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Phase II Study of Gemcitabine Chemotherapy Alone for Locally Advanced Pancreatic Carcinoma: JCOG0506

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Objective: Chemoradiotherapy with 5-fluorouracil has been accepted as a standard care for locally advanced pancreatic cancer; however, it has not been shown to be superior to chemotherapy alone in the gemcitabine era. The present multicentre phase II study was conducted to evaluate the efficacy and safety of Gem monotherapy against locally advanced pancreatic cancer in comparison with the historical data of chemoradiotherapy with 5-fluorouracil.

Methods: Eligibility criteria included patients with histologically proven locally advanced pancreatic cancer, all lesions encompassed by a square of 15 cm on one side, no prior treatment, good performance status and adequate organ function. Gemcitabine was given intravenously at a dose of 1000 mg/m^2 over 30 min on days 1, 8 and 15, repeated every 4 weeks. The primary endpoint was %1-year survival. Expected and threshold %1-year survival were 40 and 25%, respectively.

Results: Between January 2006 and February 2007, 50 locally advanced pancreatic cancer patients were registered. The major grade 3–4 adverse events were neutropaenia (62%), thrombocytopaenia (18%), fatigue (12%) and infection-biliary tree (12%). Haematological toxicity was mostly transient and there was no episode of infection with grade 3–4 neutropaenia. Up to the final follow-up in February 2009, the median overall survival was 15.0 months with a %1-year survival of 64.0%.

Conclusions: Gemcitabine monotherapy demonstrated far better survival than historical data for chemoradiotherapy with 5-fluorouracil with mild toxicities. Gemcitabine could be consider as a standard treatment for locally advanced pancreatic cancer.

Trial Registration: This trial was registered in UMIN-CTR (http://www.umin.ac.jp/ctr/index-j.htm), identification number (C000000308).

Key words: locally advanced pancreatic cancer – gemcitabine – chemotherapy – chemoradiotherapy

INTRODUCTION

Pancreatic cancer (PC) currently represents the fifth leading cause of cancer-related mortality in Japan, with an estimated 22 927 deaths attributable to the disease in 2005 (1). The prognosis of patients with this disease remains extremely poor, with a 5-year survival rate after diagnosis of less than 5%. Despite recent improvements in diagnostic techniques, PC is diagnosed at an advanced stage in most patients. Among these patients, roughly one-third are diagnosed as having locally advanced disease radiographically confined to the pancreas and surrounding tissues. In patients with locally advanced pancreatic cancer (LAPC), concurrent 5-fluorouracil (5-FU) therapy and external-beam radiation therapy (5-FU EBRT) has been shown to offer a survival benefit in comparison with radiotherapy alone (2,3) or chemotherapy alone (4).

Recently, gemcitabine (Gem) has improved the outcome of patients with advanced PC, including both locally advanced and metastatic diseases, by improving survival with higher clinical benefit response (5). Since the introduction of Gem in 1997, there have been many randomized trials of Gem combination chemotherapy against Gem monotherapy for LAPC and metastatic PC. Subset analysis of these trials demonstrated that the median survival period of LAPC patients treated with Gem alone or in combination was approximately consistent with those treated with 5-FU EBRT in previous trials, i.e. 10–11 months (2–4,6–11). In Japan, there have been many arguments for and against radiotherapy as a partner with chemotherapy for LAPC because chemoradiotherapy leads to a similar outcome when compared with modern chemotherapy with Gem and may produce higher proportion of toxicity. At the time of the current study preparation, 2005, about one-half of the attending institutes in our group used 5-FU EBRT, and the remaining half Gem chemotherapy, in the practical setting of LAPC treatment.

The current study is being conducted as a phase II trial to clarify the outcomes of Gem alone, prior to an anticipated phase III trial comparing Gem monotherapy with conventional chemoradiotherapy, because there has been no prospective data as for Gem alone in the treatment of the patients with LAPC having the indication of EBRT to our knowledge.

METHODS

Patients

The eligibility criteria for enrolment into this study were patients with histologically or cytologically proven pancreatic adenocarcinoma or adenosquamous carcinoma, patients with International Union Against Cancer clinical stage III (T4N0-1 and M0), all lesions assumed to be included in a square radiation field of 15 cm on one side in order to enable us to compare with the historical data of EBRT, age 20 or older, no prior surgical resection for LAPC, no prior anti-cancer chemotherapy or radiotherapy for any malignancies, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1 or 2, adequate bone marrow (leukocyte count $\geq$3500/mm^3, platelet count $\geq$100 000/mm^3 and haemoglobin $\geq$9.0 g/dl), adequate renal function (serum creatinine concentration $\leq$1.2 mg/dl), adequate hepatic function (serum bilirubin level $\leq$2.0 mg/dl, serum alanine and aspartate transaminase levels $\leq$100 IU; if biliary drainage was performed for jaundice before registration, the former $\leq$3.0 mg/dl and the latter $\leq$150 IU), adequate nourishment (serum albumin $\geq$3.0 g/dl), no serious complications, and provision of written informed consent from the patient.

This study protocol was approved by the Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) and Institutional Review Board (IRB) of each institutions.

Patients were recruited from January 2006 to February 2007 from 14 hospitals out of 24 hospitals with IRB approval (see Appendix).

Protocol treatment

Eligible patients received Gem intravenously at a dose of 1000 mg/m^2 over 30 min on days 1, 8 and 15, repeated every 4 weeks as one course. The patients were requested to start the treatment within 7 days after their registration. Patients with grade 4 haematological toxicities underwent dose reduction to 800 mg/m^2. Prophylactic granulocyte-colony stimulating factor support was not allowed. Treatment was continued until disease progression, unacceptable toxicity or patient's refusal to continue the protocol treatment. Disease progression was defined in the protocol as follows: computed tomography (CT) progression (unequivocal enlargement of the primary tumour, occurrence of definitive new metastatic lesion or moderate to massive ascites) or general deterioration, which was not related to adverse drug reaction.

Response and toxicity assessment

Toxicities were evaluated at each patient visit, as per the Common Terminology Criteria for Adverse Events version 3.0. The toxicity data were collected in each course for the first six courses, and only the worst grade of toxicity per patient was recorded thereafter.

Computed tomography or magnetic resonance imaging scans were performed at the baseline and after every two courses to confirm imaging progression of the disease. Radiological tumour shrinkage of the primary tumour of the pancreas was not assessed in the current study.

Clinical benefit response was assessed using the three following measures: pain intensity (measured on a 100 mm visual analogue scale), daily analgesic consumption (measured in oral morphine-equivalent milligrams) and Karnofsky PS. They were recorded at the baseline and 6 weeks after the start of the treatment. Each patient was classified as either positive, stable or negative for each

Table 1. Classification of clinical benefit measures[a]

Pain intensity (measured on a 100 mm visual analogue scale)	
Positive	≥20 mm at the baseline and an improvement of ≥50% from the baseline
Negative	Any worsening from the baseline
Stable	Any other result
Analgesic consumption (measured in oral morphine-equivalent milligrams)	
Positive	≥10 mg equivalent to oral morphine at the baseline and a decrease of ≥50% from the baseline
Negative	Any worsening from the baseline
Stable	Any other result
Karnofsky performance status	
Positive	≤70 points at the baseline and an improvement of ≥20 points from the baseline
Negative	Any worsening of ≥20 points from the baseline
Stable	Any other result

[a]The three measures were recorded at the baseline and 6 weeks after the start of the treatment.

measure (pain intensity, daily analgesic consumption and Karnofsky PS) (Table 1). In total, the clinical benefit response was defined as at least one positive and no negative measures. Patients stable in all three measurements were judged to have stable disease, and those with at least one negative measure were classified as non-responders. Patients with no measures were regarded as not evaluable.

Serum level of carbohydrate antigen 19-9 (CA19-9) was measured at the baseline and 6–10 weeks after the start of the treatment. The CA19-9 response was assessed for patients with a serum level of ≥100 U/ml at baseline, and a decrease of ≥50% from the baseline was defined as a positive response.

Statistical considerations

The primary endpoint of this study was the %1-year survival. A sample size of 50 was required for a one-sided α of 0.20 and a β of 0.10 with an expected %1-year survival of 40% and a threshold %1-year survival rate of 25%. If the null hypothesis (%1-year survival) is rejected, the subsequent phase III trial will be designed to confirm the non-inferiority of Gem monotherapy (less-toxic testing arm) to 5-FU EBRT (standard arm).

Overall survival was determined as the time from the date of registration to the date of death owing to any cause, and was censored at the date of the last follow-up for surviving patients. Estimation of %1-year survival was performed by the Kaplan–Meier method and confidence interval (CI) was calculated with Greenwoods' formula. An exploratory analysis of time-to-treatment failure (TTF) was carried out. TTF was defined as time from the date of registration to the date of death owing to any cause or discontinuation of protocol treatment, and was censored at the date of last follow-up for a surviving patient without treatment discontinuation.

The analysis were carried out with the SAS release 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Characteristics

A total of 50 patients from 14 institutions were registered. Patient characteristics are shown in Table 2. Although the protocol allowed enrolment of patients with PS 2 into the study, all the patients were generally in good condition.

Toxicity

The major grade 3–4 adverse events were neutropaenia (62%), leucopaenia (32%), thrombocytopaenia (18%), fatigue (12%), infection-biliary tree (10%), anorexia (8%) and nausea (6%). Haematological toxicity was mostly transient and there was no episode of infection with grade 3–4 neutropaenia (Table 3). Severe adverse events were recorded in three patients (6%), i.e. grade 4 serum amylase elevation in two and grade 4 alanine aminotransferase elevation in the other one. The severe adverse events of the three patients were transient and recovered with non-invasive treatment. They were judged to be related to

Table 2. Patient characteristics

Sex	Male/female	35/15
Age	median (range)	67.5 (45–80)
ECOG performance status	0/1/2	30/20/0
Tumour location	Head/body	26/24
Histology	Adenocarcinoma/ adenosquamous carcinoma	50/0
Arterial encasement		
Celiac axis	Present/absent	32/18
Superior mesenteric artery	Present/absent	45/5
Staging computed tomography	Present/absent	50/0
Staging magnetic resonance imaging	Present/absent	19/31
Regional lymph node metastasis		
	Superior	5
	Inferior	5
	Anterior	1
	Posterior	5
	Splenic	0
	Celiac	1
	Absent	37
Distant metastasis	Present/absent	0/50

Table 3. Adverse events after gemcitabine monotherapy in locally advanced pancreatic carcinoma

Adverse event, short name	G2	G3	G4	%G3-4	%G4
Leukocytes	22	16	0	32	0
Haemoglobin	22	4	2	12	4
Platelet	12	9	0	18	0
Neutrophils	10	29	2	62	4
Albumin	7	0	–	0	–
Total bilirubin	3	3	0	6	0
Aspartate aminotransferase	8	9	0	18	0
Alanine aminotransferase	15	6	1	14	2
Hyponatraemia	–	2	0	4	0
Hyperkalaemia	5	1	0	2	0
Hypocalcaemia	2	0	0	0	0
Hypercalcaemia	0	1	0	2	0
Fatigue	9	6	0	12	0
Fever (in the absence of neutropaenia)	2	1	0	2	0
Anorexia	6	4	0	8	0
Constipation	10	2	0	4	0
Diarrhoea	5	2	0	4	0
Nausea	6	3	0	6	0
Vomiting	4	2	0	4	0
Haemorrhage, GI-duodenum	0	1	0	2	0
Infection with normal ANC–catheter	1	1	0	2	0
Infection with normal ANC–biliary tree	5	6	0	12	0
Infection with normal ANC–gall bladder	0	1	0	2	0
Infection with normal ANC–lung	1	1	0	2	0

GI, gastrointestinal; ANC, absolute neutrophil count.

disease progression (obstruction of pancreatic duct or biliary tract owing to primary tumour enlargement), and not to be related to the treatment.

CA19-9 and Clinical Benefit Response

A baseline CA 19-9 level of $\geq$100 U/ml was documented in 40 of the 50 patients. Of the 40, 15 (37.5%) and 21 showed positive and negative CA 19-9 responses, respectively, while the remaining four did not have any available data.

As for the clinical benefit response, positive, stable, negative and non-evaluable results were obtained in 6 (12.0%), 29, 13 and 2 for pain intensity, in 1 (2.0%), 31, 16 and 2 for daily analgesic consumption, and in 6 (12.0%), 29, 13 and 2 in terms of Karnofsky PS. In total, positive, stable, negative and non-evaluable clinical benefit responses were obtained in 3 (6.0%), 22, 23 and 2, respectively.

Survival

Up to the final follow-up on 23 February 2009, one patient was still receiving protocol treatment. Of the remaining 49, the reason for discontinuation of the protocol treatment was disease progression in 43, unacceptable adverse events in 2 and patient's refusal related to adverse events in 4. There were no treatment-related deaths during the study. The median TTF was 6.0 months (95% CI, 5.3–9.3 months; Fig. 1). The percentages for treatment failure at 1, 2, 3 and 4 months were 4.0, 8.0, 18.0 and 28.0%, respectively. After the discontinuation of the protocol treatment, 39 patients received various anti-cancer treatments and the remaining 10 received the best supportive care. Of the 39 treated with the second-line therapy, 32 received S-1 monotherapy ($n = 29$) or S-1 combination chemotherapy ($n = 3$).

The median overall survival was 15.0 months (95% CI, 12.7–19.4 months) with a %1-year survival of 64.0% (95% CI, 49.1–75.6%; Fig. 2), and the null hypothesis (%1-year survival $\leq$25%) was rejected (one-sided $P < 0.0001$).

DISCUSSION

LAPC is generally defined as having a surgically unresectable pancreatic tumour in the absence of clinically detectable metastases. A CT scan is the standard modality in the staging of PC; however, CT-occult metastases were found in

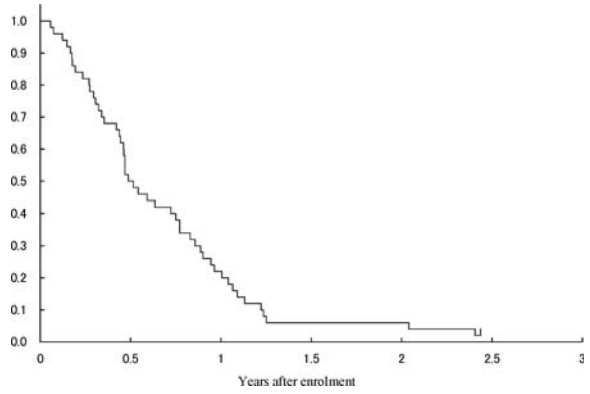

Figure 1. Time-to-treatment failure curve of 50 patients with locally advanced pancreatic cancer (PC) treated with gemcitabine monotherapy.

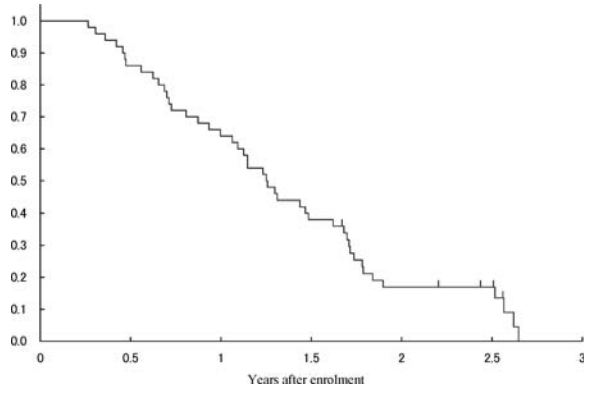

Figure 2. Overall survival curve of 50 patients with locally advanced PC treated with gemcitabine monotherapy.

6% (12) and 36% (13,14) of patients with resectable and LAPC, respectively, by surgical staging. The high incidence of distant recurrence and low %5-year survival even after curative surgery (15) may indicate that most localized PC patients have already developed minute systemic spread at the first presentation. Therefore, full systemic chemotherapy from the start of treatment is thought to be a reasonable strategy even for LAPC.

Since Gem was introduced, a lot of phase III trials between Gem and Gem combination chemotherapy have been reported for advanced PC (8–11). The subset analysis of those trials suggested that Gem chemotherapy yielded good survival outcomes, which were almost equivalent to historical survival data of 5-FU EBRT for LAPC. A previous ECOG trial (16) failed to show superiority of 5-FU EBRT over 5-FU monotherapy. In 2006, Chauffert et al. (17) reported a significant survival benefit of Gem alone compared with concurrent EBRT plus 5-FU and cisplatin. Although it should not be considered conclusive because they failed to complete because of poor recruitment, Gem monotherapy could be a good alternative treatment to chemoradiotherapy for LAPC.

Because Gem also acts as a radiosensitizer, Gem EBRT has been tested in many studies. Those studies suggested that dose reduction of Gem (18,19) and/or radiation (20), or target volume reduction of the radiation field (21) are necessary to avoid excessive toxicities. Recently, Loehrer et al. (22) reported the results of E4201, i.e. a randomized comparison between Gem and Gem EBRT. This combination employed low-dose Gem, i.e. 600 mg/m^2 weekly, and a limited target volume without a prophylactic radiation field. Gem EBRT was quite toxic, but significantly superior in long-term survival after 8–9 months when compared with Gem alone. However, this should not be considered conclusive for the same reason as the Chauffert's study (18). Although there have been no standard regimens with strong evidence for LAPC treatment (23,24), the consensus of referential treatment in phase III trials is thought to be Gem alone.

As expected, Gem toxicities were generally mild in the current study. All three severe adverse events were related to tumour progression, and there were no febrile neutropaenia. The Gem toxicity profile for patients with LAPC seemed to be equivalent to other studies (5,8–11), which include advanced (approximately 70–80% metastatic) PC patients. On the other hand, survival data (median: 15 months) was beyond our expectations (10–11 months). A possible reason was good patient selection, i.e. good PS and relatively small tumour volume. As we referred E4201 (22) at the time of planning the current study, patient eligibility criteria might be comparable to E4201. However, there was not a little discrepancy about survival between both studies. Although the exact reason of relatively poor survival in a GEM arm (9.2 months) of E4201 was unknown, small number of patients ($n = 35$) might make a bias in some prognostic background factors.

At the planning of the current study, we planned the subsequent phase III trial, where we would compare 5-FU-EBRT as the standard arm and Gem monotherapy as the testing arm. However, 5-FU EBRT has no longer been used even in our group institution, because the previous ECOG trial (16) and the study of Chauffert et al. (17) failed to show a good survival of chemoradiotherapy and the survival data of the current study was far better than our expectation. Nowadays, Gem monotherapy has come to be regarded as the provisional standard therapy even in our group, and we are now planning another phase III trial as we mention in the next paragraph.

As a new treatment strategy for LAPC, induction chemotherapy followed by chemoradiotherapy has received attention based on some recent studies (25–29). The role of induction chemotherapy is to spare patients with rapidly progressive disease from potentially toxic radiotherapy. Such a therapeutic strategy may help to define the subset of patients who can benefit from chemoradiotherapy. We are now planning a post JCOG0506 (the current study), i.e. a randomized phase II trial of concurrent chemoradiotherapy with a novel orally administered fluorouracil, S-1, with or without induction Gem. Toxicities of EBRT plus full-dose S-1 therapy are tolerable (30,31) and pre-final analysis of a phase II study indicates promising %1-year survival over 70% (unpublished data). S-1 EBRT or Gem induction followed by S-1 EBRT is a candidate for a new investigation arm of our next step phase III study, where Gem monotherapy will be a referential arm and outcomes in the current study will be useful in statistical considerations.

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Conflict of interest statement

None declared.

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APPENDIX

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The following institutions and investigators participated in the trial: Hokkaido University Hospital (Yoshito Komatsu and Masahiro Asaka), Aomori Prefectural Central Hospital (Satoshi Saito), Iwate Prefectural Central Hospital (Akihiko Murakami and Hiroshi Higuchi), Yamagata Prefectural Central Hospital (Hiroshi Saito), Ibaraki Prefectural Central Hospital (Kenji Amagai and Hisanao

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