolled, and there were 46 cases of percutaneous IRE as IRE group, and 46 cases of IRE combined NK cell therapy as IRE-NK group. The clinical information of all the patients was collected, and the short-term efficacy, changes in the serum immunological indicators after treatment, carbohydrate antigen 19-9 (CA19-9) level, and incidence of adverse reactions were compared between the two groups of patients. Besides, the overall survival (OS) and disease-free survival (DFS) of patients were followed up and recorded.*

Results: *On 1 month after treatment, all the patients underwent efficacy assessment, which showed the overall response rate of patients in IRE-NK group was significantly superior to that in IRE group. One and 7 days after operation, the level of CA19-9 was obviously raised in the two groups, with a statistically significant difference, and it declined 30 days postoperatively. Seven and 30 days after operation IRE-NK group had a notably lower level of CA19-9 than IRE group. After treatment, all the patients exhibited considerably higher lymphocyte count and notably enhanced lymphocyte function, and all the indicators in IRE-NK group were higher than those in IRE group. Besides, the levels of serum interleukin (IL)-2, TNF-β and IFN-γ in IRE-NK group were remarkably higher than those in IRE group, whereas there were no statistically significant differences in the levels of IL-4, IL-6 and IL-10 between the two groups. All the patients were followed up for 6-29 months, and there were no statistically significant differences in the DFS and OS between IRE group and IRE-NK group.*

Conclusions: *IRE ablation combined with NK cells has excellent efficacy in treating LAPC, and they can exert a synergistic treatment effect to enhance the immune function of patients and reduce CA19-9 expression, with tolerable adverse reactions.*

Key words: *irreversible electroporation, natural killer cells, locally advanced pancreatic cancer, efficacy*

Introduction

Pancreatic cancer is a common tumor of the digestive system with extremely high malignant potential. Although surgical resection may be now the only way to radically treat pancreatic cancer, only 15-20% of patients diagnosed with pancreatic cancer can undergo surgical treatment, with the 5-year survival rate <1%, and the other patients suffer from locally advanced pancreatic cancer (LAPC) or metastatic pancreatic cancer [1-3]. As defined in the seventh edition of the American Joint Committee on Cancer Cancer Staging Manual, LAPC refers to a tumor that entraps the superior mesenteric artery, celiac trunk, and superior mesenteric or portal vein junction, without distant metastasis [4,5].

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The main target of treating LAPC is to mitigate the intractable pain of patients and prolong their overall survival (OS). Irreversible electroporation (IRE) ablation is an emerging tumor ablation technique that has been confirmed to be feasible and safe in unresectable pancreatic tumors [6-9]. Its mechanism of action is to induce tumor cell apoptosis via high-voltage direct current without damaging peripheral structures and tissues, such as the blood vessels and nerves.

Natural killer (NK) cells, as important components in the innate immune system, play a pivotal role in the defense against tumors in organisms [10,11]. With the advance in the NK cell amplification technique, *in vitro* amplification and reinfusion of NK cells have shown promising prospects in the treatment of kidney cancer, nasopharyngeal carcinoma and breast cancer [12-14]. Therefore, the present study explored the efficacy and safety of IRE ablation combined with NK cells in treating LAPC, hoping to provide a novel clinical treatment method.

Methods

General information

This study prospectively enrolled 92 LAPC patients treated in our hospital from January 2016 to January 2017, and included 52 males and 40 females, aged 57.6±10.6 years old. They were randomly assigned into IRE group (n=46) and IRE-NK group (n=46) to receive IRE treatment and IRE ablation combined with NK therapy, respectively. Inclusion criteria: 1) Patients pathologically diagnosed with pancreatic cancer; 2) those with the lesions in adjacent tissues, such as the duodenum, bile duct and superior mesenteric artery, presence or absence of local lymph node metastasis, no distant lymph node metastasis and international stage tumor node metastasis (TNM) III pancreatic cancer, as shown in imaging examinations; 3) those with the total T-cell count of 603-2990/μL, cytotoxic T-cell count of 125-1312 /μL and T helper cell count of 441-2156 /μL and prothrombin time international normalized ratio of 0.8-1.5; and 4) those with predicted survival >3 months and ECOG PS≤2 points. Exclusion criteria: 1) Patients with severe heart disease or liver or kidney dysfunction; 2) those suffering from immune disease; 3) those with T-cell lymphoma; or 4) those who underwent organ transplantation. The pre-treatment baseline information was not statistically significantly different between the two groups of patients (p>0.05) (Table 1). The present study was approved by the Ethics Committee of Shandong Binzhou Central Hospital, and all the subjects abided by the Declaration of Helsinki, were informed of the present study, and signed the informed consent.

Treatment schemes

IRE operation was performed using the NanoKnife™ HVP01 IRE system (AngioDynamics, Queensbury, NY, USA). An electrode probe was first percutaneously inserted into tumors 0-5 mm away from the margin through computed tomography (CT)-guided positioning combined with the guidance of the IU22 ultrasonic equipment system (Philips, Eindhoven, Netherlands) and/or MAXIO V2 image-guided positioning system for puncture tools (Perfint Healthcare Private Limited, Hong Kong, China), and the parameters of the IRE generator were set. Specifically, there were 7-9 discharges and 70-90 pulses in total at 10 pulses/discharge, and the pulse width was 70-90 μs, with the average electric field strength of 1,200-1,500 V/cm and ablation time of 1-2 min. The oversized tumors, which could not be ablated once according to assessment, were divided and ablated for several times. At the end of ablation, whether ablation was successful was verified by the real-time changes in resistance or current as well as intraoperative ultrasound and CT findings. After the operation, the patients continued to be sedated and breathed for 2 h with the assistance of a ventilator. Then, a gastric feeding tube was indwelled, and the patients were transferred to the ICU

Table 1. Baseline characteristics of the studied patients

Parameters	*IRE group (n=46) n (%)*	*IRE-NK group (n=46) n (%)*	*p value*
Age (years)	58.4±10.3	56.8±10.9	0.471
Gender (Male/ Female)	28/18	24/22	0.528
Tumor location			0.370
Pancreatic head and neck	34 (36.6)	29 (40.8)	
Pancreatic body and tail	12 (54.9)	17 (53.5)	
Tumor diameter (cm)	4.1±1.9	4.4±2.0	0.463
Vascular invasion			0.818
Celiac trunk	18 (55.9)	21 (50)	
Superior mesenteric artery	8 (44.1)	7 (50)	
Portal vein or superior mesenteric vein	20 (55.9)	18 (55.9)	
ECOG PS score	0.9±0.8	0.8±0.7	0.525

IRE: irreversible electroporation; NK: natural killer cell; PS: performance status

with electrocardiogram monitoring overnight. When the monitoring indicated stable physical signs, the patients were administered drugs for the inhibition of the secretion of pancreatic juice, and anti-infection, stomach-protective, dehydration and detumescence medicines and received intravenous nutrition support therapy in the general ward.

IRE-NK treatment: 7 days prior to treatment, 80 mL of peripheral blood was withdrawn from healthy volunteers and centrifuged to harvest peripheral blood mononuclear cells and plasma. On the 9th day of culture, quality inspection and counting were performed in cells to ensure the quality of NK cells, and absence of growth of bacteria, fungi or mycoplasmas, and the purified NK cells were collected. Then, the patients underwent IRE treatment for pancreatic cancer. Before the reinfusion of NK cells, infectious diseases such as hepatitis, AIDS and syphilis were detected. After being cultured for 13-15 days, NK cells were intravenously reinfused into the patients in IRE-NK group. The qualified group consisting of an inspector and a supervisor were responsible for the culture and quality control of NK cells. Each patient was reinfused with about 300 mL of cells (1×10^{10} cells in total) within 3 days. Finally, the adverse reactions to reinfusion were observed and recorded.

Observation indicators

Short-term efficacy: At 1 week before operation, and at 1 and 3 months after operation, all the patients completed the plain and enhanced CT scans of the upper and middle abdomen, and according to the Response Evaluation Criteria in Solid Tumors 1.0, the short-term efficacy was classified into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The overall response rate (ORR) of the patients was calculated. The level of serum carbohydrate antigen 19-9 (CA19-9) in patients was determined before operation and at 1, 3, 7 and 30 days after treatment, with the reference range of 0-40 U/mL.

Immunological indicators: Immune function tests were conducted 1 day before treatment and 3 days after treatment in the IRE group, and 1 day before IRE operation, and at 3 days after NK cell reinfusion in the IRE-NK group. A flow cytometer was used to analyze T-cell count, cluster of differentiation 4$^+$ (CD4$^+$) count and CD8$^+$ T lymphocyte count, NK cell count and B-cell count, and determine the levels of interleukin (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor-beta (TNF-β) and interferon gamma (IFN-γ) to evaluate the immune function of patients.

Before operation, and at 1, 3, 7 and 10 days after operation, the changes in serum amylase in patients were observed to determine whether there was pancreatic injury. The intraoperative and postoperative adverse reactions and acute complications were observed and assessed based on the Common Terminology Criteria for Adverse Events v4.0.

The survival of patients was followed up and recorded based on the following criteria: Disease-free survival (DFS) is defined as the duration from the commencement of treatment to disease recurrence or death of progressive disease (PD). The local recurrence, primary lesions or metastases in the present study were confirmed via CT scans or magnetic resonance imaging (MRI). OS refers to the duration from the beginning of treatment to the time of death of any cause.

Statistics

In the present study, SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were presented as mean ± standard deviation, and inter-group comparisons were made using pairwise t-test. Clinical data were compared with x^2 test or Fisher's exact test. Comparison between multiple groups was done using One-way ANOVA test followed by Post Hoc Test (Least Significant Difference). Short-term efficacy and incidence of adverse reactions were compared as the one-way ranked ordinal data using the Mann-Whitney U test. $P<0.05$ suggested statistically significant differences.

Results

Comparison of short-term efficacy

At 1 month after treatment, the efficacy was evaluated in all the patients, and it was found that IRE group had 7 cases of CR (15.2%), 19 cases of PR (41.3%), 16 cases of SD (34.8%) and 4 cases of PD (8.7%), with ORR of 56.5% (26/46), while the IRE-NK group exhibited 14 cases of CR (30.4%), 19 cases of PR (41.3%), 12 cases of SD (26.1%) and 1 case of PD (2.2%), with ORR of 71.7% (33/46). The

Table 2. Clinical effective rates of the two studied groups

	IRE group (n=46) n (%)	*IRE-NK group (n=46) n (%)*	*p value*
CR	7 (15.2)	14 (30.4)	
PR	19 (41.3)	19 (41.3)	
SD	16 (34.8)	12 (26.1)	
PD	4 (8.7)	1 (2.2)	
ORR	26 (56.5)	33 (71.7)	0.038

IRE: irreversible electroporation; NK: natural killer cell; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate

comparison showed that the ORR of patients in the IRE-NK group was considerably higher than that in the IRE group, with a statistically significant difference (p=0.038) (Table 2).

Surgical conditions

In the IRE treatment, the time depended on tumor size and the number of probes must be enough to cover the whole lesion. The differences in the median ablation time (37.5 min *vs.* 39.1 min), the median operation time (155.2±22.3 min *vs.* 159.6±25.4 min), and the total length of hospital stay (7.9±2.4 days *vs.* 7.4±2.5 days) between the two groups were not statistically significant (p>0.05). None of severe complications of IRE in treating pancreatic cancer, such as arrhythmia, bile leakage, hemorrhage of large blood vessels, deep vein thrombosis or pancreatic fistula, were observed in patients intraoperatively and postoperatively. Table 3 lists the adverse reactions occurring in all the patients within 30 days after operation, which were grade 1-2 and resolved after general supportive and symptomatic treatments. There was no statistically significant difference in the incidence of adverse reactions between the two groups of patients (p>0.05).

Comparisons of serum amylase and CA19-9 in the two groups before treatment and after treatment

At 1 day before operation, all the patients had a normal level of serum amylase. One day after operation, there were 5 and 3 patients with increased serum amylases and upper abdominal pain in the two groups, respectively, and after symptomatic treatment with octreotide, the level of serum amylase fell to normal 7-10 days postoperatively. The difference in serum amylase level before operation and after was not statistically significant (p>0.05).

The level of CA19-9 was obviously raised at 1 and 7 day after operation in the two groups, with a statistically significant difference (p<0.05), and it declined at 30 days postoperatively (p<0.05). The difference in the level of CA19-9 at 1 d after operation between the two groups was not statistically signifi-

Table 3. Comparison of parameters related to surgery

Parameters	*IRE group (n=46) n (%)*	*IRE-NK group (n=46) n (%)*	*p value*
Operation time (min)	155.2±22.3	159.6±25.4	0.380
In-hospital time (days)	7.9±2.4	7.4±2.5	0.330
Complications	31 (67.4)	38 (82.6)	0.148
Nausea and vomiting	4 (8.7)	5 (13.0)	
Hypoglycemia	3 (6.5)	4 (8.7)	
Fever	14 (30.4)	17 (37.0)	
Fatigue	8 (17.4)	11 (23.9)	
Gastric retention	1 (2.2)	0 (0)	
Gastric and duodenal edema	1 (2.2)	0 (0)	
Abdominal hemorrhage	0 (0)	1 (2.2)	

IRE: irreversible electroporation; NK: natural killer cells

Table 4. Comparison of serum amylase and CA19-9 level of patients in the two studied groups

	IRE group (n=46)	*IRE-NK group (n=46)*	*p value*
Serum amylase level (U/L)			
1 day Pretreatment	50.9±8.8	52.2±9.3	0.330
1 day Posttreatment	161.4±20.4	155.6±18.9	0.221
3 days Posttreatment	138.8±17.7	134.6±15.9	0.409
7 days Posttreatment	106.5±13.8	100.3±14.6	0.194
CA19-9 level (U/L)			
1 day Pretreatment	622.6±56.5	630.7±51.8	0.475
1 day Posttreatment	1533.9±78.1	1450.2±98.0	0.088
7 days Posttreatment	1386.7±61.4	1192.1±57.7	0.001
30 days Posttreatment	475.6±49.4	359.1±41.3	0.019

IRE: irreversible electroporation; NK: natural killer cells

cant (p=0.088), while at 7 and 30 days after operation, the IRE-NK group had a notably lower level of CA19-9 than the IRE group, showing statistically significant differences (p<0.001, p=0.019) (Table 4).

Comparisons of immunologic indicators before and after treatment

After treatment, the total T lymphocyte count, $CD4^+$ T lymphocyte count, $CD8^+$ T lymphocyte count, NK cell count and B-cell count were substantially raised in both IRE group and IRE-NK group (p<0.05). Before treatment, the two groups showed no statistically significant differences in all the indicators (p>0.05), whereas after treatment, the indicators in the IRE-NK group were notably higher than those in the IRE group, with statistically significant differences (p<0.05). Besides, the levels of serum IL-2, IL-4, IL-6, IL-10, TNF-β and IFN-γ were not statistically significantly different between the two groups before treatment. After treatment, the IRE-NK group had remarkably higher levels of serum IL-2, TNF-β and IFN-γ than the IRE group after treatment, with statistically significant differences (p<0.05), while no statistically significant differences in the levels of IL-4, IL-6 and IL-10 between the two groups were observed (p>0.05) (Table 5).

Follow-up results of patient survival

All the 92 patients were followed up for 6-29 months until June 2019. According to the results,

Table 5. Comparison of immunological indicators of patients in the two studied groups

	IRE group (n=46)	*IRE-NK group (n=46)*	*p value*
Total T cell (/μL)			
Pretreatment	1451±65	1460±69	0.390
Posttreatment	1667±74	1880±71	0.001
$CD4^+$ T cell (/μL)			
Pretreatment	724±33	730±29	0.299
Posttreatment	818±37	850±35	0.009
$CD8^+$ T cell (/μL)			
Pretreatment	620±9	623.7±8	0.385
Posttreatment	729±22	772±19	0.008
NK cell (/μL)			
Pretreatment	424±34	426±40	0.301
Posttreatment	565±61	636±57	0.006
B cell (/μL)			
Pretreatment	321±13	318±11	0.213
Posttreatment	477±21	550±23	0.001
IL-2 (pg/mL)			
Pretreatment	9.3±3.0	9.5±3.2	0.463
Posttreatment	17.9±4.1	21.4±4.4	0.001
IL-4 (pg/mL)			
Pretreatment	10.6±2.5	10.9±3.3	0.272
Posttreatment	11.1±4.6	11.4±3.6	0.343
IL-6 (pg/mL)			
Pretreatment	12.4±4.0	12.7±4.3	0.289
Posttreatment	15.8±4.2	16.1±5.1	0.164
IL-10 (pg/mL)			
Pretreatment	9.5±2.6	9.7±2.7	0.512
Posttreatment	10.0±3.5	10.3±2.9	0.327
TNF-β			
Pretreatment	3.6±2.3	3.8±3.3	0.355
Posttreatment	9.8±2.8	12.8±3.2	0.001
IFN-γ			
Pretreatment	3.5±3.2	3.7±3.5	0.451
Posttreatment	12.9±3.9	16.6±3.6	0.001

IRE: irreversible electroporation; NK: natural killer cells

there were no statistically significant differences in the DFS and OS between the IRE and IRE-NK group (6.1±3.9 months *vs.* 7.2±4.3 months, and 11.8±4.6 months *vs.* 12.4±5.2 months) (p=0.202, p=0.559).

Discussion

The overwhelming majority of pancreatic cancer patients basically have no indications for surgical resection, so radiotherapy, chemotherapy or other palliative treatments take its place [15]. IRE is a novel soft tissue tumor ablation technique that uses high-voltage direct current to produce multiple nanoscale micropores on cell membranes and irreversibly destruct the intracellular and extracellular balance, thus inducing cell apoptosis [16]. It is such an ablation property that gives IRE ablation treatment an advantage in treating pancreatic cancer, especially LAPC over other local ablation therapies, such as radiofrequency ablation, microwave ablation and cryoablation, resulting in no obvious damage to vital structures, including the nerves, vessels, bile duct and intestine. IRE ablation technique has been applied in the treatment of liver cancer, lung cancer and kidney cancer and achieved certain efficacy in pancreatic cancer [17-19]. Bagla et al [20] firstly reported that after 6-month follow-up, the patient with unresectable pancreatic cancer, who was treated with percutaneous IRE ablation, had no residual tumor and decreased CA19-9 level, which was confirmed by MRI. In recent years, Dunki-Jacobs et al [21] prospectively evaluated the local recurrence rate and DFS in 65 patients diagnosed with advanced pancreatic cancer and undergoing IRE. According to the results, there were 48 cases of no local recurrence, and their DFS was markedly higher than that of the patients with local recurrence (12.6 months *vs.* 5.5 months, p=0.03). Martin et al conducted a multicenter perspective evaluation in 200 patients with stage III advanced pancreatic cancer and receiving IRE treatment, of whom there were 50 cases of combined resection. Moreover, all the patients received induction chemotherapy preoperatively, 52% of whom underwent radiochemotherapy for 6 months on average before operation, and it was found that there were 6 cases of local recurrence after follow-up for 29 months, with mean overall survival of 24.9 months [22].

In addition, many studies have corroborated that the formation and progression of pancreatic cancer are affected by tumor immune response, indicating that immunotherapy has an obvious effect on the treatment of pancreatic cancer [23]. NK cells, the important component in the innate immune responses in organisms, can more easily recognize and resolve tumor cells since they do not need to go through the MHC molecular pathway. NK cell therapy can be performed using autologous cells and allogeneic cells. For example, the reinfusion of autologous NK cells enables some glioma patients to reach clinical partial remission, but exhibits no clinical efficacy in others with metastatic tumors and lymphoma [24]. According to a study report, the *in vitro* amplification and reinfusion of allogeneic NK cells combined with chemotherapy is clinically efficacious to a certain degree in treating ovarian cancer and recurrent metastatic breast cancer [25].

Pancreatic cancer metastasizes under the premise that pancreatic cancer cells enter into peripheral blood vessels via the mediation of micrometastasis, and subsequently, the tumor cells can reach other tissues or organs in the body. Therefore, NK cells were reinfused after IRE treatment in the present study. According to the findings, IRE ablation combined with NK cells played a synergistic role in the treatment of pancreatic cancer patients, improved the anti-tumor effect, notably enhanced the immune function of patients and lowered the CA19-9 level. It is worth noting that after IRE ablation, the level of CA19-9 rose significantly to 2-fold than before treatment, which may be caused by the release of CA19-9 into the blood after tumor ablation and necrosis. Its level declined from the 1st month after operation, with the absorption of necrotic tumor tissues and tumor shrinkage. Additionally, the incidence of adverse reactions between the two groups of patients was not statistically significant (p>0.05), and the patients in the IRE-NK group had superior tolerance.

The present study has some limitations, such as not large enough sample size and less comprehensive follow-up contents. Therefore, large-sample prospective multi-center randomized controlled trials remain to be designed more strictly and scientifically in the future to corroborate the results of this preliminary study, thereby providing references for the options of treatment schemes for LAPC patients.

Conclusions

IRE ablation combined with NK cells has excellent efficacy in treating LAPC. IRE ablation combined with NK cells can exert a synergistic effect to enhance the immune function of patients and reduce CA19-9 expression, with tolerable adverse reactions.

Conflict of interests

The authors declare no conflict of interests.

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