Clinical Case Report

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Percutaneous intratumoral injection of gemcitabine plus cisplatin mixed with fibrin glue for advanced pancreatic carcinoma

Case Report

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Abstract

Rationale: The aim of this study was to determine the effectiveness of intratumoral injection of chemotherapeutics in improving the quality of life and survival of patients with pancreatic carcinoma.

Patient concerns: We present a case series of 5 patients with unresectable pancreatic adenocarcinoma.

Diagnoses: Patients diagnosed with unresectable poorly differentiated pancreatic ductal adenocarcinoma by intraoperative frozen biopsyor percutaneous biopsy.

Interventions: Five patients with unresectable pancreatic adenocarcinoma received a computed tomography-guided percutaneous intratumoral injection of gemcitabine plus cisplatin mixed with fibrin glue.

Outcomes: Mean overall survival was 16.2±3.7 months. Local control rates were 100% and 80% at postoperative 3 and 6 months, respectively. Mean Visual Analogue Scale pain score decreased from 7.2±.84 preoperatively to 2±1.22 at postoperative 4 weeks. There were no complications associated with the procedure.

Lessons: Percutaneous intratumoral injection of gemcitabine plus cisplatin mixed with fibrin glue for advanced pancreatic may be safe and effective.

Abbreviations: CA = carbohydrate antigen, CEA = carcinoembryonic antigen, CT = computed tomography, EUS = endoscopic ultrasound, MRI = magnetic resonance imaging, RECIST = response evaluation criteria in solid tumors, TACE = transartery chemoemboliztion.

Keywords: cisplatin, fibrin glue, gemcitabine, intratumoral injection, pancreatic cancer

1. Introduction

Pancreatic cancer is the second most common gastrointestinal cancer and the fourth leading cause of cancer deaths in the United States (1999 statistic) [1]; however, only 10% to 20% of patients present with resectable disease.[2] Approximately 30% to 40% of patients are diagnosed with locally advanced pancreatic cancer, and 50% have distant metastases.[3] For these patients, palliative management that provides symptomatic relief of intestinal obstruction, pain, and jaundice is essential to improve quality of life.[4] Intratumoral injections under computed tomography (CT) or ultrasound guidance represent innovative strategies for delivering chemotherapeutic agents, that avoid the side effects

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BY, J-PH, M-LY contributed equally to this study.

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The study was approved by the ethics committee of West China Hospital. Written, informed consent to participate in the study was obtained from all participants.

Written informed consent for publication of this case series was obtained from all patients. A copy of the written consent is available for review by the Editor of this journal.

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associated with systemic chemotherapy.[5] According to the 2014 National Comprehensive Cancer Network guideline, gemcitabine plus cisplatin is recommended as a first-line treatment for nonresectable pancreatic cancer.[6] Fibrin glue is an adherent hemostat that can slow the release of high concentrations of anticancer drugs, including gemcitabine and cisplatin, to cancer cells.[7,8] In a nude mouse model, gemcitabine plus cisplatin mixed with fibrin glue obviously reduced the volume of orthotopically implanted pancreatic neoplasms.[8] Here, we present a case series of patients with pancreatic cancer who received a CT-guided percutaneous intratumoral injection of gemcitabine plus cisplatin mixed with fibrin glue. Outcomes included prolonged overall survival, good local control, and pain relief.

2. Materials and methods

2.1. Patient description and diagnosis

Five patients diagnosed with unresectable poorly differentiated pancreatic ductal adenocarcinoma by intraoperative frozen biopsy (Patient 1) or percutaneous biopsy (Patients 2–5) were included in this study. All patients had refused chemotherapy but presented at our hospital for pain and jaundice relief (Table 1). The study was approved by the West China Hospital ethics committee, and all patients provided written informed consent. All patients underwent preoperative enhanced CT/magnetic resonance imaging (MRI), to evaluate the best puncture routine (Fig. 1A and B).

2.2. Solution preparation

COL solution: 30-mg cisplatin (Jiangsu Hansoh Pharmaceutical Co Ltd, China) was dissolved in 2-mL iohexol (Omnipaque; GE Healthcare, Co, Ltd, China) and 2-mL 2% lidocaine. Solution A consists of fibrinogen and factor XIII dissolved in aprotinin solution (1.5 mL). Solution B consists of thrombin mixed with calcium chloride solution (1.5 mL). Solution C consists of gemcitabine (600 mg, Jiangsu Hansoh Pharmaceutical Co) dissolved in Solution B.

2.3. Procedure

Patients were placed in the prone or supine position and administered a local anesthetic (2% lidocaine, Shanghai Zhpharma Co, Ltd, China). The radiologist carefully inserted an 8-cm, 25-gauge needle into the tumor. Step I: COL solution (1 –2 mL) was injected into the tumor; the distribution of the COL solution in the tumor was carefully evaluated. Step II: 0.5 to 1 mL of Solution A was injected into the tumor followed by 1 mL of solution C. Subsequently, step I and step II were repeated (Fig. 1C and D). All procedures were guided by CT. Four patients (patients 2–5) with liver metastasis underwent conventional transartery chemoemboliztion (TACE) with 1000 mg/m^2 gemcitabine plus 100 mg/m^2 cisplatin mixed with lipiodol, 2 to 7 days after the previous procedures.

2.4. Statistical analyses

Data were analyzed using SPSS 19.0 (SPSS Inc, Chicago, IL). Continuous variables are summarized as means and standard deviations. The differences in numerical variables before and after treatment were evaluated using the paired t test. Ranked data, including the Visual Analogue Scale pain score (VAS), were compared using the rank-sum test. All statistical tests were 2-sided, and $P < .05$ was considered statistically significant.

3. Results

This study included 5 patients that attended the Department of Abdominal Oncology, West China Hospital between April 2015 and January 2017. Baseline demographic and clinical characteristics of the patients are detailed in Table 1. Patient mean age was 60.2 ± 6.99 years, 2 patients were male, 3 patients were female, and 4 patients were suffering from liver metastases. Patient 2 had undergone gastroduodenectomy and cholecystotomy 3 months before the study.

Patient perioperative data are shown in Table 2. Among all patients, the mean number of intratumoral injections and TACE procedures were 1.5 ± 0.89 and 1.2 ± 0.84, respectively. Overall mean survival was16.2 ± 3.7 months. Local control rates were 100% and 80% at postoperative 3 and 6 months, respectively (Fig. 1Eand F). Mean VAS pain score decreased from 7.2 ± 0.84 preoperatively to 2.0 ± 1.22 by postoperative week 4. Patient 1 experienced obvious relief from jaundice on postoperative day 2. Based on CT or MRI evaluation, and according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), 3

Table 1

Characteristics of included patients.

No.	Sex	Age	Surgery	Location	Symptoms	Dilatation	TNM stages	ECOG performance status	Liver metastasis size, cm	Pancreas cancer size, cm	Invasion	Jaundice
1	Female	65	No	Pancreatic head	Abdominal distension, abdominal pain, jaundice	Choledochectasia	T3N1M0	2	No	3.98 × 2.96	Portal vein, superior mesenteric vein	Yes
2	Female	61	Yes	Pancreatic head	Abdominal pain	Main pancreatic duct dilatation	T2N0M1	2	Lobus dexter (1.9 × 1.2)	2.5 × 2.4	No	No
3	Male	63	No	Pancreatic body/tail	Abdominal pain	Main pancreatic duct dilatation	T3N0M1	1	Multiple nodules in lobus sinister (3 × 2.5)	7.7 × 5.8	Portal vein, superior mesenteric vein, splenic vein, left diaphragm angle	No
4	Male	48	No	Pancreatic body	Low back pain; abdominal pain	Main pancreatic duct dilatation	T3N0M1	2	Multiple nodules in both lobules (2.3 × 2.07)	5.7 × 5	Splenic vein, superior mesenteric vein	No
5	Female	64	No	Pancreatic head	Abdominal pain	Choledochectasia, main pancreatic duct dilatation	T3N0M1	2	Multiple nodules in both lobules s (3.1 × 2.09)	3.8 × 4.1	Inferior vena cava	No

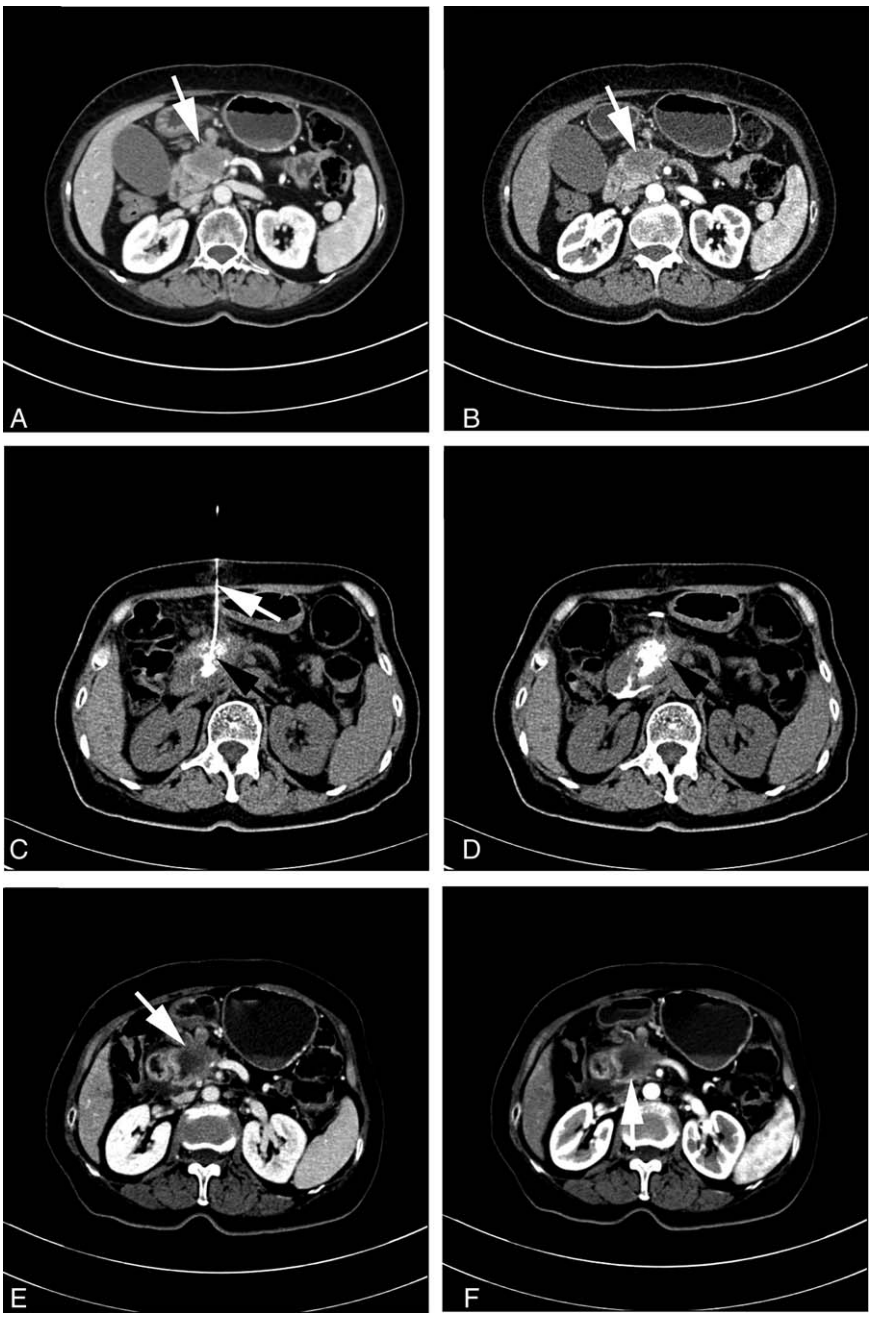

Figure 1. Preoperative and postoperative computed tomography (CT) scans (A, B) Axial CT showing carcinoma in the head of the pancreas (white arrow); (C, D) CT images during percutaneous intratumoral injection with gemcitabine plus cisplatin mixed with fibrin glue (black arrow); (E, F) 2 days after the treatment, CT showing tumor necrosis (white arrow).

patients showed complete response, 1 patient showed partial response, and 1 patient had stable disease at postoperative 1 month. There were no significant differences in pre- and postoperative carbohydrate antigen 19–9, carbohydrate antigen, or carcinoembryonic antigen levels.

No adverse events, such as emesis or serious pain, were observed during the procedures. There were no procedures associated patient side-effects such as fever, gastrointestinal bleeding, or acute pancreatitis. Patients 1, 2, and 4 did not experience any postoperative adverse events. Postoperatively, patient 3 experienced grade 2 emesis (3 episodes in 24 hours), which spontaneously resolved within 24 hours. Patient 5 also experienced grade 2 emesis (4 episodes in 24 h), which spontaneously resolved in 48 hours. Patient 3 experienced ascites 6 months postoperatively, owing to disease progression.

4. Discussion

For patients with unresectable pancreatic cancer, current chemotherapies have negligible survival benefits as pancreatic carcinomas have concentration- and time-dependent sensitivity to locoregional chemotherapy.[9,10] Therefore, the development of effective and minimally invasive strategies that selectively deliver antitumor drugs to the tumor site, release high

Table 2

Perioperative data.

Variables		Case						
		1	2	3	4	5		
Procedure		PGPI	PGPI + TACE	PGPI + TACE	PGPI + TACE	PGPI + TACE	Mean ± SD	*P*
CA19–9, U/mL	Preop	>1000	14.67	7.32	24	8.81	210.96 ± 441.14	
	Postop 1 wk	>1000	17.94	7.21	11.86	8.85	209.17 ± 442.11	.539
	Postop 1 mo	785.33	25.27	7.4	10.21	8.93	167.43 ± 345.5	.368
	Postop 3 mo	21.65	25.53	7.44	17.62	8.66	16.18 ± 7.94	.376
CEA, ng/mL	Preop	6.1	2.14	50.29	7.99	2.54	13.81 ± 20.54	
	Postop 1 wk	3.28	2.41	32.1	2.85	3.24	8.78 ± 13.04	.219
	Postop 1 mo	3.35	3.4	111.3	2.62	2.93	24.72 ± 48.4	.435
	Postop 3 mo	3.32	3.52	111.3	5.12	23.16	29.28 ± 46.6	.273
CA125, U/mL	Preop	28.92	93	807.8	424.67	19.95	274.87 ± 340.96	
	Postop 1 wk	38.76	31.77	435.31	56.23	24.51	117.32 ± 178.15	.147
	Postop 1 mo	32.55	29.97	544.38	45.83	16.88	133.92 ± 229.69	.14
	Postop 3 mo	17.64	18.1	765.92	21.24	17.12	168 ± 334.25	.228
TBIL, μmol/L	Preop	106.6	9.8	12	17	6.7	30.42 ± 42.75	
	Postop 1 wk	314.9	7	14.9	14.7	14.4	73.18 ± 135.17	0.36
	Postop 1 mo	256.8	8.3	9.9	15.2	11.1	60.26 ± 109.9	.378
	Postop 3 mo	23.7	10.8	9.9	14.3	9	13.54 ± 6.02	.365
DBIL, μmol/L	Preop	96.5	4.8	3.9	4.8	2.1	22.42 ± 41.42	
	Postop 1 wk	268.5	3.3	5.7	7.2	4.6	57.86 ± 117.76	.358
	Postop 1 mo	236.3	3.5	3.6	6.5	3.4	50.66 ± 103.78	.369
	Postop 3 mo	21.5	5.6	3.6	4	2.6	7.46 ± 7.92	.375
IBIL, μmol/L	Preop	10.1	5	9.1	12.2	4.6	8.2 ± 3.3	
	Postop 1 wk	46.4	3.7	9.2	12.4	8.7	16.08 ± 17.23	.333
	Postop 1 mo	20.5	4.4	6.3	11.6	7.7	10.1 ± 6.39	.46
	Postop 3 mo	2.2	5.2	6.3	10.3	6.4	6.08 ± 2.91	.269
ALT, IU/L	Preop	413	50	19	12.2	13	101.44 ± 174.86	
	Postop 1 wk	283	26	20	11.9	36	75.38 ± 116.4	.39
	Postop 1 mo	177	27	35	10.5	35	56.9 ± 67.88	.41
	Postop 3 mo	54	54	35	17	27	37.4 ± 16.44	.434
AST, IU/L	Preop	285	61	22	19	32	83.8 ± 113.69	
	Postop 1 wk	333	31	23	18	37	88.4 ± 136.93	.732
	Postop 1 mo	133	23	37	20	42	51 ± 46.76	.353
	Postop 3 mo	62	65	37	19	41	44.8 ± 19	.445
ALB, g/L	Preop	38	30.1	51.8	44.3	29	38.64 ± 9.64	
	Postop 1 wk	38.6	41.5	34.4	43.6	33.5	38.32 ± 4.38	.95
	Postop 1 mo	35.1	42.4	36.8	43.8	39.1	39.44 ± 3.66	.879
	Postop 3 mo	28.3	44.6	34.9	43.5	43.1	38.88 ± 7.06	.971
Number of PGPI (TACE) sessions		1 (1)	1 (0)	2 (1)	2 (2)	1 (2)	1.4 ± 0.55 (1.2 ± 0.84)	
Follow-up, mo		17	19	11	14	20	16.2 ± 3.7	
Adverse events				Emesis		Emesis		
VAS	Preop	7	6	8	8	7	7.2 ± .84	<.001
	Postop	2	1	4	2	1	2 ± 1.22	
Pancreatic tumor response		CR	PR	SD	CR	CR		
Outcome		Alive	Alive	Death	Alive	Alive		

ALB = serum albumin, ALT = alanine transaminase, AST = aspartate transaminase, CA 125 = carbohydrate antigen 125, CA 19–9 = carbohydrate antigen 19–9, CEA = carcinoembryonic antigen, CR = complete response, DBIL = direct bilirubin, IBIL = indirect bilirubin, PGPI = percutaneous gemcitabine pus cisplatin mixed with fibrin glue injection, postop = postoperative, PR = partial response, preop = preoperative, SD = stable disease, TACE = transarterial chemoembolization, TBIL = total bilirubin, VAS = visual analogue scale.

concentrations of antitumor drugs for extended periods of time, and minimize distribution of antitumor drugs throughout the body remains an unmet need.[9]

In the current case series of patients treated with CT-guided percutaneous intratumoral injection of gemcitabine plus cisplatin mixed with fibrin glue, mean overall survival was 16.2 ± 3.7 months, and the patients reported substantial pain relief. A search of the PubMed database from January 1990 to December 2016, revealed that case reports or case series focused on intratumoral drug administration in pancreatic cancer are scarce (Table S1, http://links.lww.com/MD/B858). However, the findings from the current case series are in accordance with previously published studies. Chang et al[11] reported a median survival of 13.2 months in a Phase I clinical trial of 8 pancreatic cancer patients treated with a single injection of cytoimplant immunotherapy by endoscopic ultrasound (EUS)-guided fine-needle injection. Hanna et al[12] reported that 7 pancreatic cancer patients survived ≥6 months and 2 patients survived ≥12 months, following 2 weeks of twice weekly CT- or EUS-guided BC-819 intratumoral injections. Schad et al[13] investigated intratumoral mistletoe (Viscum album L) therapy in

patients with unresectable pancreatic carcinoma. The median survival of patients at stages III and IV were 11.8 months and 8.3 months, respectively. Hecht et al [14] reported a phase I/II trial of EUS-guided ONYX-015 intratumoral injection, in which 21 patients with locally advanced adenocarcinoma of the pancreas or metastatic disease achieved a median survival of 7.5 months. In a Phase I trial, Endo et al found that preoperative EUS-guided fine-needle injection of immature dendritic cells with OK-432 in pancreatic cancer patients (n = 9) undergoing resection resulted in a median survival of 1.5 years, compared to 1.4 years in patients operated without immature dendritic cell injection (n = 15).[15] Jin et al[16] reported a case study on pancreatic cancer, where EUS-guided celiac ganglion radiofrequency ablation reduced the VAS pain score from 8 to 2 in a 57-year-old male patient.

In this case series, the procedures administered to the patients were associated with some complications; however, all resolved spontaneously. There were no serious complications, such as acute pancreatitis or death, emphasizing the safety of this approach. The complication rate in the current case series was similar to that observed in previous studies.[15,12] Hanna et al[12] reported asymptomatic elevation of lipase as an adverse event in their trial of twice weekly CT- or EUS-guided BC-819 intratumoral injections in pancreatic cancer patients. Endo et al[15] noted 1 transient grade 3 fever among their pancreatic cancer patients, following preoperative EUS-guided fine-needle injection of immature dendritic cells with OK-432.

Fibrin glue is a water-insoluble gel matrix that is formed when fibrinogen is activated by thrombin in the presence of Ca^{2+} and factor XIII.[17] Evidence suggests that fibrin glue is an effective therapeutic tool for slowing the release of drugs, including antibiotics, growth factors, and chemotherapeutic agents, at a local site.[8,18,19] Sugitachi et al[7] reported that release of adriamycin or cisplatin from a fibrin clot was sustained over 15 days in cancer bearing rats. Fbrin clot-adriamycin/cisplatin-treated rats survived >200 days and the tumors disappeared. In comparison, rats treated with adriamycin/cisplatin injected intraperitoneally died within 20 days. In a nude mouse model, Ogura et al[8] demonstrated that the concentration of gemcitabine in the pancreas in mice treated with a mixture of gemcitabine and fibrin glue, that adhered to the pancreatic tail, was 10-fold higher than mice treated with an intraperitoneal injection. Furthermore, the growth of orthotopically implanted pancreatic neoplasms was decreased by 62% compared to control mice.[8] Median survival time of mice in the control, fibrin glue group, and gemcitabine and fibrin glue group was 44, 48, and 57 days, respectively.[8]

5. Conclusion

This study was limited by its small sample size; however, the findings suggest that gemcitabine plus cisplatin mixed with fibrin glue administered by CT-guided percutaneous intratumoral injection has potential as a safe and effective approach to decrease pain and improve survival in patients with advanced unresectable pancreatic cancer.

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References

[1] Al Efishat M, Wolfgang CL, Weiss MJ. Stage III pancreatic cancer and the role of irreversible electroporation. BMJ 2015;350:h521.
[2] Miyanishi K, Ishiwatari H, Hayashi T, et al. A Phase I trial of arterial infusion chemotherapy with gemcitabine and 5-fluorouracil for unresectable advanced pancreatic cancer after vascular supply distribution via superselective embolization. Jpn J Clin Oncol 2008;38: 268–74.
[3] Zou YP, Li WM, Zheng F, et al. Intraoperative radiofrequency ablation combined with 125 iodine seed implantation for unresectable pancreatic cancer. World J Gastroenterol 2010;16:5104–10.
[4] Sharma C, Eltawil KM, Renfrew PD, et al. Advances in diagnosis, treatment and palliation of pancreatic carcinoma: 1990-2010. World J Gastroenterol 2011;17:867–97.
[5] Micames CG, Gress FG. Local EUS-guided injection of chemotherapeutic agents as adjuvant to systemic treatment: the first steps are made. Gastrointest Endosc 2007;65:454–6.
[6] Tempero MA, Malafa MP, Behrman SW, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines. J Natl Compr Canc Netw 2014;12:1083–93.
[7] Sugitachi A, Shindo T, Matsuda Y, et al. A newly designed anticancer tumor immunity drug delivery system. ASAIO Trans 1991;37:M177–8.
[8] Ogura Y, Mizumoto K, Tanaka M, et al. Strategy for prevention of local recurrence of pancreatic cancer after pancreatectomy: antitumor effect of gemcitabine mixed with fibrin glue in an orthotopic nude mouse model. Surgery 2006;140:66–71.
[9] Ikeda O, Kusunoki S, Kudoh K, et al. Evaluation of the efficacy of combined continuous arterial infusion and systemic chemotherapy for the treatment of advanced pancreatic carcinoma. Cardiovasc Intervent Radiol 2006;29:362–70.
[10] Huang ZM, Pan CC, Wu PH, et al. Efficacy of minimally invasive therapies on unresectable pancreatic cancer. Chin J Cancer 2013;32:334–41.
[11] Chang KJ, Nguyen PT, Thompson JA, et al. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. Cancer 2000;88:1325–35.
[12] Hanna N, Ohana P, Konikoff FM, et al. Phase 1/2a, dose-escalation, safety, pharmacokinetic and preliminary efficacy study of intratumoral administration of BC-819 in patients with unresectable pancreatic cancer. Cancer Gene Ther 2012;19:374–81.
[13] Schad F, Atxner J, Buchwald D, et al. Intratumoral mistletoe (Viscum album L) therapy in patients with unresectable pancreas carcinoma: a retrospective analysis. Integr Cancer Ther 2014;13:332–40.
[14] Hecht JR, Bedford R, Abbruzzese JL, et al. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. Clin Cancer Res 2003;9:555–61.
[15] Endo H, Saito T, Kenjo A, et al. Phase I trial of preoperative intratumoral injection of immature dendritic cells and OK-432 for resectable pancreatic cancer patients. J Hepatobiliary Pancreat Sci 2012;19:465–75.
[16] Jin ZD, Wang L, Li Z. Endoscopic ultrasound-guided celiac ganglion radiofrequency ablation for pain control in pancreatic carcinoma. Dig Endosc 2015;27:163–4.
[17] Yu BG, Kwon IC, Yong HK, et al. Development of a local antibiotic delivery system using fibrin glue. J Control Release 1996;39:65–70.
[18] Ishihama H, Nagai S, Umezu H, et al. The usefulness of fibrin glue spraying combined with CDDP for lung cancer. Gan To Kagaku Ryoho 1997;24:981–5.
[19] Spotnitz WD. Commercial fibrin sealants in surgical care. Am J Surg 2001;182:8S–14S.