A Phase I/II Study of Fixed-dose-rate Gemcitabine and S-1 with Concurrent Radiotherapy for Locally Advanced Pancreatic Cancer

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Keyward: pancreatic cancer, gemcitabine, S-1, chemoradiotherapy, radiosensitizer

Running title: FDR-gem plus S-1 with RT for pancreatic cancer

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Abstract

Purpose: This study was conducted to identify the maximum-tolerated dose (MTD) of fixed-dose-rate gemcitabine (FDR-gem) administered concurrently with S-1 and radical radiation for locally advanced pancreatic cancer (LAPC) and to provide efficacy and safety data.

Methods: Patients with unresectable pancreatic cancer confined to the pancreatic region were treated with FDR-gem (300-400mg/m^2, 5mg/m^2/min) on days 1, 8, 22, 29 and 60mg/m^2 of S-1 orally on days 1-14, 22-35. A total radiation dose of 50.4 Gy (1.8 Gy/day, 28fractions) was delivered concurrently.

Results: Twenty-five patients were enrolled; all were evaluable for toxicity assessment. In phase I, eight patients were treated in sequential cohorts of three to five patients per dose level. The MTD was reached at level 2, and dose-limiting toxicities were neutropenia and thrombocytopenia. The recommended doses were 300mg/m^2 of gemcitabine and 60mg/m^2 of S-1 daily. The overall response rate was 25% and disease control rate (partial response plus stable disease) was 92%. The progression-free survival was 11.0 months. The median overall survival and 1-year survival rate were 16.0 months and 73%, respectively.

Conclusion: The combination of FDR-gem and S-1 with radiation is a feasible regimen that shows favorable antitumor activity with an acceptable safety profile in patients with LAPC.

Introduction

Pancreatic cancer (PC) is one of the most fatal malignancies worldwide [1]. Despite recent improvements in diagnostic techniques, PC is diagnosed at an advanced stage in most patients. Among these patients, roughly one-third is diagnosed with locally advanced disease [2]. The combination of radiotherapy (RT) and infusional 5FU has been considered by many as the standard of care. The pivotal trials have shown a survival benefit of chemoradiotherapy (CRT) relative to RT or chemotherapy alone [3]. A meta-analysis has also confirmed the significant survival advantage of CRT [4]. However, overall survival (OS) of CRT with 5FU is approximately 10 months, indicating that the prognosis remains poor.

Recently, gemcitabine has been used in some studies because of its systemic activity in pancreatic cancer and potent radiosensitizing properties. A number of phase I – II trials have combined gemcitabine with RT [5-9]. A phase III trial showed improved overall survival in patients with locally advanced pancreatic cancer (LAPC) treated with gemcitabine plus radiotherapy compared to gemcitabine alone [10]. In addition, gemcitabine administration via infusion at a fixed dose rate of 10mg/m^2/min (FDR-gem) has been found to increase accumulation of 2',2'-difluorodeoxycytidine

5’-triphosphate (dFdCTP), an active gemcitabine metabolite, compared with gemcitabine at a standard dose rate infusion over a period of 30 min. Several studies have reported that FDR-gem would be a more effective radiation sensitizer than standard injection of gemcitabine based on the higher levels of dFdCTP [11,12].

S-1 is an oral fluoropyrimidine derivative that is designed to improve the antitumor activity of 5FU while reducing gastrointestinal toxicity. In S-1, tegafur is combined with two 5FU modulators, 5-chloro-2,4-dihydroxypyridine (gimeracil) and potassium oxonate (oteracil) in a 1:0.4:1 molar concentration ratio. Gimeracil in S-1 also acts as a radiosensitizer, and preclinical and clinical studies have demonstrated the radiosensitizing potency of S-1 [13]. S-1 has been combined with RT for LAPC in several trials [14-16]. In a phase III trial on patients with advanced disease, the combination chemotherapy with S-1 and gemcitabine has also shown a higher response rate and more favorable progression-free survival (PFS) than monotherapy with S-1 or gemcitabine [17].

Given the synergy of gemcitabine and S-1, and their respective radiosensitization effects, we conducted this phase I/II study to determine the maximum tolerated dose (MTD) of FDR-gem combined with S-1 and radical RT and to evaluate the toxicity and efficacy in patients with LAPC.

Materials and methods

Eligibility

Patients diagnosed with LAPC by histopathological or cytological confirmation were enrolled to this study. Eligibility criteria were age ≥ 20 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; no evidence of distant metastasis; adequate oral intake; no earlier treatment for pancreatic cancer; adequate hematological function (hemoglobin ≥ 10 g/dl, leucocytes ≥ 3,000/mm^3, platelets ≥ 100,000/mm^3); adequate hepatic function (serum total bilirubin ≤ 2.0 mg/dl and serum transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) ≤ 2.5 times upper normal limit (UNL); adequate renal function (serum creatinine ≤ 1.0 mg/dl); written informed consent. The exclusion criteria were watery diarrhea; pleural effusion or ascites; active infection; active gastroduodenal ulcer; severe complications such as heart disease or renal disease; mental disorder; history of drug hypersensitivity; active concomitant malignancy; pregnant and lactating females. Multi-detector row computed tomography (CT) of the abdomen and chest X-ray were performed for pretreatment

staging in order to assess the local extension of the tumor and exclude the presence of distant metastasis. The CT-based criteria for tumor nonresectability included tumor encasement of the celiac trunk, superior mesenteric artery or bilateral invasion of the portal vein. All patients with obstructive jaundice underwent endoscopic retrograde biliary drainage before treatment. This study was approved by the institutional review boards of the Tokushima University Hospital and Hokkaido Cancer Center and conducted in accordance with the Declaration of Helsinki Principles.

Treatment schedule

Figure 1 shows a general schema of the trial. S-1 was administered orally to all patients at a dose of 60mg/m^2/day on days 1 to 14 and days 22 to 35. Gemcitabine was administered by fixed-dose-rate (FDR) intravenous infusion of 5mg/m^2/min on days 1, 8, 22, and 29. The S-1 dosage was set according to the protocol of the previous study of S-1 and gemcitabine [17]. Gemcitabine doses were planned to be escalated to 300, 400, or 500mg/m^2 in subsequent cohorts. Radiotherapy was initiated on day 1 of the study using a 10-MV photon beam by a linear accelerator (PRIMUS High-Energy; Toshiba Medical Systems Co., Tochigi, Japan) with a four-field technique with each patient in

the supine position. A fractional daily dose of 1.8 Gy (5 days/week) at an isocenter, up to a total dose of 50.4 Gy, was prescribed. Treatment planning was performed using a CT simulator (Asteion, Toshiba Medical Systems Co., Tokyo, Japan) for all patients. CT scan was performed with the total breathing phase scan (slow scan) in the free-breathing state. CT images were reconstructed with a 2 mm slice thickness. Gross tumor volume (GTV) was defined as the primary tumor and involved lymph nodes visible on CT images. The clinical target volume (CTV) encompassed the GTV with 0.5 cm isotropic margin and the planning target volume was defined as CTV with an isotropic margin of 0.8 cm for daily patient set-up variation. All dose distributions were computed with the Convolution Algorithm implemented in the Xio planning system (CMS Inc., MO, USA). No prophylactic nodal irradiation was performed.

Study design

This study was an open-label, multi-center, single-arm phase I/II study performed in two steps. For the dose-escalation phase (step 1), the primary endpoint was to establish the recommended phase II dose. At least three patients were enrolled at each dosage level. If dose limiting toxicity (DLT) was observed in one of the initial

three patients, up to three additional patients were enrolled at the same dose level. The highest dosage level at which more than two DLT cases occurred was considered the MTD. The recommended dose (RD) for the phase II part was defined as the dose level one level below the MTD. DLT was defined as grade 4 neutropenia continuing for more than 3 days or febrile neutropenia; grade 4 thrombocytopenia; grade 3 or 4 non-hematological toxicity; any toxicity that necessitated a treatment delay of more than 15 days. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. In step 2, the effect of this combination therapy on the objective tumor response was evaluated. Tumor response was evaluated at the completion of CRT and every 8 weeks thereafter until tumor progression, according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 [18]. The severity of adverse events, PFS and OS were investigated as secondary objectives.

Results

Patient characteristics

Twenty-five patients were enrolled in this study between September 2008 and

February 2013. In phase I of the study, eight patients were treated in sequential cohorts at each dose level. After the MTD was defined, 17 additional patients were enrolled to confirm the suitability of this RD in phase II of this study. The characteristics of the patients are listed in Table 1. Patients had a median age of 68 years (range: 47-81 years). ECOG performance status was 0 in 12 patients (48%), 1 in 12 patients (48%), and 2 in 1 patient (4%). The median maximum tumor size was 42 mm (range: 24-86 mm). The causes of the unresectable pancreatic cancers were invasion of the celiac trunk in nine patients, invasion of the superior mesenteric artery in six patients, invasion of both regions in five patients and invasion of the bilateral portal vein in five patients.

DLTs and RD level

Eight patients were enrolled in phase I of the study and were administered two dose levels of gemcitabine combined with 60 mg/m^2/day of S-1 and concurrent radiotherapy (50.4Gy). At the starting dose of gemcitabine (300 mg/m^2), no DLT was observed in the three patients. At the dose level 2 of gemcitabine (400 mg/m^2), one of the first three patients had grade 4 thrombocytopenia, thus an additional three patients would have been recruited for the same level. However, the first two of the additional

patients experienced DLTs. One of these patients developed grade 4 neutropenia continuing for more than 3 days, and the other patient required suspension of treatment for more than 15 days due to continuing grade 3 thrombocytopenia. Therefore, this dose level was identified as the MTD for this study. We concluded that dose level 1 should be considered as the RD for further study.

Toxicity

All 25 patients were evaluated for toxicity. Table 2 summarizes the treatment-related clinical adverse events in the patients treated at each dose level throughout the treatment period. Major treatment toxicities included myelosuppression. Grade 3/4 neutropenia was recorded in 12 of 25 patients (48%). Of the 20 patients receiving the RD, eight patients (40%) experienced grade 3/4 neutropenia. Grade 3/4 thrombocytopenia was observed in five of 25 patients (20%), with three patients (15%) presenting with grade 3/4 thrombocytopenia at RD. Grade 1/2 anemia was detected in 14 patients (54%) with none of them experiencing grade 3/4 toxicity. Non-hematological adverse events were manageable. Acute grade 3 or higher non-hematological toxicities experienced during the protocol were observed in only

12% of the patients and were mild. As a late toxicity, duodenal ulcer was observed 4 months after treatment in one patient at the RD level. In the phase II part, one patient died from septic shock. This patient experienced high fever and abdominal pain 35 days after starting chemoradiotherapy. *Klebsiella pneumonia* was detected in a blood culture, but a CT scan showed no specific change. Although antibiotics were administered, the patient did not improve. A definitive cause of sepsis could not be determined since autopsy was denied. Other treatment-associated symptoms were infrequent or negligible.

Efficacy

Twenty-four patients were available for response assessment, including eight in the phase I part and 16 in the phase II part. Five patients achieved a partial response and one patient experienced complete response, giving an overall response rate of 25%. Nearly all of the remaining patients experienced stable disease as their best response to therapy, and only two patients had progressive disease. The overall disease control rate was 92% (22/24). At the time of this report, the progression-free survival (PFS) and the median overall survival time (MST) were 11.0 months and 16.0 months, respectively (Figure 2), and the 1- and 2-year overall survival rates were 73% and 20%, respectively.

We compared the patients with arterial-involved tumor (n = 20) with the patients with portal-involved tumor (n = 5). However, there is no significant difference between the PFS and OS of the two groups.

Discussion

In this trial we established that combination therapy with FDR-gem and S-1 can be administered safely with concurrent radical RT. The dose of 300 mg/m^2 of FDR-gem and 60 mg/m^2/day of S-1 was determined to be the RD. The regimen was overall well tolerated, and the toxicity profile concurs with chemoradiotherapy studies using either agent alone [16,10]. The DLT associated with this regimen was hematological toxicity, consisting of neutropenia and thrombocytopenia. However, the overall toxicity profile in our study was almost identical to those of previous gemcitabine-based chemoradiotherapy regimens [5-10]. In the randomized trial which compared gemcitabine plus RT and gemcitabine monotherapy, the most frequently reported grade 3 and 4 toxicities of gemcitabine plus RT were neutropenia (38%) and GI toxicities (nausea: 28% and anorexia: 17%) [10], which were similar to those of the present study.

Concurrent radiotherapy with S-1 or gemcitabine, respectively, produced very favorable results, with mild toxicities, in patient with LAPC [5-10,14-16]. Moreover, the combination chemotherapy with gemcitabine and S-1 reportedly has higher anticancer activity (objective response rate 29.3%) compared with either treatment alone and a favorable median PFS (5.7 months) in patients with advanced disease [17]. Although the OS did not differ significantly from that in gemcitabine monotherapy, the gemcitabine and S-1 combination therapy showed a favorable hazard ratio for OS in patients with LAPC in the subgroup analyses of the phase III trial. Our data suggested that chemoradiotherapy using gemcitabine and S-1 concurrently with radiation could be a better choice for LAPC. A previous study used combination therapy with gemcitabine, S-1, and concurrent radiation as neoadjuvant therapy in patient with resectable PC [19]. It concluded that this combination therapy was feasible for patients with resectable PC, and 90% (19/21) of enrolled patients successfully underwent surgical resection without any severe postoperative complications. However, applying this combination CRT to unresectable LAPC has not yet been reported. Moreover, we utilized FDR-gem with S-1 and radical RT in the present study because several studies have reported that FDR-gem would be a more effective radiation sensitizer than bolus injection of gemcitabine based on the higher levels of 2’,2’-difluorodeoxycytidine 5’-triphosphate (dFdCTP), an active

gemcitabine metabolite [11,12].

Our study has demonstrated an overall response rate of 25%, 11.0 months of PFS, and 16.0 months of OS. The response rates of previously reported CRT regimens with gemcitabine or S-1 alone have ranged from 12% to 41%, and the median PFS have ranged from 4.4 to 9.7 months. The present concurrent CRT appears to have a favorable treatment efficacy in LAPC as compared to those in the previous reports. In LAPC patients receiving chemoradiotherapy it is important to enhance local control while simultaneously reduce the risk for distant metastases. In the present trial, the intensive combination chemotherapy with FDR-gem plus S-1 and standard-dose radiotherapy (50.4 Gy/28 fractions) was easy to administer and had a tolerable toxicity profile. Therefore, this regimen might have the dual benefit of counteracting systemic tumor spread as well as acting as a potent radiosensitizer for local control.

In conclusion, this phase I/II study has demonstrated the tolerability to combined chemotherapy with FDR-gem and S-1 with radical RT (50.4 Gy) and has shown evidence of antitumor activity.

Conflict of interest

Tetsuji Takayama has received honoraria from Taiho Pharmaceutical Co. Ltd.

All other authors declare that they have no conflict of interest relevant to this study.

References

1. Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics, 2010. CA Cancer J Clin 60 (5):277-300. doi:10.3322/caac.20073

2. Yeo TP, Hruban RH, Leach SD, Wilentz RE, Sohn TA, Kern SE, Iacobuzio-Donahue CA, Maitra A, Goggins M, Canto MI, Abrams RA, Laheru D, Jaffee EM, Hidalgo M, Yeo CJ (2002) Pancreatic cancer. Curr Probl Cancer 26 (4):176-275

3. Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, Schutt AJ, Weiland LH, Childs DS, Holbrook MA, Lavin PT, Livstone E, Spiro H, Knowlton A, Kalser M, Barkin J, Lessner H, Mann-Kaplan R, Ramming K, Douglas HO, Thomas P, Nave H, Bateman J, Lokich J, Brooks J, Chaffey J, Corson JM, Zamcheck N, Novak JW (1981) Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 48 (8):1705-1710

4. Sultana A, Tudur Smith C, Cunningham D, Starling N, Tait D, Neoptolemos JP, Ghaneh P (2007) Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. Br J Cancer 96 (8):1183-1190. doi:10.1038/sj.bjc.6603719

5. Wolff RA, Evans DB, Gravel DM, Lenzi R, Pisters PW, Lee JE, Janjan NA, Charnsangavej C, Abbruzzese JL (2001) Phase I trial of gemcitabine combined with radiation for the treatment of locally advanced pancreatic adenocarcinoma. Clin Cancer Res 7 (8):2246-2253

6. Pipas JM, Mitchell SE, Barth RJ, Vera-Gimon R, Rathmann J, Meyer LP, Wagman RS, Lewis LD, McDonnell C, Colacchio TA, Perez RP (2001) Phase I study of twice-weekly gemcitabine and concomitant external-beam radiotherapy in patients with adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys 50 (5):1317-1322

7. Epelbaum R, Rosenblatt E, Nasrallah S, Faraggi D, Gaitini D, Mizrahi S, Kuten A (2002) Phase II study of gemcitabine combined with radiation therapy in patients with localized, unresectable pancreatic cancer. J Surg Oncol 81 (3):138-143. doi:10.1002/jso.10159

8. Okusaka T, Ito Y, Ueno H, Ikeda M, Takezako Y, Morizane C, Kagami Y, Ikeda H (2004) Phase II study of radiotherapy combined with gemcitabine for locally advanced pancreatic

cancer. Br J Cancer 91 (4):673-677. doi:10.1038/sj.bjc.6602001
9. Brade A, Brierley J, Oza A, Gallinger S, Cummings B, Maclean M, Pond GR, Hedley D, Wong S, Townsley C, Brezden-Masley C, Moore M (2007) Concurrent gemcitabine and radiotherapy with and without neoadjuvant gemcitabine for locally advanced unresectable or resected pancreatic cancer: a phase I-II study. Int J Radiat Oncol Biol Phys 67 (4):1027-1036. doi:10.1016/j.ijrobp.2006.10.015
10. Loehrer PJ, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, Flynn P, Ramanathan RK, Crane CH, Alberts SR, Benson AB (2011) Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol 29 (31):4105-4112. doi:10.1200/JCO.2011.34.8904
11. Morgan M, El Shaikh MA, Abu-Isa E, Davis MA, Lawrence TS (2008) Radiosensitization by gemcitabine fixed-dose-rate infusion versus bolus injection in a pancreatic cancer model. Transl Oncol 1 (1):44-49
12. Ben-Josef E, Schipper M, Francis IR, Hadley S, Ten-Haken R, Lawrence T, Normolle D, Simeone DM, Sonnenday C, Abrams R, Leslie W, Khan G, Zalupski MM (2012) A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 84 (5):1166-1171. doi:10.1016/j.ijrobp.2012.02.051
13. Fukushima M, Sakamoto K, Sakata M, Nakagawa F, Saito H, Sakata Y (2010) Gimeracil, a component of S-1, may enhance the antitumor activity of X-ray irradiation in human cancer xenograft models in vivo. Oncol Rep 24 (5):1307-1313
14. Sudo K, Yamaguchi T, Ishihara T, Nakamura K, Hara T, Denda T, Tawada K, Imagumbai T, Araki H, Sakai M, Hatano K, Kawakami H, Uno T, Ito H, Yokosuka O (2011) Phase II study of oral S-1 and concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 80 (1):119-125. doi:10.1016/j.ijrobp.2010.01.027
15. Shinchi H, Maemura K, Noma H, Mataki Y, Aikou T, Takao S (2007) Phase-I trial of oral fluoropyrimidine anticancer agent (S-1) with concurrent radiotherapy in patients with unresectable pancreatic cancer. Br J Cancer 96 (9):1353-1357. doi:10.1038/sj.bjc.6603735
16. Ikeda M, Ioka T, Ito Y, Yonemoto N, Nagase M, Yamao K, Miyakawa H, Ishii H, Furuse J, Sato K, Sato T, Okusaka T (2013) A multicenter phase II trial of S-1 with concurrent radiation therapy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 85 (1):163-169. doi:10.1016/j.ijrobp.2012.03.059
17. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, Fukutomi A, Sugimori K, Baba H, Yamao K, Shimamura T, Sho M, Kitano M, Cheng AL, Mizumoto K, Chen JS, Furuse J, Funakoshi A, Hatori T, Yamaguchi T, Egawa S, Sato A, Ohashi Y, Okusaka T,

Tanaka M (2013) Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol 31 (13):1640-1648. doi:10.1200/JCO.2012.43.3680

18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45 (2):228-247. doi:10.1016/j.ejca.2008.10.026

19. Eguchi H, Nagano H, Kobayashi S, Kawamoto K, Wada H, Hama N, Tomimaru Y, Akita H, Sakai D, Satoh T, Kudo T, Isohashi F, Mori M, Doki Y (2014) A phase I trial of combination therapy using gemcitabine and S-1 concurrent with full-dose radiation for resectable pancreatic cancer. Cancer Chemother Pharmacol 73 (2):309-315. doi:10.1007/s00280-013-2357-9

Table. 1: Patient charactaristics

Caractaristics	No. of patient
Gender	
Men	11
Women	14
Age (years)	
Median (range)	68 〔47-81〕
ECOG performance status	
0	12
1	12
2	1
Tumor location	
Head	11
Body/Tail	14
Involved vessels	
Celiac trank	9
Superior mesenteric artery	6
Both of above	5
Portal vein	5
Tumor size,mm	
Median(range)	42 〔24-86〕
UICC-TNM	
ⅡA	3
ⅡB	2
Ⅲ	20

Table. 2 Treatment related adverse events

	Phase I								Phase II					All patients (n=25)				
Dose level (gemcitabin)	1 (300mg/m2, n=3)				2 (400mg/m2, n=5)				300mg/m2, n=17									
Toxicity/grade	G1/2	G3	G4	≥G3 (%)	G1/2	G3	G4	≥G3 (%)	G1/2	G3	G4	G5	≥G3 (%)	G1/2	G3	G4	G5	≥G3 (%)
Neutropenia	2	1	0	33	1	3	1	80	9	5	2	0	41	12	9	3	0	48
Anemia	1	0	0	0	4	0	0	0	9	0	0	0	0	14	0	0	0	0
Thrombocytopenia	1	0	0	0	3	1	1	40	8	3	0	0	18	12	4	1	0	20
Nausea	3	0	0	0	2	0	0	0	8	1	0	0	6	13	1	0	0	4
Fatigue	2	0	0	0	3	0	0	0	9	0	0	0	0	14	0	0	0	0
Anorexia	2	0	0	0	4	0	0	0	8	3	0	0	18	14	3	0	0	12
Diarrhea	0	0	0	0	1	0	0	0	4	0	0	0	0	5	0	0	0	0
Mucogitis	0	0	0	0	1	0	0	0	4	0	0	0	0	5	0	0	0	0
Duodenal ulcer	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0
Sepsis	-	-	0	0	-	-	0	0	-	-	0	1	6	-	-	0	1	4

Fig.1: Treatment schedule

Total 50.4Gy (1.8Gy/day, 5times/week, 28 fractions) of radiation was administered along with concurrent intravenous infusion of gemcitabine on days 1,8, 22, and 29 and S-1 orally on days 1-5, 8-12, 22-26, and 29-33.

Fig.2: Kaplan-Meier curves of progression free survival (A) and overall survival (B) for 25 patients.

Fig.1

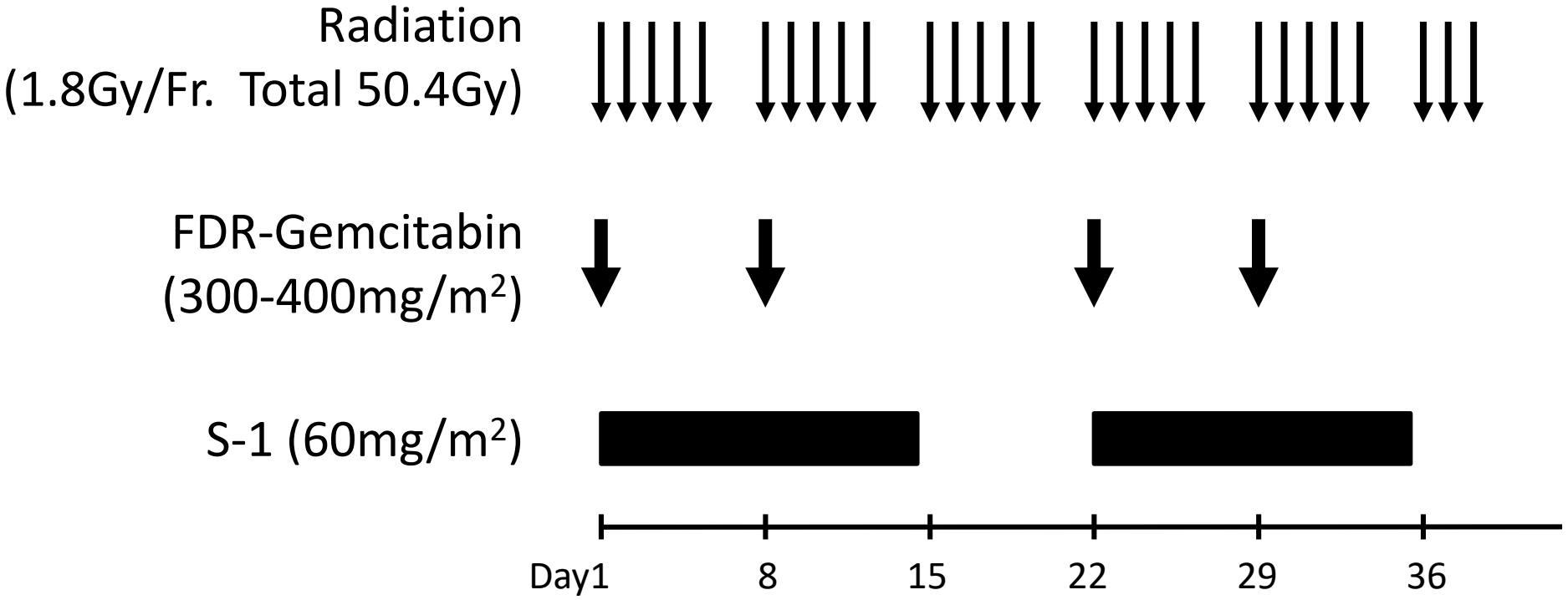
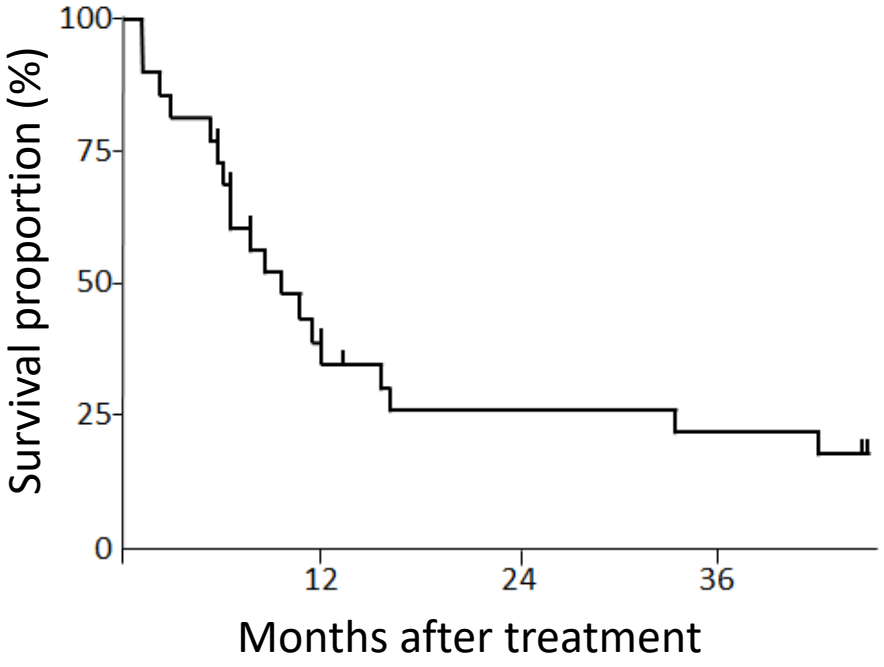
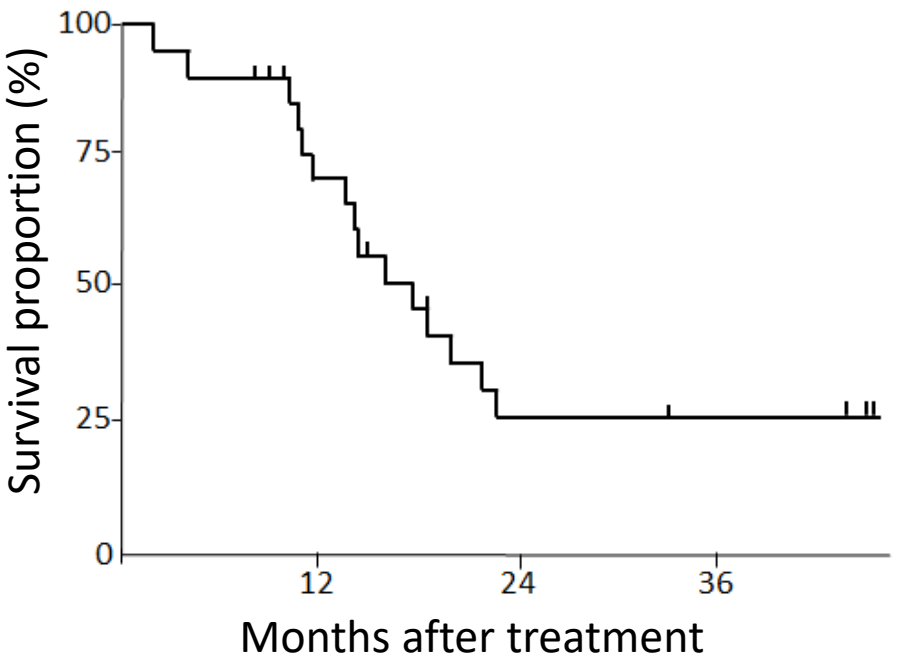

Radiation
(1.8Gy/Fr. Total 50.4Gy)
FDR-Gemcitabin
(300-400mg/m2)
S-1 (60mg/m2)
Day1
8
15
22
29
36

Fig. 2

A


Survival proportion (%)
100
75
50
25
0
12
24
36
Months after treatment

B


Survival proportion (%)
100
75
50
25
0
12
24
36
Months after treatment