Original paper

Effects of a Sequential Combination of Hyperthermia and Gemcitabine in the Treatment of Advanced Unresectable Pancreatic Cancer: A Retrospective Study

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Abstract: Gemcitabine (GEM) has improved both overall survival and tumor-related symptoms in patients with advanced pancreatic cancer when compared to 5-FU, and is a widely accepted treatment for such patients. However, pancreatic cancers remain extremely resistant to chemotherapy. Empiric chemotherapy based on GEM has had no major successes in treating patients with advanced disease. The objective of this study was to evaluate the response rate, survival, and toxicity of the sequential combination of GEM and hyperthermia. Between November 2005 and November 2007, 7 patients with unresectable pancreatic cancer received sequential combination therapy with GEM and hyperthermia at the Matsushita Memorial Hospital. Data were then compared with 7 historical controls treated with GEM alone at the same institution. There were no significant differences in age, performance status or UICC stage between the GEM plus hyperthermia and GEM monotherapy groups. The disease control rate (CR+PR+SD) was 14.3% for patients treated GEM alone and 57.1% for patients treated with GEM plus hyperthermia. The median survival time was 198 days for patients treated with GEM alone, and 327 days for patients treated with GEM plus hyperthermia. Combination therapy with GEM and hyperthermia thus improves overall survival when compared with GEM monotherapy ($p=0.0275$). The sequential combination of GEM plus hyperthermia showed a potential therapeutic effect, and was at least as effective as GEM monotherapy. To clarify the effects of this combination therapy, a larger prospective clinical trial is required.

Key Words: pancreatic cancer, hyperthermia, gemcitabine

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Introduction

Pancreatic cancer is the fifth leading cause of cancer-related death in Japan and remains one of the most lethal human cancers. Approximately 85% of the patients present with advanced unresectable disease[1], and because pancreatic cancer remains extremely resistant to standard cytotoxic and targeted chemotherapies, the median survival after diagnosis for these patients is approximately 6 months. Systemic treatment is used for patients with widespread disease. Historically, these patients received 5-fluorouracil (FU), and 5-FU has been studied very extensively and used with a variety of doses and schedules, but the response rate rarely exceeds 20%, and no consistent effects on survival have been demonstrated. Burris *et al.*[2] reported that gemcitabine hydrochloride (GEM) was more effective than 5-FU in alleviating some disease-related symptoms in patients with advanced pancreatic cancer, and GEM improved overall survival rates when compared with 5-FU. However, the overall objective response rate remains low, and additional improvements are clearly needed in the treatment of advanced pancreatic cancer. In recent years, several studies have evaluated new combinations and have demonstrated higher or similar response rates and survival rates than those seen with GEM monotherapy. Cunningham *et al.*[3] has reported on the efficacy of capecitabine (CAP) on survival rates in combination with GEM, while Herrmann *et al.*[4] have shown that CAP in combination with GEM did not improve overall survival rates when compared with GEM alone. Moore *et al.*[5] found that the addition of erlotinib to GEM significantly improves survival and progression-free survival in advanced pancreatic cancer. However, the median overall survival time (MST) in the erlotinib plus GEM group was extended by only 0.5 months when compared with GEM alone. Moreover, new active treatments for metastatic pancreatic cancer have yet to be established.

Hyperthermia has been shown to increase the cytotoxic effects of some anticancer agents by facilitating drug penetration into tissue, and can also cause the thermal destruction of cancer cells[6]. GEM has recently been shown to be a potent hyperthermic sensitizer in preclinical studies[7]. Moreover, it was recently found that hyperthermia inhibits gemcitabine-induced activation of NF-kB, resulting in the enhancement of the GEM cytotoxicity[8]. These studies suggest that the combination of GEM and hyperthermia may improve survival in patients with advanced pancreatic cancer. In the present study, the clinical efficacy and toxicity of the combination of GEM and hyperthermia in untreated patients with unresectable pancreatic cancer was examined.

Patients and methods

Patient population

This study was a retrospective analysis of patients with advanced unresectable pancreatic cancer who were treated with a sequential combination of GEM and hyperthermia at the Matsushita Memorial Hospital between November 2005 and November 2007. The current study population was compared with a historical control comprising patients treated with GEM alone at the same hospital between December 2003 and April 2005. All patients who fulfilled the following requirements were selected for analysis : (1) inoperable advanced pancreatic cancer ; (2) no prior treatment for pancreatic cancer ; (3) at least 2 courses of chemotherapy received ; and (4) Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less at the time of diagnosis. Informed consent was obtained from each

patient before beginning treatment.

Chemotherapy

One cycle of the current chemotherapy regimen consisted of a drip infusion of 1000 mg/m^3 of GEM over 30 minutes weekly for 3 consecutive weeks, and then one week with no therapy. This schedule was repeated every 4 weeks until disease progression or unacceptable toxicity was observed.

Hyperthermia

Hyperthermia treatments were delivered by means of an 8 MHz capacitive heating device, the "Thermotron RF-8" (Yamamoto Vinita Co. Ltd., Osaka, Japan). An electromagnetic field with a power ranging from 529 to 1336 W was used, depending on the patients' condition. This was applied between a pair of electrodes with diameters of 30 cm which were placed on the opposite sides of the target area. A saline solution maintained at 2-37 degrees Celsius degrees was circulated in boluses to avoid overheating of the skin. For patients who received hyperthermia once per week at the Inui clinic, each hyperthermia session was scheduled for the day after the administration of GEM, and hyperthermia was administered by using a radiofrequency (RF) capacitive heating device (Thermotron RF8, Yamamoto Vinita, Osaka, Japan). The duration of the heating session was from 40 minutes to 50 minutes. This schedule was based on an *in vitro* study showing that hyperthermia enhanced the cytotoxicity of GEM, particularly when hyperthermia was performed 24 h before or after GEM treatment[8].

Evaluations

At 4 to 8 weeks after therapy, patients were reassessed by taking a history, physical examination and computed tomography (CT). The response of measurable target lesions was objectively evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Complete response (CR) was defined as the disappearance of all disease. Partial response (PR) was defined as at least a 30% reduction in the sum of the longest diameters of all measured lesions after at least 4 weeks. Progressive disease (PD) was defined as an increase of 20% or more in lesion size, or the appearance of new lesions. Responses not falling into any of these categories were classified as stable disease (SD). Overall survival (OS) was calculated from the first day of treatment until the last follow-up. Toxicity was evaluated according to the National Cancer Institute common toxicity criteria (NCI-CTC) version 2.0.

Statistical analysis

Clinical characteristics were analyzed by the χ^2 test for categorical variables and the t-test for interval data. OS was estimated with the method of Kaplan and Meier. Comparisons of survival were performed using the Logrank test. Stat View software version 5.0 (SAS, Cray, NC, USA) was used to analyze the data.

Results

Patient characteristics

Seven patients treated with the sequential combination of GEM and hyperthermia (GEM+HT group) were selected for analysis. Five of these patients had histologically or cytologically confirmed adenocarcinoma, and two patients were diagnosed with serum biochemistry, endoscopic retrograde pancreatography and computed tomography plus their clinical appearance and course. Patient

characteristics are shown in Table I. Median patient age was 66 years (range 57-70). The frequency of thermotherapy ranged from 12 to 67 sessions, and the mean was 35 sessions. The historical control group comprised 7 patients who were treated with GEM alone (GEM group). As shown in Table II, the mean total dose for the patients receiving GEM alone was 14100 mg compared to 28110 mg in patients receiving GEM plus HT ($p=0.048$). There were no significant differences in median age, sex, performance status, tumor location, tumor size, UICC stage or the treatment dose of GEM between the two groups.

Response

Tumor responses after treatment are shown in Table III. No patients achieved CR or PR in either group. With regard to target lesions, there were two SDs in the GEM group and five SDs in the GEM+

Table I. Clinical data for 7 patients treated with Gem plus hyperthermia.

Patients no.	Age /Sex	Total dose of Gem (mg)	Hyperthermia			Response	Survival time (days)	Outcomes
			Duration[a]	Frequency	Power output[a]			
1	62/M	44,800	42 min	45	1298 W	SD	415	died
2	68/F	25,200	48 min	33	654 W	SD	248	alive
3	64/M	22,400	42 min	25	1336 W	PD	286	died
4	69/M	22,000	49 min	37	1302 W	PD	327	died
5	70/M	10,775	49 min	25	622 W	PD	236	died
6	66/F	53,400	50 min	67	1150 W	SD	414	alive
7	57/F	18,200	47 min	12	529 W	SD	221	died

[a]Mean

Table II. Patient characteristics.

	Gem alone (n=7)	Gem+Hyperthermia (n=7)	*p*-value
Age (yrs)[a]	66 (60-81)	66 (57-70)	0.617
Sex (male/female)	3/4	4/3	0.593
Performance status 0/1/2	5/2/0	5/2/0	–
Tumor location (dominant)			
Ph/Pb/Pt	2/4/1	1/5/1	0.800
Tumor size, cm ≤2/2-4/4≤	0/5/2	0/4/3	0.576
Stage (UICC < 6th edition>) III/IV	4/3	3/4	0.593
Total dose of Gem (mg)[b]	14100 (11220-16800)	28100 (10775-53400)	0.048
Dose intensity of Gem[b]	433 (384-574)	606 (462-699)	0.359

a Median (range)
b Median (inter-quartile range)

HT group. With regard to overall response, there was one SD in the GEM group and four SDs in the GEM+HT group. The rates of PD for the GEM group and GEM+HT group were 71.4% and 42.9%, respectively. One patient in the GEM group was not assessed for response to chemotherapy. Disease control rates (complete response+partial response+stable disease: DCR) for the GEM group and GEM+HT group were 14.3% and 57.1%, respectively.

Overall survival

All patients in the GEM group, and 5 of 7 patients in GEM+HT group, were known to have died by the time of the final analysis. Median survival times were 198 days and 327 days for GEM group and GEM+HT group, respectively (Fig. 1). Patients treated with GEM+HT had significantly better survival times than the GEM group ($p=0.0275$).

Toxicity

Treatment-related toxicities are listed in Table IV. The most common toxicities in patients treated

Table III. Objective response.

	Gem alone (n=7)		Gem+Hyperthermia (n=7)	
	Number	Rate	Number	Rate
Target lesion response				
Complete response	0	0%	0	0%
Partial response	0	0%	0	0%
Stable response	2	28.6%	5	71.4%
Progressive disease	4	57.1%	2	28.6%
Could not be evaluated	1	14.3%	0	0%
Overall response				
Complete response	0	0%	0	0%
Partial response	0	0%	0	0%
Stable response	1	14.3%	4	57.1%
Progressive disease	5	71.4%	3	42.9%
Could not be evaluated	1	14.3%	0	0%

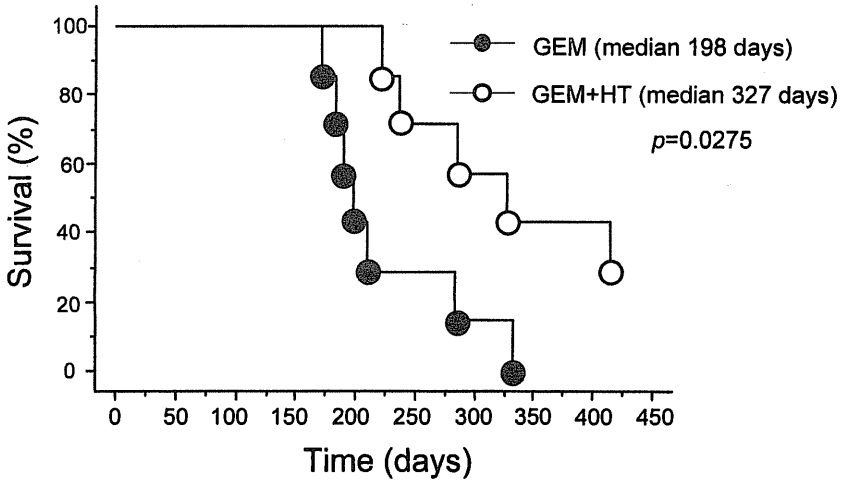

Fig. 1. Kaplan-Meier graph for overall survival.

with GEM and HT was anemia (seven patients), followed by leucopenia (six patients), neutropenia (six patients) and elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (six patients), but these symptoms were mild in all patients. No grade 3 or 4 toxicities occurred in the GEM+HT group. There were no burn injuries during heating among the patients who underwent hyperthermia. There were no treatment-related deaths in either group. As with GEM monotherapy, the sequential combination of GEM and HT was well tolerated.

Table IV. Adverse events.

	Gem alone (n=7)		Gem+Hyperthermia (n=7)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Leucopenia	6 (85.7)	2 (28.6)	6 (85.7)	0 (0)
Neutropenia	6 (85.7)	2 (28.6)	6 (85.7)	0 (0)
Anemia	6 (85.7)	0 (0)	7 (100)	0 (0)
Thrombocytopenia	6 (85.7)	0 (0)	3 (42.9)	0 (0)
AST	5 (71.4)	1 (14.3)	7 (100)	0 (0)
ALT	5 (71.4)	1 (14.3)	7 (100)	0 (0)
Bilirubin	1 (14.3)	0 (0)	1 (14.3)	0 (0)
Creatinie	0 (0)	0 (0)	2 (28.6)	0 (0)
Fatigue	6 (85.7)	0 (0)	3 (42.9)	0 (0)
Anorexia	4 (57.1)	0 (0)	3 (42.9)	0 (0)
Nausea	3 (42.9)	0 (0)	1 (14.3)	0 (0)
Diarrhea	2 (28.6)	0 (0)	0 (0)	0 (0)

Discussion

GEM is considered to be the standard treatment for patients with advanced unresectable pancreatic cancer, improving OS and offering a statistically significant clinical benefit over the best supportive care[2]. However, the overall objective response rate remains low. To improve treatment efficacy, various anticancer agents in combination with or without GEM are being investigated in clinical trials[4,5,9–12]. Some combination regimens have demonstrated higher or similar response and survival rates when compared with GEM monotherapy. Moore *et al.*[5] found that the addition of erlotinib to GEM significantly improves OS and progression-free survival in advanced pancreatic cancer. However, the median overall survival time (MST) in the erlotinib plus GEM group was extended by only 0.5 months when compared with the GEM monotherapy group. In most clinical trials, the MST after treatment with anticancer agents plus GEM was similar to the MSTs observed using GEM monotherapy, and marked improvements in survival have not been observed.

A sequential combination of GEM and hyperthermia was used for patients with advanced unresectable pancreatic cancer, and it was found that the DCR was 57.1% and that the MST was 10.8 months. Both of these data are better than those seen for GEM monotherapy (historical controls). In previous clinical trials[3,4,5,10–12], the MST for unresectable pancreatic cancer patients treated with GEM alone has ranged from 4.6 to 7.2 months, and these values were similar to those of the historical controls (MST : 6.5 months) reported in this study. There was a 4.3 month improvement in median survival

duration for patients treated with GEM+HT when compared with those who received GEM monotherapy. While additional improvement is clearly needed, these results are encouraging. In comparing the characteristics of the GEM monotherapy group with the GEM+HT group, there were different total doses of GEM in used in the GEM+HT group ($p=0.048$), but this was because the period used for chemotherapy was longer for patients in the GEM+HT group, and as a result the patients in the GEM+HT group demonstrated a better prognosis. Therefore, there was a difference in the total GEM exposure between the two groups, but the difference between single doses was minimized between the two groups ($p=0.359$). The toxicity associated with the sequential combination of GEM and hyperthermia was low and was mainly associated with myelosuppression. Grade 3 or 4 toxicities did not occur. When comparing the toxicity profile to the GEM monotherapy group, no major differences were seen. The results of the present study also seem to indicate that the sequential combination of GEM and hyperthermia is a relatively effective and well-tolerated regimen.

The biological rationale for using hyperthermia for malignant tumors is that malignant tumor cells may have a lower thermal death threshold point than normal cells[13]. Hypovascular tumors, such as pancreatic cancer, retain more heat than surrounding tissues, and consequently, the tumor temperature rises above the temperatures in normal tissues. Therefore, pancreatic cancer is considered to be good target for hyperthermic treatment.

Hyperthermia has been shown to enhance the cytotoxicity of several chemotherapeutic agents[13,14], although the timing of hyperthermia plays a critical role in its efficacy[15]. Generally, simultaneous treatment with hyperthermia and chemotherapeutic agents has a synergistic effect on neoplastic cells. In the case of GEM, the administration of GEM with simultaneous hyperthermia was reported to be effective in a mouse model[16]. However, it has been demonstrated that simultaneous treatment with GEM and hyperthermia led to decreased cytotoxicity, whereas an interval of 20 or 24 h between GEM and hyperthermia led to enhanced cell death[7]. Haveman *et al.*[7] speculated that the decreased cytotoxicity observed after simultaneous hyperthermia and GEM probably results from inhibition of GEM activation of the triphosphate metabolite.

It has been reported that NFκB, which induces the expression of multiple genes, including COX-2, VEGF and IAP, is sometimes activated by chemotherapy in tumor cells[17,18], and that NFκB activation is one mechanism through which tumors can become resistant to chemotherapy[19]. It has recently been reported that GEM activates NFκB binding activity in pancreatic cancer cell lines, and it was found here that hyperthermia inhibits the GEM-induced activation of NFκB, and that hyperthermia enhances the cytotoxicity of GEM, particularly when hyperthermia is performed at 24 h before or after GEM treatment[8]. These results support the clinical efficacy of the sequential combination of GEM and hyperthermia.

In conclusion, the present study demonstrates that a sequential combination of hyperthermia and GEM is a safe and effective treatment in patients with advanced unresectable pancreatic cancer. To clarify the effects of a sequential combination of hyperthermia and GEM when compared to GEM monotherapy, further studies should be performed, particularly proprospective randomized trials.

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Abstract in Japanese

切除不能進行膵癌に対するゲムシタビン・温熱異時併用療法の有効性についての検討

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要　　旨:【目的】ゲムシタビン (Gem) は，それまでの標準治療であった 5-FU と比較して，生存率および症状緩和効果ともに優れていたため，現在，切除不能進行膵癌に対する治療として広く用いられている．しかし，その治療成績は未だ不十分なものである．そこで，切除不能進行膵癌に対する Gem 温熱異時併用療法の効果および有害事象について検討を行った．【方法】2005 年 11 月から 2007 年 11 月の間に，松下記念病院にて切除不能膵癌と診断され Gem 温熱異時併用療法を 2 コース以上施行できた 7 例を検討対象とした．温熱療法は Gem 投与翌日に行い，同施設において Gem 単独治療を行った 7 例を historical control として比較検討した．【結果】Gem 温熱異時併用群と Gem 単独群 (historical control) の間には，治療開始時の年齢，performance status，臨床病期に有意な差はなかった．Disease control rate (CR＋PR＋＋SD) は Gem 温熱併用群 57.1%，Gem 単独群 14.3%と温熱併用群で良好であった．累積生存率でも温熱併用群 (MST327 日) は Gem 単独群 (同 198 日) に比し有意に良好であった ($p=0.0275$)．【結論】Gem 温熱異時併用療法は，Gem 単独療法に比し抗腫瘍効果が増強されることが期待され，今後，前向き試験において多数例で評価することが必要である．