RESEARCH COMMUNICATION

Continuous Transarterial Infusion Chemotherapy with Gemcitabine and 5-Fluorouracil for Advanced Pancreatic Carcinoma

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Abstract

Purpose: Pancreatic carcinoma is one of the most malignant tumors of the alimentary system, with relatively high incidence rates. The purpose of this study was to assess the efficacy and safety of two regimens for advanced pancreatic carcinoma: continuous transarterial infusion versus systemic venous chemotherapy with gemcitabine and 5-fluorouracil. Methods: Of the 48 patients with advanced pancreatic carcinoma receiving chemotherapy with gemcitabine and 5-fluorouracil, 24 received the selective transarterial infusion, and 24 the systemic chemotherapy. For the continuous transarterial infusion group (experimental group), all patients received gemcitabine 1000 mg/m^2,given by 30-minute transarterial infusion, on day 1 of a 4-week cycle for 2 cycles, and a dose of 600 mg/m^2 5-fluorouracil was infused on days 1~5 of a 4-week cycle for 2 cycles. For the systemic venous group (control group), gemcitabine and 5-fluorouracil were infused through a peripheral vein, a dose of 1000 mg/m^2 gemcitabine being administrated over 30 min on days 1 and 8 of a 4-week cycle for 2 cycles, and a dose of 600 mg/m^2 5-fluorouracil was infused on days 1~5 of a 4-week cycle for 2 cycles. The effectiveness and safety were evaluated after 2 cyclesaccording to WHO criteria. Results:The objective effective rate in transarterial group was 33.3% versus 25% in the systemic group, the difference not being significant (P=0.626). Clinical benefit rates(CBR) in the transarterial and systemic groups were 83.3% and 58.3%, respectively (P=0.014). The means and medians for survival time in transarterial group were higher than those of the systemic group (P < 0.005). at the same time, the adverse effects did not significantly differ between the two groups (P > 0.05). Conclusion: Continuous transarterial infusion chemotherapy with gemcitabine and 5-fluorouracil could improve clinical benefit rate and survival time of patients with advanced pancreatic carcinoma, compared with systemic venous chemotherapy. Since adverse effects were limited in the transarterial group, the regimen of continuous transarterial infusion chemotherapy can be used more extensively in clinical practice. A CT and MRI conventional sequence can be used for efficacy evaluation after chemotherapy in pancreatic carcinoma.

Keywords: Advanced pancreatic carcinoma - clinical benefit rates - survival rate - radiology - interventional - gemcitabine

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Introduction

Pancreatic carcinoma is one of the most malignant tumors of alimentary system,and its incidence rate had a tendency to rise in the past decades (Hua et al., 2009; Tuli et al., 2012; Zhou et al., 2012). Early diagnosis of pancreatic carcinoma is still difficult, the majority patients with pancreatic carcinoma are in an advanced stage at the time of diagnosis (Ikeda et al.,2009; Klauss et al., 2012; Zhou et al., 2012). Chemotherapy is one of the most important therapeutic methods in the treatment of pancreatic carcinoma. However at present, the commonly used chemotherapy still cannot produce a satisfactory clinical curative affect,and the adverse reactions are serious.Under such conditions, it is of great value to develop new alleviative treatment regimens, especially those that can improve the patients,quality of life (Moore et al., 2003; Wilkowski et al., 2006; Ouaissi et al., 2008; Hwang et al., 2009).

In this study, 48 patients with advanced pancreatic carcinoma were treated, 24 receiving continuous transarterial infusion of gemcitabine and 5-fluorouracil, and 24 given systemic venous chemotherapy. Clinical effectiveness and safety were evaluated for comparison.

Materials and Methods

Patients

During the period from January 2007 to December 2010, a total of 48 patients (35 males and 13 females) of advanced pancreatic carcinoma were treated at our hospital. All the 48 patients were pathologically diagnosed

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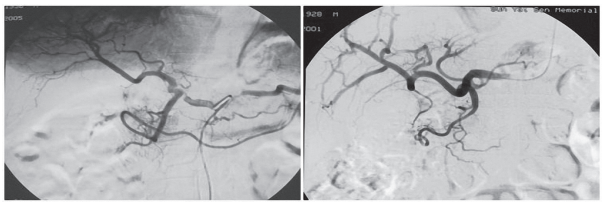
as pancreatic carcinoma. According to stage criteria UICC (1997),There were 20 patients at stage III and 28 patients at stage IV. All patients had never received operation,radiotherapy or chemotherapy before. Patients with other pancreatic and periampullary neoplasms, such as endocrine tumor,intraductal papillary mucinous neoplasm, were excluded. All patients were randomly devided into two groups: the continuous transarterial infusion group (experimental group) and the systemic venous group (control group). The trial was conducted with the approval of the local ethics committee at each institution. Information of patients were summarized in Table 1.

Treatment methods

For the continuous transarterial infusion group (experimental group), the Seldinger technology was adopted. Angiography of abdominal cavity artery and upper mesentery artery were first carried out respectively to observe the status of pancreatic carcinoma (Philips Integris 3000 DSA system). Target arteries of cancer were determined according to the location, infringing range, and blood supply of the carcinoma. Then, a catheter was inserted into the target vessel. For 14 patients, the catheters were inserted through femoral artery, and for the other 10 cases, the catheters were inserted through the left subclavian artery (Figure 1). Gemcitabine and 5-fluorouracil were continuously transarterial infused into the reserved catheter. A dose of 1000 mg/m^2 gemcitabine was given 30 minutes on day 1 of a 4-week cycle for 2 cycles, and a dose of 600 mg/m^2 5-fluorouracil was infused on days 1~5 of a 4-week cycle for 2 cycles.



1A 1B

Figure 1. Treatment Methods of the Transarterial Group. 1A. retention catheter through femoral artery; 1B. catheter was inserted through the left subclavian artery

Table 1. Clinical Characteristics of the 48 Advanced Pancreastic Carcinoma Patients (n<48)

	transarterial group	venous group	P value
N	24	24	
Age	61(26~75)	58 (37~75)	0.312
<60	8	13	
≥60	16	11	
Gender			0.204
Male	15	19	
Female	9	5	
Clinical stage			0.771
III	10	11	
IV	14	13	
CA19-9			0.303
abnormal	20	17	
normal	4	7	
KPS score			0.551
≥70	14	16	
50~70	10	8	
Pain intensity			0.913
Lightly	4	3	
middle	8	8	
Severe	12	13	
Location			0.89
Head of pancreas	15	16	
Body or tail of pancreas	6	6	
Entire pancreas	3	2	

For the systemic venous group (control group), gemcitabine and 5-fluorouracil were infused trough peripheral vein, a dose of 1000 mg/m^2 gemcitabine was administrated 30 min on days 1 and 8 of a 4-week cycle for 2 cycles, and a dose of 600 mg/m^2 5-fluorouracil was infused on days 1~5 of a 4-week cycle for 2 cycles.

Effectiveness and safety were evaluated after 2 cycles.

Evaluation criteria

Clinical curative effect: Curative effectiveness was evaluated according to World Health Organization (WHO) solid tumor effectiveness judgment criteria, and the effectiveness was classified into completed response(CR), partial response(PR), stable disease(SD) and progression disease(PD). Tumor volume was measured by CT or MRI. The evaluation procedure was conducted every 2 months during the chemotherapy. Survival time was considered from the day of the first dose to the date of death or the last follow-up visit, regardless of the cause of death.

Clinical benefit response (CBR)*:* Clinical benefit response (CBR) was assessed according to pain, physical strength and weight change (Jia et al., 2002).Clinical benefit was defined as the following criteria maintaining for 4 weeks and no worsening of any of the following items: (1) Pain relief: ≥ 50% reduction of the dosage of pain killer or at least 50% pain relief; (2) Improvement of performance status by at least 20 points on the KPS scale; (3) Body weight: ≥ 7% increase in body weight (excluding the increase induced by hydrops in body lumen or retention of body fluids).

Safety assessment: Safety assessments, including acute and sub-acute toxic reactions,were assessed according to the World Health Organization(WHO) guidelines (Miller et al.,1981).The adverse effects were inspected and parameters to be observed mainly included as below: blood system, hepatic and renal functions, and gastrointestinal reaction and so on.

Follow-up imaging evaluation

The baseline reference was performed at 1-7 days before chemotherapy by using a multi-detector row helical CT scanner (Simens Sensation 16) or a 1.5-T MR Scanner (Philips Intera). Follow-up CT or MRI was performed at 1-, 3-, and 6-month intervals after the initial chemotherapy session. Tumor volume was measured by CT or MRI.

CT: 20 cases of patients underwent MDCT, including routine plain scanning and contrast enhancement with a 16 slides CT scanner (SOMOTOM Sensation 64, SIEMENS, Germany). The protocol of scanning before the intravenous injection was 1.5 mm collimation, 0.5-second gantry rotation time, pitch 1.5, 120 KVp, 140~220 mA, 3 mm thickness. Then contrast medium was injected(3 mL/s, total 80~90 ml Ultravist) with a power injector with the

Table 2. Comparison of Efficacy Between Two Groups

Curative effect	transarterial group	venous group	P value
CR			
PR	8	6	
SD	10	9	
PD	6	9	
RR(%)	33.3	25	0.626

Table 3. Comparison of CBR Between Two Groups

	transarterial group	venous group	P value
Reducing pain degree≥50%	19	11	
Decrease of pain-killer≥50%	17	10	
Physical strength (KPS score≥20)	14	5	
Weight gain≥7%	12	4	
Responder according to CBR	20	12	
CBR rate (%)	83.3	58.3	0.014

Table 4. Comparison of Adverse Reactions Between Two Groups

	transarterial group	venous group	P value
Leukopenia			
I~II	7	8	0.755
III	1	2	0.551
Thrombocytopenia			
I~II	10	11	0.771
III	1	2	0.551
Anemia			
I~II	5	7	0.505
III	1	2	0.551
Nauseal/vomiting			
I~II	4	4	1
III	2	2	1
Arrhythmia			
I~II	1	2	0.551
III	0	0	
Aminotransferase			
I~II	5	7	0.505
III	0	0	

same parameters.

MRI: 31 cases of patients underwent MR Imaging with a 1.5T MRI scanner (Philips, Inteta Gyroscan, Holand). Routine plain scanning included T1/WATS (TR/TE, 350/7 ms), T1/IP (TR/TE, 250/6 ms) and T2W/SPIR (TR/TE, 1600/70 ms). The thickness and the gap of slices were 3 mm and 1 mm respectively. Gd-DTPA enhancement was performed after plain scaning. 0.1 mmol/kg Gd-DTPA was injected with a rate of 2 ml/s using a power injector. The size and signal intensity of lesions were observed.

Statistical analysis

All statistical tests were two-sided and performed in SPSS (version 16.0) for Windows. Curative effectiveness was compared by chi-square test; survival analysis was made by Kaplan-Meier methods, and survival rate curves were compared by Log-Rank test and Breslow test. P<0.05 was considered statistically significant.

Results

Objective curative effects

Curative effectiveness was evaluated according to

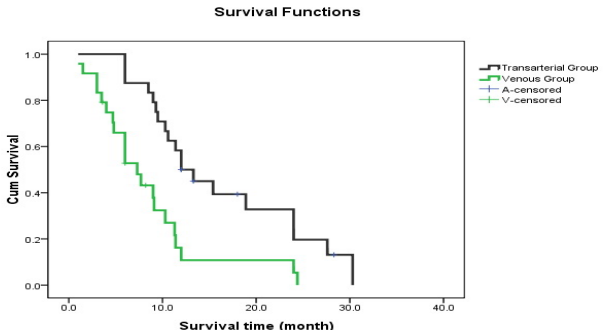


Figure 2. Survival Curves were Drawn by Kaplan-Meier Method

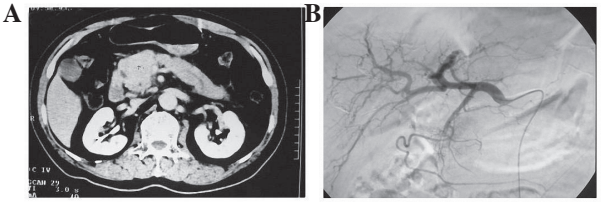


Figure 3. 60-year-old Man with Head of Pancreas Carcinoma (Transarterial Group). A. Transverse CT image shows enhancement of tumor; B. Hepatic angiogram shows tumor stain in the head of pancreas

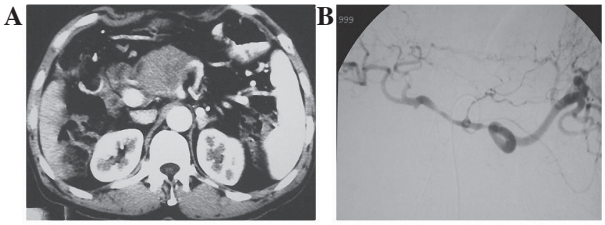


Figure 4. 60-year-old Man with Head of Pancreas Carcinoma (Transarterial Group). A. Transverse CT image shows that the common hepatic artery and splenic arteria were invaded; B. Hepatic angiogram shows the common hepatic artery and splenic arteria were invaded

WHO solid tumor effectiveness judgment criteria. The detailed information was shown in Table 2. From Table 2, we can see that the the objective effective rate of the transarterial group (33.3%) was higher than that of the systemic group (25%), but the difference was no significant (P=0.626, chi-square test).

Clinical benefit response (CBR)

According to the evaluation of 3 parameters about pain, physical strength and weight change, 20 cases and 12 cases had CBR in the transarterial group and the systemic group respectively, and the CBR were 83.3% and 58.3% respectively. The difference was significant (P=0.014, chi-square test, Table 3).

Survival condition

The survival analysis was made by Kaplan-Meier methods. The means and medians for survival time in transarterial group were 16.3 months and 12.0 months respectively. The means and medians for survival time in the systemic venous group were 8.6 months and 7.3 months respectively. The means and medians for survival time in transarterial group were longer than those of the systemic venous group, and the differences were statistically significant by Log-Rank test and Breslow test

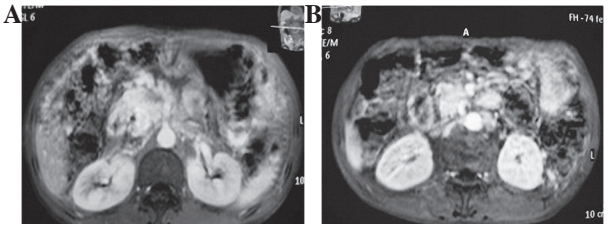


Figure 5. 63-year-old Woman with Head of Pancreas Carcinoma (Transarterial Group). A. MRI shows the mass before treatment; B. The mass was diminution slightly three months post-treatment, the objective curative effects was PR (partial response)

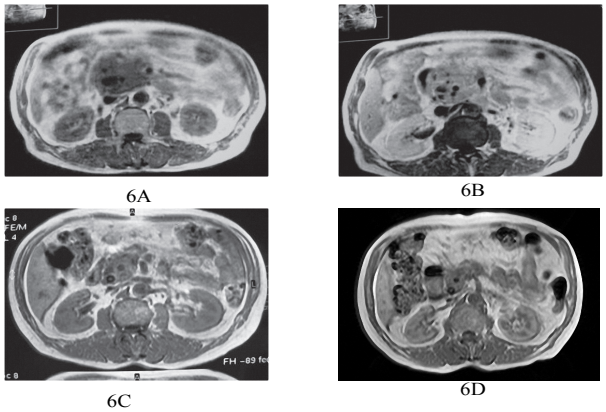


Figure 6. 76-year-old Man with Head of Pancreas Carcinoma (Transarterial Group). A~B. MRI findings before treatment; C. The mass was diminution slightly three months post-treatment, the objective curative effects was PR(partial response); D. The mass was diminution slightly 1-year post-treatment, the objective curative effects was PR

($P < 0.005$).

The survival curces was shown in Figure 2. The curces for survival time in transarterial group were higher than those of the systemic venous group.

Adverse effects

No treatment-related grade IV adverse reactions and deaths occurred in both groups, according to WHO criteria. The main adverse reactions included hematologic toxicity and hepatic function damage (degree I-II). The detailed information of adverse reactions of two groups was shown in Table 4. The diffenences of adverse reactions between the two groups were not statistically significant ($P>0.05$, chi-square test).

Discussion

Pancreatic carcinoma is one of the most malignant tumors of alimentary system (Hua et al., 2009; Zhou et al., 2012). The majority of pancreatic carcinoma are in an advanced stage at the time of diagnosis, as early diagnosis of pancreatic carcinoma is still difficult (Ikeda et al., 2009). Unfortunately, the curative effect of advanced pancreatic carcinoma is very poor. Previously used chemotherapy and radiotherapy regiments often can not produce a satisfactory curative effect (Moore et al., 2003; Wilkowski et al., 2006; Ouaissi et al., 2008; Hwang et al., 2009). Under such conditions, it is of great value to develop new alleviative treatment regiments, especially those that can improve the patients'quality of life.

Chemotherapy is one of the most important therapeutic methods in the treatment of pancreatic carcinoma (Hua et al., 2009). The literature reports regarding chemotherapy of pancreatic carcinoma through peripheral vein mainly concentrate on drug choice and medicine compatibility, and the results differ (Moore et al., 2003; Tomoo et al., 2006; Wilkowski et al., 2006; Ouaissi et al., 2008; Hwang et al., 2009). Because of low regional concentration and low medicine sensibility, the effectiveness of systemic chemotherapy in the treatment of pancreatic carcinoma is dissatisfactory and the adverse reactions are serious in most literatures.

In recent years, more and more literatures report the experiments and clinical applications of regional transarterial infusion chemotherapy to cure pancreatic cancer. Homma et al. (2000) reported the super selective catheter scheme after part of blood supply to pancreas was cut by tiny spring, then hemodynamics of pancreas was changed, one end of catheter was placed in spleen artery and/or hepatic artery (if having hepatic metastasis), the other end of the catheter was connected to chemotherapy pump, and continuous transarterial infusion chemotherapy was carried out through chemotherapy pump. The super selective catheter scheme was very effective to primary and hepatic metastatic pancreatic cancer, and average survival time of the 23 patients with pancreatic cancer was 19 months. Aigner et al. (1998) reported the random-control experiment regarding regional infusion chemotherapy and systemic venous chemotherapy in the treatment of advanced pancreatic cancer, and the patients adopted were at stage III or stage IV. Median survival times of the systemic group and regional group were 11 weeks and 33 weeks respectively, one patient experienced 2 phases resection. The effectiveness of chemotherapy is in direct proportion to the concentration and action time of drugs. Compared with systemic chemotherapy, because of avoiding first-pass effect, regional perfusion chemotherapy through artery can dramatically increase regional concentration in the tumor, thus the drugs generate strong cytotoxic effect to stimulate apoptosis and necrosis of the tumor, overcome drugresistance and inhibit tumor development and metastasis. Continuous transarterial chemotherapy prolong the action time of the regional high concentration drugs, which improve clinical benefit rate and survival time of patients with advanced pancreatic cancer. Literatures showed that the majority of regional transarterial infusion chemotherapy were proceeded with drugs perfused for one time merely. For regional infusion of pancreas, Fu et al. (2002) proved that drug concentration in target organ was several times of that of the systemic chemotherapy, and inflammatory reaction happened in surrounding tissues of pancreas. Shi et al. (2002) reported that 22 patients of advanced pancreatic cancer underwent continuous transarterial infusion chemotherapy with gemcitabine and 5-fluorouracil, and the CBR was good.

However, the reports about continuous transarterial infusion chemotherapy to cure advanced pancreatic cancer are very rare. In our research, gemcitabine and 5-fluorouracil were continuously transarterial infused, which made drugs continuously act on tumor in pretty

high concentration for longer time. Our preliminary results showed that the objective response rate, clinical benefit rate and survival time of the 25 patients in experimental group all exceeded those of the systemic group, and there were significant differences among all the parameters except objective response rate by chi-square test.

For comparison of the curative effectiveness between transarterial chemotherapy and systemic chemotherapy, internal and oversea relevant studies were rare, and the study results were extremely not consistent. The cases in this research are slightly small, and the curative effectiveness of gemcitabine and 5-fluorouracil through continuous transarterial infusion in the treatment of advanced pancreatic cancer requires further study. The prospective research composed of many centers and big samples should be carried out.

Continuous transarterial infusion chemotherapy is a minimal invasive interventional treatment technique. In our research, only one case's catheter was removed, and no other operative complications occurred in transarterial group. According to the literature report and our experience, we consider continuous transarterial infusion chemotherapy to be safe, reliable and feasible with few complications. Therefore, the selective continuous transarterial chemotherapy in the treatment of advanced pancreatic cancer, has strong feasibility and comparatively convenient operation. The method is safe and reliable, and worthy to be applied extensively.

Acknowledgements

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