Combination Chemotherapy with Low-dose 5-FU, Cisplatin, and Gemcitabine for Gemcitabine-Refractory Pancreatic Cancer

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Background: No single agent or combination therapy for advanced pancreatic cancer has been reported superior to single-agent GEM, and an effective second-line chemotherapy option is needed for patients who are resistant to first-line GEM therapy.

Methods: We analyzed six patients who had disease progression following first-line gemcitabine therapy. Patients received second-line chemotherapy with low dose cisplatin, 5-fluorouracul or S-1, and gemcitabine every 21 days.

Results: Two patients showed a partial response (33.3 %) and two showed stable disease. Four patients (66.6 %) showed a prolonged survival time with partial responses or stable disease. Median survival times were 7 and 11 months from the start of second-line therapy and the start of first-line gemcitabine therapy, respectively. In addition, all patients reported relief from pain and had a favorable performance status. The major toxicities of leucopenia, stomatitis, and diarrhea were found in one patient each.

Conclusion: This second-line chemotherapy regimen is an effective option for patients with gemcitabine-resistant pancreatic cancer. *Shinshu Med J 57 : 247—253, 2009*

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Key words: second-line chemotherapy, pancreatic cancer, 5-FU, Cisplatin, Gemcitabine

I Introduction

Since the first report of successful gemcitabine (GEM) treatment for the advanced pancreatic cancer in 1997[1)], single-agent GEM has been widely used as a standard regimen for unresectable disease. Because no single agent or combination therapy has been reported superior to single-agent GEM, the search for strategies that are more effective continues. In addition, an effective second-line chemotherapy option is needed for those patients who are resistant to first-line GEM therapy. In general, the effects of first-line GEM expire three to five months after the start of therapy, so almost all patients need second-line therapy. Combination chemotherapy using each anti-cancer agent that has been reported to be at least somewhat effective as a single agent has shown promise[2)–5)]. We found 2 Japanese case reports as abstracts, which suggested that a low-dose combination of cisplatin, 5-fluorouracil (5-FU), S-1 and gemcitabine was effective in advanced pancreatic cancer resistant to first-line gemcitabine therapy (Shimizu A, et al. The Journal of Japan Society for Cancer Therapy 38 : 763, 2003, and Hasebe O, et al. Suizou 20 : 308, 2005). Accordingly, we investigated the efficacy of combination chemotherapy including low-dose cisplatin[1)], 5-FU[3)], S-1[4)5)], and low-dose GEM as a second-line chemotherapy for patients with GEM-resistant pancreatic cancer.

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II Materials and Methods

A Patients

Between January 2003 and December 2006, 30 patients with pancreatic cancer were treated with first-line GEM in our hospital and in affiliated hospitals. We analyzed six of these patients who met the following criteria : (1) resistant to first-line GEM therapy, (2) no history of surgical treatment, (3) no chemotherapeutic history other than GEM, and (4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-3. The other 24 patients were excluded from the present study because of poor condition (15 patients) and the application for other regimen (9 patients). According to the World Health Organization criteria, progressive disease (PD) is defined by the failure to respond to first-line GEM chemotherapy. Of the six patients, three were men and three were women, the mean age of the group was 55.3 years (range, 43-72 years), and the mean duration of their first-line GEM therapy was 6.7 months (range, 2-15 months ; Table 1).

B Second-line chemotherapy regimen

The second-line chemotherapy regimen was constructed based on the two previous case reports mentioned above. The regimen comprised cisplatin 5 mg/day/body (days 1-5 and 8-12), 5-FU 500 mg/day/body (days 1-5 and 8-12), and GEM 200 mg/day/body (days 1 and 8) in two 21-day courses. Patients were hospitalized during the first two courses to ensure that they could tolerate this regimen and for nightly chronomodulation. The patients were then discharged and treated as outpatients with the following protocol : cisplatin 10 mg/day/body (days 1 and 8), S-1 or 5'-deoxy-5-fluorouridine (5'-DFUR) 4 cap/day/body (days 1-14), and GEM 200 mg/day/body (days 1 and 8) every 21 days. Full doses were given to patients with grade 0-2 toxicities ; however, for patients with grade 3-4 toxicities or probable PD, chemotherapy was stopped.

C End points

The primary end points were therapeutic response and survival. Tumor size was assessed by abdominal computed tomography (CT) according to the Japan Society for Cancer Therapy Criteria[6], which are similar to the World Health Organization criteria. Therapeutic response was also assessed by the Response Evaluation Criteria in Solid Tumors (RECIST)[7]. Briefly, complete response (CR) was defined as the complete disappearance of all measurable and assessable lesions for at least four weeks ; partial response (PR) was defined as a >50 % reduction in the sum of the values of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks ; stable disease (SD) was defined as a <50 % reduction or a <25 % increase in the sum of the values of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks ; progressive disease (PD) was defined as a >25 % increase or the appearance of new lesions. PS was scored from 0-4 according to ECOG criteria. Pain was graded from 0 (none) to 4 (very strong), and the effect of chemotherapy on pain was evaluated. Overall survival was measured from the initiation of first-line GEM and from the initiation of second-line chemotherapy until death or last follow-up visit. Physical examination, complete blood cell

Table 1 Patient and tumor characteristics at enrollment

Pt.	Age	Gender	Primary site	Protocol and Duration of first-line GEM (mg/body or mg/m^2,months)	Response to first-line GEM	PS	Pain	Liver Mets.	Ascites
1	53	M	Pb	1000 mg/body , 8	PR	1	++	+++	++
2	55	F	Ph	1000 mg/body , 15	SD	1	+++	−*	−
3	43	M	Ph	1000 mg/body , 13	PR	2	−	+++	−
4	53	F	Ph	1000 mg/body , 5	SD	2	++	+++	−
5	72	F	Ph	1000 mg/body , 2	PD	1	++	+++	++
6	56	M	Pt	1000 mg/body , 2	PD	3	+++	+++	−

*Lymph node positive.

counts, blood tests, and urinalysis were assessed at least biweekly. Chest radiography, CT, and measurements of serum carcino-embrionic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were performed once a month.

D Statistical Analysis

Statistical analysis of changes in pain, PS, and CA19-9 was performed using the Wilcoxon Signed Rank Test.

Ⅲ Results

Patient characteristics at enrollment are presented in Table 1. Three patients had PRs to first-line GEM, 1 had SD, and 2 had PD. Five patients complained of moderate or severe pain, 5 patients had liver metastasis, and 2 patients had ascites due to peritonitis carcinomatosa.

The objective tumor responses to second-line chemotherapy are shown in Table 2. Two patients had an objective PR and the overall response rate was 33.3 %. Two patients had SD. The median survival times (MST) were 6.5 months (range, 3-23 months) when measured from the start of second-line chemotherapy and 15.5 months (range, 5-33 months) when measured from the start of first-line chemotherapy.

Four months after the initiation of second-line therapy, 5 patients (83 %) reported relief from pain and 1 (17 %) reported no change ; the differences were significant (Table 3). Performance status was improved or maintained in all patients but the changes were not significant (Table 3). Serum CA19-9 decreased in 5 patients (86 %) during three months of second-line therapy, but the change was not significant (Table 3). Serum CA19-9 increased in three patients (43 %) or was maintained in three patients (43 %) after four months.

Ascites related to peritonitis carcinomatosa was found in two patients and improved in both with combination chemotherapy (100 %). Serial image findings of a representative case (patient 3) are shown in Figure 1 ; those prior to first-line GEM are shown in figure 1A and 1D, those prior to second-line low-dose combination therapy (15 months after

Table 2 Effects of second-line combination chemotherapy

Pt.	Regimen	Duration of combination therapy (months)	Response	Adverse effect	Survival time since initiation of first-line therapy (months)	Outcome
1	Cisplatin, GEM, 5-FU → S-1	23	PR	Grade 2	31	alive
2	Cisplatin, GEM, 5-FU → S-1	18	SD	Grade 2	33	alive
3	Cisplatin, GEM, 5-FU → S-1	7	PR	Grade 3	20	death
4	Cisplatin, GEM, 5-FU → S-1	6	SD	Grade 2	11	death
5	Cisplatin, GEM, 5-FU → S-1	4	PD	Grade 2	6	death
6	Cisplatin, GEM, 5-FU → S-1	3	PD	Grade 3	5	death

Table 3 Effects of second-line GEM combination chemotherapy

Pt	Response	Pain		Performance Status		CA19-9 (U/ml)	
		At therapy start	At 4 months	At therapy start	At 4 months	At therapy start	At 4 months
1	PR	2	0	1	0	105	42
2	SD	3	1	2	1	84	54
3	PR	0	0	1	2	248	15
4	SD	2	1	1	1	4094	1893
5	PD	2	0	2	2	380100	12950
6	PD	3	1	3	2	582	2863
			$P=0.031$		$P=0.375$		$P=0.156$

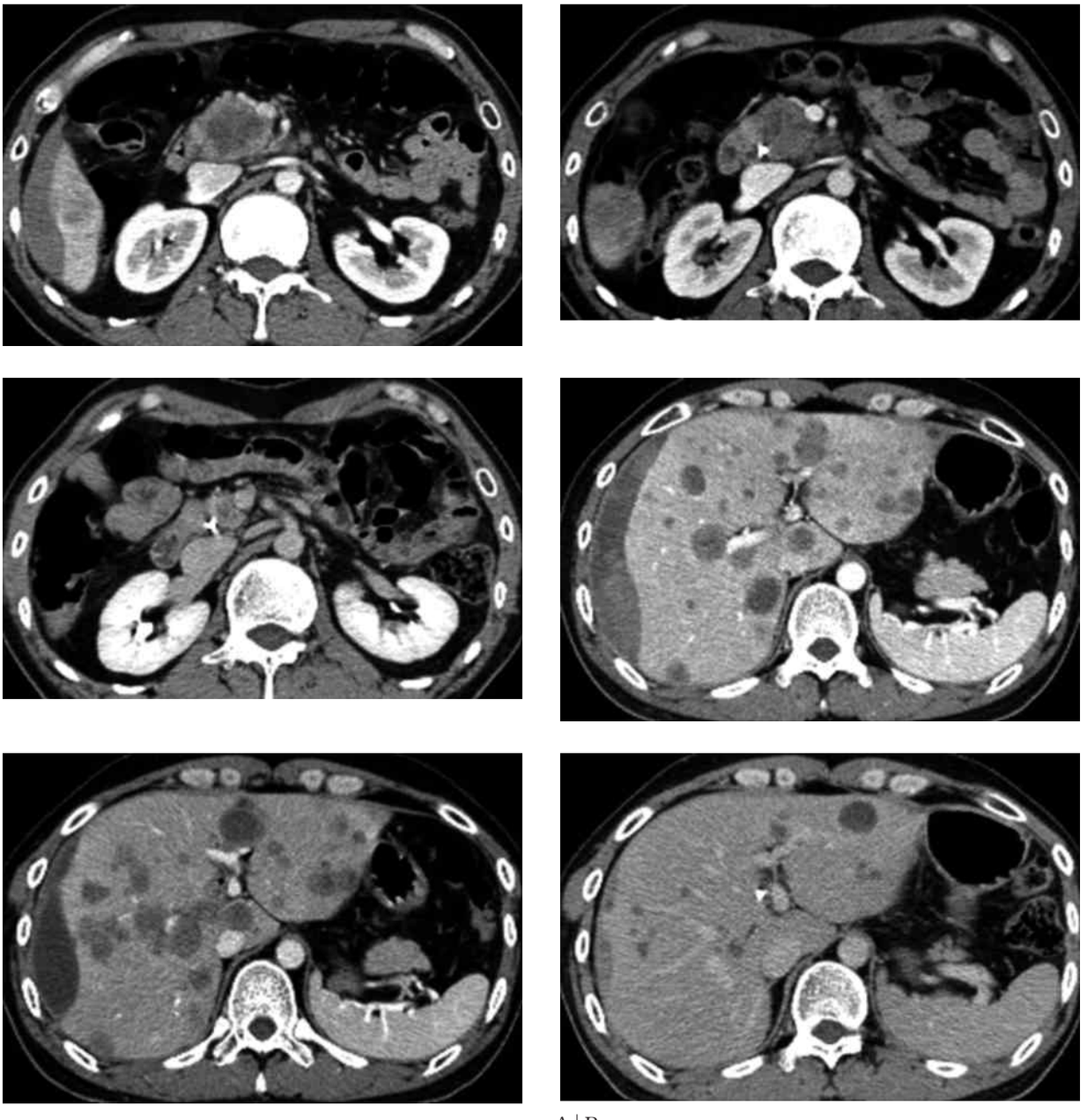

Fig. 1

A	B
C	D
E	F

A：Abdominal CT of patient 3 prior to first-line GEM showing the pancreas head region.
B：Abdominal CT of patient 3 prior to second-line low-dose combination therapy (15 months after the start of first-line GEM), showing the pancreas head region.
C：Abdominal CT of patient 3 seven months after the initiation of second-line low-dose combination therapy, showing the pancreas head region.
D：Abdominal CT of patient 3 prior to the initiation of first-line GEM showing the umbilical portion of the liver.
E：Abdominal CT of patient 3 prior to the initiation of second-line low-dose combination therapy (15 months after the start of first-line GEM), showing the umbilical portion of the liver.
F：Abdominal CT of patient 3 seven months after the initiation of second-line low-dose combination therapy showing the umbilical portion of the liver.

the start of first-line GEM) in Figure 1B and 1E, and those of seven months after the initiation of second-line low-dose combination therapy in Figure 1C and 1F. Two patients with PRs after second-line chemotherapy had experienced PRs after first-line GEM. Of two patients with SD after second-line chemotherapy, 1 had experienced PR and 1 had experienced SD after first-line GEM therapy. Adverse events related to second-line therapy are listed in Table 4. Three patients developed three different grade-3/4 toxicities : leucopenia, stomatitis or diarrhea.

At last follow-up (18 and 23 months since the beginning of second-line therapy), second-line chemotherapy was ongoing in two patients who showed no evidence of disease progression.

Ⅳ Discussion

Many chemotherapy regimens for advanced pancreatic cancer have been proposed since the introduction of GEM in 1997 in hopes of exceeding the efficacy of single-agent GEM ; however, little evidence showing superior effect has been demonstrated. One exception is the combination of GEM and erlotinib, which prolonged MST to 6.4 months as compared to 5.9 months with GEM alone, but severe interstitial pneumonia was associated with this regimen[8]. In a study comparing the combination of GEM and 5-FU with single-agent GEM, the combination regimen prolonged MST as compared to single agent GEM ; however, the prolongation was not statistically significant[3]. Gemcitabine is believed to enhance the effect of the 5-FU metabolite, 5-FdUMP, by reducing the levels of its physiological competitor through ribonucleotide reductase inhibition[9]. Fluorouracil enhances the cell uptake of GEM in the GEM plus 5-FU combination regimen[10]. In recent reports, S-1, a pro-drug of fluorouracil, produced a favorable response rate of 37.5 % and an MST of 8.8 months in the treatment of for treating advanced pancreatic cancer[11]. The combination of GEM plus S-1 showed even more promising results[4][5]. Improvements in response rates and MST were also reported for the combination of GEM and cisplatin, although there were no significant differences as compared to GEM monotherapy[2]. The combination of GEM, cisplatin, and fluorouracil produced a response rate of 19 % and an MST of 9 months[12]. Most of the reports discussed here have concerned first-line therapy for local or disseminated advanced pancreatic cancer ; however, they may provide guidance for developing effective second-line therapies for GEM-resistant disease, and we planned our second-line chemotherapy regimen based on these results.

Here, we showed that second-line chemotherapy using low-dose fluoropyrimidine, cisplatin, and GEM for GEM-resistant disease resulted in a 33 % PR rate (2/6), and that 67% (4/6) of patients had PRs or SD. The efficacy of this low-dose combination regimen was previously shown by two case reports as abstracts (Shimizu A, et al. The Journal of Japan Society for Cancer Therapy 38 : 763, 2003, and Hasebe O, et al. Suizou 20 : 308, 2005). This regimen produced a MST of 11 months as measured from the initiation of first-line GEM. Previous

Table 4 Combination therapy-associated toxicities

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Leucopenia	3 (50 %)	1 (17 %)	1 (17 %)	0
Anemia	3 (50 %)	2 (34 %)	0	0
Thrombocytopenia	2 (34 %)	2 (34 %)	0	0
Nausea/Vomiting	2 (34 %)	1 (17 %)	0	0
Diarrhea	1 (17 %)	0	1 (17 %)	0
Stomatitis	0	0	0	1 (17 %)

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

reports showed that MST of first-line GEM was around 5-7 months[2)3)8)]. Accordingly, this second-line regimen induced favorable response rates. However, we could not conclude that this regimen showed marked prolongation of survival time, because comparison of survival time between the first-line therapy of previous reports and the second-line therapy of the present study is difficult. Patients receiving this regimen had maintained or improved PS, suggesting that this therapy had a positive effect on quality of life. It is difficult to continue intensive treatment when severe adverse events are associated with second-line chemotherapy. Most toxicities associated with this low-dose regimen were lower, which was acceptable and manageable for outpatient treatment. We recommend this low dose combination regimen for candidates for second-line therapy of pancreatic cancer resistant to first-line gemcitabine therapy.

Of the 4 patients with PR or SD, 4 had experienced PR or SD with first-line GEM therapy. Two patients with PRs to second-line chemotherapy had also attained PRs on first-line GEM therapy. Therefore, this combination second-line regimen is effective in patients who experienced favorable responses to first-line GEM. The efficacy of this regimen would be better tested as a first-line therapy. The mechanisms behind the effectiveness of this second-line regimen are not clear. It is possible that the specific dosages and combinations or the administration of any single agent were crucial to the observed responses. There is no time to test the efficacy of various agents during second-line chemotherapy for advanced pancreatic cancer ; therefore, the use of multiple low-dose agents, as in this regimen, might prove the most effective strategy.

There are some limitations to this study. Firstly, the study was retrospective, and secondly, the patients were relatively young and able to tolerate this combination regimen well. We should confirm the efficacy of this regimen in an older patient group in a prospective manner.

Ⅴ Conclusions

In conclusion, this combination regimen provides an effective alternative second-line regimen for patients with advanced GEM-refractory pancreatic cancer. The roles of each drug in this regimen need to be clarified in a large, prospective trial.

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References

1) Burriis HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD : Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer : a randomized trial. J Clin Oncol 15 : 2403-2413, 1997
2) Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schonekas H, Rost A, Neuhaus H, Haag C, Clemens M, Heinrich B, Vehling-Kaiser U, Fuchs M, Fleckenstein D, Gesierich W, Uthgenannt D, Einsele H, Holstege A, Hinke A, Schalhorn A, Wilkowski R : Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 24 : 3946-3952, 2006
3) Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB 3rd : Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma : Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 20 : 3270-3275, 2002
4) Ueno H, Okusaka T, Ikeda M, Ishiguro Y, Morizane C, Matsubara J, Furuse J, Ishii H, Nagase M, Nakachi K : A phase I study of combination chemotherapy with gemcitabine and oral S-1 for advanced pancreatic cancer. Oncology 69 : 421-427, 2005

5) Nakamura K, Yamaguchi T, Ishihara T, Sudo K, Kato H, Saisho H : Phase II trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. Br J Cancer 94 : 1575-1579, 2006
6) 10. Japan Society for Cancer Therapy : Criteria for the evaluation of the clinical effects of solid cancer chemotherapy. J Ipn Soc Cancer Ter 28 : 101-130, 1993
7) Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L : New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92 : 205-216, 2000
8) Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W : National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer : a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 25 : 1960-1966, 2007
9) Heinemmann V, Xu YZ, Chubb S, Sen A, Hertel LW, Grindey GB, Plunkett W : Inhibition of ribonucleotide reduction in CCRF-CEM cells by 2'2'-difluorodeoxycytidin. Mol Pharmacol 38 : 567-572, 1990
10) Tsujie M, Nakamori S, Nakahira S, Takeda S, Takahashi Y, Hayashi N, Okami J, Nagano H, Dono K, Umeshita K, Sakon M, Monden M : Schedule-dependent therapeutic effects of gemcitabine combined with uracil-tegafur in a human pancreatic cancer xenograft model. Pancreas 33 : 142-147, 2006
11) Ueno H, Okusaka T, Ikeda M, Takezako Y, Morizane C : An early phase II study of S-1 in patients with metastatic pancreatic cancer. Oncology 68 : 171-178, 2005
12) Novarino A, Chiappino I, Bertelli GF, Heouaine A, Ritorto G, Addeo A, Bellone G, Merlano M, Bertetto O : Phase II study of cisplatin, gemcitabine and 5-fluorouracil in advanced pancreatic cancer. Ann Oncol 15 : 474-477, 2004

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