Concurrent gemcitabine and high-intensity focused ultrasound therapy in patients with locally advanced pancreatic cancer

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This phase II trial was conducted to evaluate the safety and efficacy of concurrent gemcitabine and high-intensity focused ultrasound (HIFU) therapy in patients with locally advanced pancreatic cancer. Patients with localized unresectable pancreatic adenocarcinoma in the head or body of the pancreas received gemcitabine (1000 mg/m^2) intravenously over 30 min on days 1, 8, and 15, and concurrent HIFU therapy on days 1, 3, and 5. The treatment was given every 28 days. Thirty-seven (94.9%) of the 39 patients were assessable for response, and two cases of complete response and 15 cases of partial response were confirmed, giving an overall response rate of 43.6% [95% confidence interval (CI), 28.0–59.2%]. The median follow-up period was 16.5 months (range: 8.0–28.5 months). The median time to progression and overall survival for all patients were 8.4 months (95% CI, 5.4–11.2 months) and 12.6 months (95% CI, 10.2–15.0 months), respectively. The estimates of overall survival at 12 and 24 months were 50.6% (95% CI, 36.7–64.5%) and 17.1% (95%CI, 5.9–28.3%), respectively. A total of 16.2% of patients experienced grade 3/4 neutropenia. Grade 3 thrombocytopaenia was documented in two (5.4%) patients. Grade 3 nausea/vomiting and diarrhea were observed in three (8.1%), and two (5.4%) patients, respectively. Grade 1 or 2 fever was detected in 70.3% of patients. Twenty-eight patients (71.8%) complained of abdominal pain consistent with tumor-related pain before HIFU therapy. Pain was relieved in 22 patients (78.6%). In conclusion, concurrent gemcitabine and HIFU is a tolerated treatment modality with promising activity in patients with previously untreated locally advanced pancreatic cancer. ***Anti-Cancer Drugs*** **21:447–452 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

It is estimated that nearly 38 000 individuals were diagnosed with pancreatic adenocarcinoma in the United States in 2008 [1]. Surgical resection gives the best chance for a possible cure; however, only 10–20% of patients present with potentially resectable pancreatic cancer. The majority of patients with pancreatic cancer present with locally advanced or metastatic disease that is inoperable [2]. Gastrointestinal Tumor Study Group trials showed a survival benefit for patients with locally advanced pancreatic cancer (LAPC) who were treated with external-beam radiotherapy and 5-fluorouracil compared with patients who were treated with radiotherapy alone [3,4]. The results of recent phase I and II studies on gemcitabine-based chemoradiotherapy were successful, and improved therapeutic response and survival [5–8]. However, LAPC is a challenging malignancy to treat. Approaches that use chemotherapy, chemoradiotherapy, or both have significant limitations [9]. Many studies were designed to evaluate local ablation therapies in patients with pancreatic cancer, such as cryosurgery [10–12], radiofrequency ablation therapy [13], and high-intensity focused ultrasound (HIFU) therapy [14,15].

HIFU therapy is a new treatment for solid malignant tumors that has emerged in recent years [16,17]. This approach is based on the fact that ultrasound (US) beams can be focused and transmitted through solid tissues within the body, resulting in some effects that can destroy and coagulate in-depth tissue through thermal effects and cavitation [18]. HIFU coagulates target lesions through intake skin without surgical exposure or insertion of instruments. HIFU techniques for solid tumors treatment have been reported as noninvasive and conforming with real-time monitoring [19,20]. In animal experiments and clinical studies, it has been proven that HIFU can selectively target and destroy primary or metastatic lesions through intake skin, thereby treating

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tumors in the liver [19,21,22], kidney [23,24], bone [25], prostate [26], and pancreas [14,15]. Wu *et al.* [15] found that preexisting severe back pain disappeared, and that an absence of tumor blood supply and shrinkage of the ablated tumor were observed in the follow-up images in patients with advanced pancreatic cancer after HIFU treatment. They concluded that HIFU therapy is safe and feasible in the treatment of advanced pancreatic cancer. Another study published in literature in Chinese reported similar findings of safety and pain relief, even suggesting a survival benefit of chemotherapy (gemcitabine and cisplatin) in combination with HIFU in patients with advanced pancreatic cancer [27]. On the basis of these favorable results, we conducted the present phase II trial to evaluate the safety and efficacy of concurrent gemcitabine and HIFU therapy in patients with LAPC.

Patients and methods

Eligibility criteria

Eligible patients had a histological or cytological diagnosis of localized unresectable pancreatic adenocarcinoma in the head or body of the pancreas with at least one unidimensionally measurable lesion (i.e. a diameter of ≥ 1 cm, as assessed by spiral computed tomography), with metastatic disease excluded on the basis of whole-body computed tomography (CT) series. Unresectability was based on institutional criteria that used either CT or magnetic resonance imaging (MRI) within 4 weeks of protocol entry. The tumors were staged according to the American Joint Committee on Cancer (AJCC) staging system (6th edition). Other inclusion criteria included Eastern Cooperative Oncology Group performance status of 0–2; adequate bone marrow function (white blood cell count $\geq 3.5 \times 10^9$/l, absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, and haemoglobin ≥ 10.0 g/dl); and serum creatinine ≤ 150 mmol/l. Exclusion criteria included earlier cytotoxic chemotherapy, significant loss of body weight (e.g. $>15\%$ weight loss since surgery or diagnosis), and earlier abdominal radiotherapy. Patients with second primary malignancy, except in-situ carcinoma of the cervix, adequately treated nonmelanomateous skin cancers or other malignancy treated at least 5 years earlier with no evidence of recurrence, were also excluded. The institutional review board of the author's institution approved the protocol, and written informed consent was obtained from all patients before enrollment.

Treatment plan

Patients received gemcitabine 1000 mg/m^2 intravenously over 30 min on days 1, 8, and 15, and concurrent HIFU therapy on days 1, 3, and 5. The treatment was given every 28 days and continued until disease progression, patient refusal, or an unacceptable toxicity. HIFU treatment was performed under regional anesthesia with the patients lying either in the supine position or prone depending on the shortest distance from the transducer to the target volume, so that a pulsed, focused US beam produced by the transducer arrived at the target by the shortest distance from intake skin [20]. The tumor mass was selected through the directional movement of the diagnostic scanner in the target region. The tumor lesion was divided into two-dimensional cross-slices by scanning with real-time US. On the basis of the images of each slice, the target region was selected and then damaged by ejecting pulse-focused US beams. Through this partial coverage, complete targeting of the tumor volume was achieved slice by slice. Granulocyte colony-stimulating factor was administered at the physician's discretion or after taking into consideration the insurance status of the patients.

Equipment and apparatus

The HIFUNIT-9000 HIFU tumor therapy equipment made by Shanghai A&S Sci-Tech Co., Ltd (Shanghai, PR China) consists of three parts: a firing system located in a tank filled with degassed water; an imaging system consisting of a US scanner coupled with a stereotaxic localizing arm; and a computer that controls the firing sequence and the movement of the firing head through a three-dimensional micropositioning system. The main parameters of the equipment include input power, 3 kW/cm^2; effective therapy depth, 2–15 cm; practice-focused sphere, $3 \times 3 \times 10$ mm; unit transmit time (t_1), 0.2 s; intermission time (t_2); $t_1/t_2 = 2:1$; and treatment times at each location, 6–8. All of the parameters can be adjusted according to the different depths of tumors.

Response to treatment and adverse effects

All patients underwent a pretreatment evaluation consisting of medical history, physical examination, laboratory tests including serum carbohydrate antigen (CA) 19-9, chest radiographs, and high-resolution pancreatic CT scans. These tests were performed within 2 weeks before the start of treatment. Endoscopic retrograde cholangiopancreatography and biliary drainage procedures were performed if necessary. The patients underwent a physical examination, a subjective/objective symptom evaluation, and routine blood tests twice weekly. Every 4 weeks, a biochemistry blood examination was added to this basal evaluation. After every two treatment cycles, the response was evaluated using Response Evaluation Criteria In Solid Tumors. In cases of partial or complete response, a confirmative CT scan was performed 4 weeks later, and this was followed by a CT scan after every two treatment cycles. Objective responses were reported according to an intention-to-treat basis. Before and after every treatment cycle, the pain was also evaluated with a visual analog scale (VAS). The VAS consisted of a nongraduated 10-cm line ranging from 'no pain' to 'pain as bad as it could be' [28]. Toxicity was reported using a National Cancer Institute-Common Toxicity Criteria version 2.0 toxicity scale.

Statistical analysis

The primary endpoint of this study was 1-year overall survival (OS) rate, and the secondary endpoints were objective response rate, time to progression (TTP), and side effects. On the basis of the most conservative assumption of a 30% survival rate at 1 year (null hypothesis) in historic controls with locally advanced pancreatic cancer [7], an increase of 50% or more (alternative hypothesis) could be shown with a power of 80% by investigating a sample size of at least 35 patients (α=0.05, one-sided test) [29]. Allowing for a follow-up loss rate of 10%, the total sample size was 39 patients. OS and TTP were analysed using the Kaplan–Meier method with 95% confidence intervals (CIs). The TTP was calculated from the initiation of treatment to the date of disease progression, whereas the OS was measured from the initiation of treatment to the date of the last follow-up or death. The statistical data were obtained using an SPSS software package (SPSS 11.5 Inc., Chicago, Illinois, USA).

Results

Patient characteristics

From June 2006 to June 2008, 39 patients were enrolled in the study. The baseline characteristics of the patients are summarised in Table 1. The patient group consisted of 23 men and 16 women with a median age of 55 years (range: 28–74 years). The majority of the patients (94.9%) had an Eastern Cooperative Oncology Group performance status of either 0 or 1. Fourteen patients (35.9%) showed obstructive jaundice at diagnosis. Endoscopic biliary drainage with a plastic stent was performed on nine patients and percutaneous biliary drainage was performed on five patients. Thirty-four patients (87.2%) had elevated CA19-9 levels (> 37 U/ml) at initial diagnosis.

Table 1 Baseline patient characteristics

Characteristics	Number of patients [*N*=39 (%)]
Age (years)	
Median (range)	55 (28–74)
Sex	
Male	23 (59.0)
Female	16 (41.0)
ECOG performance status	
0	15 (38.5)
1	22 (56.4)
2	2 (5.1)
Diabetes mellitus	
Yes	12 (30.8)
No	27 (69.2)
Symptoms at baseline	
Abdominal pain	28 (71.8)
Jaundice	14 (35.9)
Weight loss	10 (25.6)
Tumor site	
Head	27 (69.2)
Body	12 (30.8)
Tumor size (longest diameter, cm)	
Median (range)	3.4 (1.7–8.5)
Tumor stage	
IIA	3 (7.7)
IIB	5 (12.8)
III	31 (79.5)
CA19-9 increased (>37 U/ml)	
Yes	34 (87.2)
No	5 (12.8)

CA, carbohydrate antigen; ECOG, Easter Cooperative Oncology Group.

Efficacy and survival

Thirty-seven (94.9%) of the 39 patients were assessable for response; of the two patients not assessable, both were lost to follow-up after the first treatment cycle. All efficacy data are reported using the intention-to-treat principle. Two cases of complete response and 15 cases of partial response were confirmed, giving an overall response rate of 43.6% (95% CI, 28.0–59.2%) (Table 2). Among the 34 patients who had elevated serum CA19-9 levels at the baseline, seven (20.6%) had normalized CA19-9 levels and 18 (52.9%) achieved more than a 25% reduction in CA19-9 levels after two cycles of concurrent gemcitabine and HIFU treatment. After completion of four treatment cycles, five patients (12.8%) underwent surgery, four had R0 resections (margin negative), and one had R1 resections with positive margins. In all, 34 (87.2%) of 39 patients without surgery received treatment with a median of 4 cycles (range: 1–8 cycles). The median follow-up period was 16.5 months (range: 8.0–28.5 months). The median TTP for all patients was 8.4 months (95% CI, 5.4–11.2 months). The estimated median OS was 12.6 months (95% CI, 10.2–15.0 months) (Fig. 1). The estimate of OS at 12 months and 24 months were 50.6% (95% CI, 36.7–64.5%) and 17.1% (95% CI, 5.9–28.3%), respectively.

Toxicity

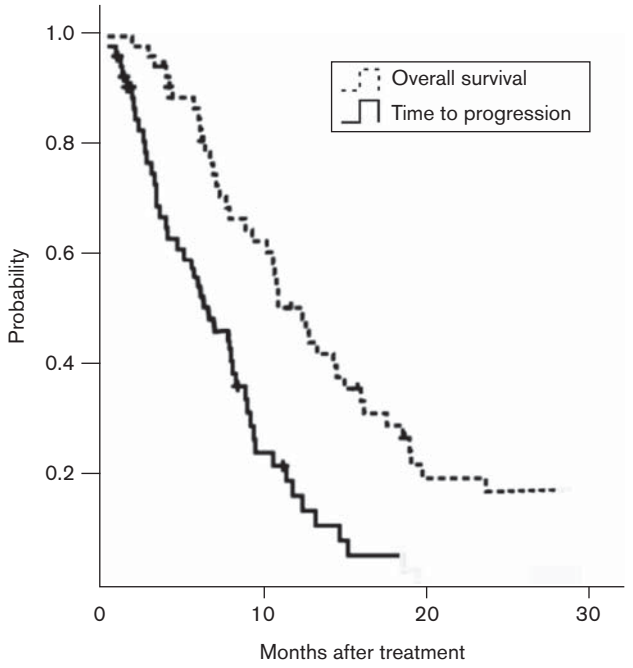
Thirty-seven (94.9%) patients were assessable for safety. The toxic effects observed during the study are listed in Table 3. The most common toxic effects were neutropenia, thrombocytopaenia, nausea/vomiting, diarrhea, and fever. Most patients experienced neutropenia during their course of therapy, with 10.8% of patients (n=4) with grade 3 and 5.4% (n=2) with grade 4 neutropenia. Grade 1 or 2 neutropenia was detected in 32.4% of the patients (n=12). Grade 3 thrombocytopaenia was documented in two (5.4%) patients. Nausea/vomiting, diarrhea, and fever were the most common nonhematological toxicities. Grade 3 nausea/vomiting and diarrhea were observed in three (8.1%) and two (5.4%) patients,

Table 2 Tumor response (intention-to-treat analysis)

Response	Number (*N*=39, %)
Confirmed response	17 (43.6)[a]
Complete response	2 (5.1)
Partial response	15 (38.5)
Stable disease	15 (38.5)
Progressive disease	5 (12.8)
Not assessable	2 (5.1)

[a]95% confidential interval=28.0–59.2%.

Fig. 1



Time to progress and overall survival rate for all patients.

Table 3 Toxicities of concurrent gemcitabine and HIFU therapy (by patients)

	Grade [number of patients $N=37$, n(%)][a]			
Toxicities	1	2	3	4
Hematology				
Neutropenia	5 (13.5)	7 (18.9)	4 (10.8)	2 (5.4)
Anemia	6 (16.2)	8 (21.6)	–	–
Thrombocytopenia	10 (27.0)	4 (10.8)	2 (5.4)	–
Nonhematology				
Nausea/vomiting	9 (24.3)	8 (21.6)	3 (8.1)	–
Mucositis	3 (8.1)	4 (10.8)	–	–
Diarrhea	4 (10.8)	3 (8.1)	2 (5.4)	–
Fever	14 (37.8)	12 (32.4)	–	–
Neuropathy	2 (5.4)	1 (2.7)	–	–
Infection	4 (10.8)	–	–	–
Elevated transaminase	5 (13.5)	2 (5.4)	–	–

HIFU, high-intensity focused ultrasound.
[a]National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.

respectively. However, no grade 4 nonhematologic toxicity was observed in this study. Grade 1 or 2 fever was detected in 70.3% of patients ($n=26$). No skin burns caused directly by HIFU were observed in this study. During the hospital stay, no signs of tumor hemorrhage, large blood vessel rupture, or gastrointestinal perforation were detected in any patient. There was no evidence of postinterventional pancreatitis or peritonitis in any patient during the follow-up period. No patient was discontinued from the study because of toxic effects. There were no treatment-related deaths during this study.

Pain relief

Twenty-eight patients (71.8%) complained of abdominal pain consistent with tumor-related pain before HIFU therapy. Pain was relieved in 22 patients (78.6%). Complete remission of pain (0 pain score and no need for opioid analgesics) was observed in nine patients (32.1%), a partial remission of pain (decrease in pain score by 2 or more) was observed in 13 patients (46.4%), and no improvement of pain was observed in six patients (21.4%). Pain relief was observed in 88.2% (15 of 17) of patients who had an objective tumor response and in seven patients who did not show an objective tumor response.

Discussion

Treatments for locally advanced pancreatic adenocarcinoma have significant efficacy limitations. Concurrent chemoradiotherapy is a standard treatment option that seems to modestly prolong median survival through enhanced tumor control [30]. However, objective treatment response is uncommon. Approaches that use chemotherapy, chemoradiotherapy, or both have significant limitations [9]. Several energy sources, such as radio frequency, microwave, cryotherapy, and lasers, have been used to induce coagulation necrosis of a target tumor in clinical practice. With most of these techniques, the energy is applied percutaneously with needle applicators. The energy is therefore concentrated around the applicator, and there is heterogeneous distribution of heat through a target lesion. The result is that a maximum tumor diameter of 5 cm can be generally treated. As a noninvasive treatment, HIFU is not restricted by these limitations. It does not require the insertion of an applicator into a target tissue, and an extracorporeal source can be used to treat large-volume tumors with real-time imaging guidance. US energy deposited in the target tumor induces coagulation necrosis. Both the thermal and the cavitation effects caused by US energy are responsible for tissue damage [20]. HIFU for treatment of pancreatic cancer is widely available in China, with limited availability in South Korea and England. Several studies on pancreatic cancer are planned in Europe and the United States [31].

This phase II study showed that gemcitabine and concurrent HIFU therapy was active and well tolerated as first-line therapy in patients with LAPC. The 1-year OS rate of 50.6% in this study is comparable with recently published phase II trials on chemoradiotherapy in LAPC, which are summarized in Table 4 [9,32–36]. The primary endpoint was positive, and therefore further studies of this regimen in LAPC are warranted. The major grade 3 and 4 toxicities were hematological and gastrointestinal toxicities when gemcitabine was combined with HIFU therapy. The rates of grade 3 and 4 toxicities in this study were similar to reports of gemcitabine-based chemoradiotherapy [7,8,34]. In this study, grade 3 and 4

Table 4 Summary of recent published phase II trials of chemoradiotherapy in locally advanced pancreatic cancer

Study [Reference no.]	No. of patients	ORR (%)	Median TTP (months)	Median OS (months)	1-year survival (%)	2-year survival (%)
[32]	41	7.3	7.1	11.7	46.3	9.8
[33]	48	8.5	7.3	10.2	40	–
[34]	41	24.4	8.9	16.7	63.3	27.9
[9]	82	26	8.6	11.9	47	–
[35]	91	47	9.9	16.2	–	–
[36]	55	42	5.9	12.4	52	19

ORR, overall response rate; OS, overall survival; TTP, time to progression.

neutropenia occurred in 16.2% of patients and was reversible with conservative therapy. This study shows that there were no severe complications or adverse events related to HIFU therapy observed in any of the patients treated. Pain management for patients with LAPC is an ongoing challenge. This pain can be both neuropathic and inflammatory, resulting from both tumor expansion and tumor invasion of the celiac and mesenteric plexus [37–39]. Nonsteroidal anti-inflammatory drugs and narcotic analgesics are principally used for pain control in clinical practice. At disease progression, however, these may not be sufficient. Therefore, anesthetic blocking of the celiac plexus by means of injection of a chemical solution [40,41], external radiation therapy [42,43], and chemotherapy [44,45] was used to palliate pain in patients with pancreatic cancer. These modalities can achieve pain control, but the duration of pain relief is limited. As almost 70% of patients with pancreatic cancer are at least 65 years of age at diagnosis, side effects related to external radiation and antitumor drugs may be very severe [15]. In this study, pain was relieved in 22 (78.6%) of 28 patients after HIFU treatment. Complete remission of pain (0 pain score and no need for opioid analgesics) was observed in nine patients (32.1%), and partial remission of pain (decrease in pain score by 2 or more) was observed in 13 patients (46.4%). As ionizing radiation is not used with HIFU, this treatment is not restricted by the limitation of the radiation dose and may be used repeatedly. Although the mechanism is still unclear, HIFU might be an effective treatment option for pain control, particularly in patients with tumors infiltrating the celiac plexus and in whom conventional pain treatments are not considered an effective option.

This study had several weaknesses. First, because some pancreatic cancers (small tumors) cannot be detected with US, it is not possible to perform US-guided HIFU in patients with these malignancies. Second, the imaging equipment that was used to assess the follow-up results in this study, compared with current state-of-the-art equipment of ^{18}F-FDG positron emission tomography scan [46], was not sufficient to allow us to determine treatment effectiveness or to detect metastatic disease.

In conclusion, concurrent gemcitabine and HIFU is a tolerated treatment modality with promising activity in patients with previously untreated LAPC. On the basis of these results, concurrent gemcitabine and HIFU can be a good therapeutic option for the treatment of LAPC. However, a prospective, randomized study comparing this regimen with chemoradiotherapy in LAPC is warranted.

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