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Gemcitabine plus S-1 for metastatic pancreatic cancer

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Abstract

To investigate the treatment effects of gemcitabine plus S-1 (GS) for metastatic pancreatic cancer in our institution.

Data from 41 patients with metastatic pancreatic cancer treated with GS regimen in West China Hospital, Sichuan University were reviewed. The therapeutic efficacy and toxicity were evaluated. The influencing factors of progression-free survival (PFS) and overall survival (OS) were also explored.

At the last follow-up, all patients had died. The objective response rate was 22.0% (9/41) and the disease control rate was 65.9% (27/41). The median PFS and OS times were 5.1 (range, 1.5–21) and 10.6 months (range, 1.5–40), respectively. The 0.5-, 1-, and 2-year OS rates were 65.9%, 41.5%, and 9.8%, respectively. In multivariate analysis, body mass index and carbohydrate antigen 19-9 change were the significant influencing factors of PFS, compared to tumor site and chemotherapy cycles for OS. The adverse effects were moderate and tolerable.

The effects of GS for metastatic pancreatic cancer in our institution were good. The adverse effects were moderate and tolerable. However, further investigation in future prospective clinical studies is warranted.

Abbreviations: 5-Fu = fluorouracil, BMI = body mass index, CEA = carcinoembryonic antigen, CR = complete response, CT = computed tomography, DCR = disease control rate, DPD = dihydropyrimidine dehydrogenase, GS = gemcitabine plus S-1, MRI = magnetic resonance imaging, NCI = National Cancer Institute, ORR = objective response rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, SD = stable disease.

Keywords: gemcitabine, overall survival, pancreatic cancer, progression-free survival, S-1

1. Introduction

Pancreatic cancer is 1 of the most frequently observed gastrointestinal cancers and is becoming a leading cause of cancer-related death worldwide.[1,2] Despite extensive research, the prognosis of advanced pancreatic cancer remains poor. The incidence of the disease is nearly equivalent to the death rate associated with the diagnosis of pancreatic cancer.[3,4] In recent years, the systemic administration of gemcitabine has been accepted as a standard first-line treatment for patients with advanced pancreatic cancer, offering better overall survival (OS) than that of fluorouracil (5-Fu).[5,6] However, patients who receive this therapy have a median OS of only 5.65 months.[5] Although various gemcitabine-based combination regimens have been evaluated, only erlotinib or nab-paclitaxel added to gemcitabine showed a survival benefit over gemcitabine, and that was marginal.[7,8]

S-1 (Taiho Pharmaceutical Company, Tokyo, Japan) is an oral anticancer drug that consists of tegafur, gimeracil, and oteracil in a molar ratio of 1:0.4:1.[9] Tegafur, a prodrug of 5-Fu, is transformed into 5-Fu in the liver after oral ingestion. Gimeracil is a potent dihydropyrimidine dehydrogenase (DPD) inhibitor that inhibits the degradation of 5-Fu by inhibiting DPD, the rate-limiting enzyme for the degradation of 5-Fu. Therefore, sufficient concentrations of 5-Fu in the serum and tumor tissues can be maintained. Oteracil blocks the phosphorylation of 5-Fu in the gastrointestinal tract, decreasing gastrointestinal toxic effects and limiting toxicity of 5-Fu.[9,10]

Recently, S-1 has demonstrated single-agent activity in advanced pancreatic cancer, with a 21% to 37.5% overall response rate.[11,12] Studies of gemcitabine plus S-1 (GS) have also been initiated. Preclinical studies indicated that the combination of S-1 and gemcitabine had synergistic effects on cell growth and cell cycle arrest in pancreatic cancer cell lines.[13,14] In addition, pretreatment with S-1 could enhance the antitumor effects of gemcitabine in pancreatic cancer xenografts.[15] However, clinical studies exploring the treatment effects of GS regimen for metastatic pancreatic cancer are limited and mainly carried out in Japan.[6,16,17] Therefore, this study investigated the treatment effects of GS for metastatic pancreatic cancer in our institution.

2. Methods

2.1. Patient population and characteristics

Forty-one patients with metastatic pancreatic cancer pathologically confirmed by percutaneous biopsy were treated using a GS regimen between May 2010 and January 2015 in West China Hospital, Sichuan University. All patients had performance status

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Table 1

Patient characteristics.

Characteristics	Patients no.	*P* (PFS)	*P* (OS)
Sex			
Male	27		
Female	14	.059	.009
Age			
<60	21		
≥60	20	.710	.868
BMI			
<20	34		
≥20	7	.012	.050
Tumor sites			
Head	19		
Body and tail	22	.223	.020
Comorbidity			
Yes	23		
No	18	.962	.887
Chemotherapy cycles			
≤3	22		
>3	19	.008	.002
Second or third line chemotherapy			
Yes	9		
No	32	.408	.622
LDH elevated			
Yes	13		
No	28	.492	.369
CEA			
Increased	31		
Decreased < 50%	3		
Decreased ≥ 50%	7	.878	.443
CA19-9			
Increased	21		
Decreased < 50%	4		
Decreased ≥ 50%	16	.004	.021

BMI = body mass index, CA19-9 = carbohydrate antigen 19-9, CEA = carcino-embryonic antigen, LDH = lactic dehydrogenase, OS = overall survival, PFS = progression free survival.

scores of 0 or 1 before beginning treatment. The patient characteristics are summarized in Table 1. This study was approved by the Ethics Committee of West China Hospital, Sichuan University. All patients provided informed consent to participate in the study. The American Joint Committee on Cancer (AJCC 7th version) clinical staging system of pancreatic cancer was adopted for this study.

2.2. Chemotherapy

We administered gemcitabine at a dose of 1000 mg/m^2 on days 1 and 8 plus S-1 orally twice daily at a dose according to the body surface area (BSA) (<1.25 m^2, 80 mg/d; ≥1.25 to <1.5 m^2, 100 mg/d; ≥1.5 m^2, 120 mg/d) on days 1 through 14 of a 21-day cycle.

2.3. Evaluation of therapeutic efficacy and toxicity

The pretreatment evaluations included history and physical examination, performance status, complete blood count, serum biochemistry, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), thoracic computed tomography (CT), and abdominal CT scans or magnetic resonance imaging (MRI). Patients were evaluated weekly during treatment and monthly after treatment. Performance status, weight, complete blood count and serum biochemistry, CEA, and CA19-9 were assessed at each clinic visit. Thoracic CT and abdominal CT or MRI were repeated every 3 months during the treatment process or within 2 years after the treatment and every 6 months thereafter. In case of some conditions such as CA19-9 level increase and jaundice, a CT or MRI examination was immediately performed.

The short-term therapeutic effects of local tumor control were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to CT or MRI imaging. According to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1),[18] CR was defined as the complete disappearance of all measurable disease for 4 weeks; PR as at least a 30% decrease in the sum of the longest diameter of target lesions for 4 weeks compared to the baseline sum of the longest diameters; and PD as at least a 20% increase for 4 weeks, compared to the smallest recorded sum or the appearance of a new lesion (and at least 5 mm absolute increase). Patients whose disease did not meet the criteria for either a PR or PD were classified as having SD for 4 weeks.

The major indexes of long-term effects were progression-free survival (PFS) and OS. The PFS was counted from the date of treatment to disease progression or death from any cause. The OS was the duration from the beginning date of treatment to the date of follow-up for surviving patients or to the date of death.

The adverse events were assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 3.0.[18,19] Treatment was temporarily suspended in case of grade 3/4 hematological toxicity or grade 2 or higher nonhematological toxicity. After recovery to grade 1 toxicity or lower, treatment was restarted at the following reduced doses. First, S-1 was reduced to: 50 mg/d (<1.25 m^2); 80 mg/d (≥1.25 to <1.5 m^2); 100 mg/d (≥1.5 m^2). When dose reduction was necessary after the reduction of S-1, gemcitabine was reduced to 800 mg/m^2. No dose escalation was allowed following dose reduction.

2.4. Follow-up

The follow-up duration was defined as the time from the beginning date of treatment to the last date of follow-up for surviving patients or to the date of death. The last date of follow-up was February 9, 2018. At last follow-up, all patients had died.

2.5. Statistical analysis

SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses.[20] The Kaplan–Meier method was used to evaluate the PFS and OS. Log-rank tests were used to compare the different levels of each factor. Cox regression models were used for multivariate analysis. $P < .05$ was considered statistically significant.

3. Results

3.1. Response rate and CA19-9 change

A median of 3 GS chemotherapy cycles was administered (range, 1–13 cycles). Nine patients experienced PR during treatment, 18 experienced SD during treatment, and 14 patients experienced PD directly after treatment. The objective response rate (ORR) was 22.0% (9/41) and the disease control rate (DCR) was 65.9% (27/41). During treatment, the CA19-9 level in 16 patients decreased by more than 50% and by less than 50% in 4 patients. However, the CA19-9 level in 21 patients increased directly after treatment.

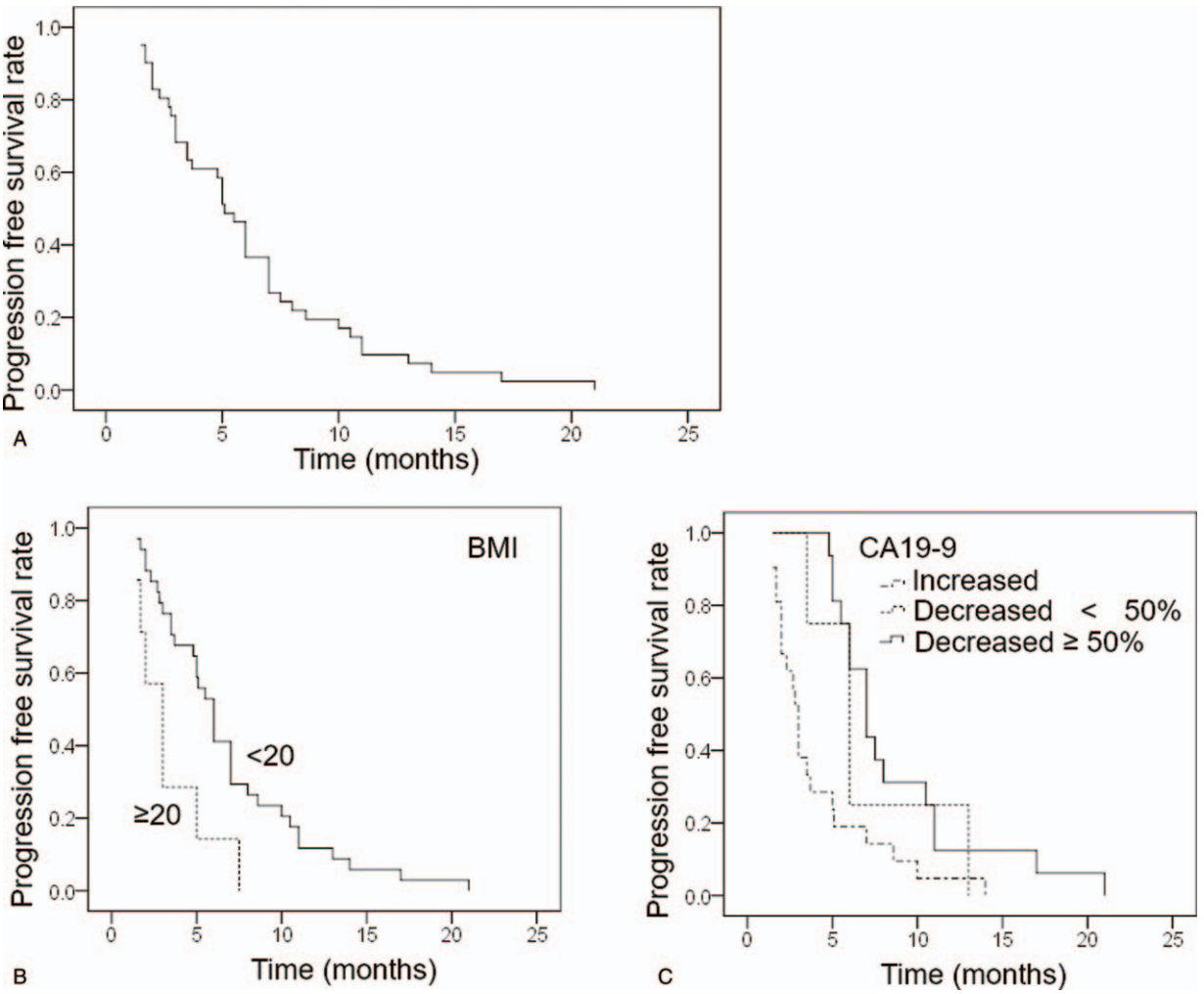

Figure 1. Progression free survival of patients with different variables. A. whole group; B. BMI; C. CA19-9 change. CA19-9 = carbohydrate antigen 19-9.

3.2. Progression-free survival

The median PFS time was 5.1 months (range, 1.5~21 months) (Fig. 1A). Univariate analysis showed that body mass index (BMI), chemotherapy cycles, and CA19-9 change significantly impacted the PFS (Table 1) ($P < .05$). However, only BMI and CA19-9 change had a significant impact on PFS in multivariate analysis (Table 2, Fig. 1B, C) ($P < .05$). After progression, 9 patients received second- or third-line chemotherapy. Five patients received a 5-Fu /leucovorin plus irinotecan and oxaliplatin (FOLFIRINOX) regimen, 2 patients received a 5-Fu /leucovorin plus oxaliplatin (FOLFOX) regimen, 2 patients received a nab-paclitaxel plus gemcitabine regimen, and 1 patient received a gemcitabine plus oxaliplatin regimen.

3.3. OS

The median OS overall was 10.6 months (range, 1.5–40 months) (Fig. 2A). The 0.5-, 1-, and 2-year OS rates were 65.9%, 41.5%, and 9.8% (Fig. 2A), respectively. Univariate analysis showed that sex, tumor sites, chemotherapy cycles, and CA19-9 change significantly impacted the OS (Table 1) ($P < .05$). However, only tumor sites and chemotherapy cycles significantly influenced the OS in multivariate analysis (Table 3, Fig. 2B and C) ($P < .05$).

3.4. Toxicity

Grade 3/4 hematological adverse effects occurred in 13 patients, grade 3 liver function damage occurred in 1 patient, and a grade 3

Table 2

Multivariate analysis of progression free survival (Cox Regression method).

							95.0% CI for Exp (B)	
factor	B	SE	Wald	df	Sig.	Exp (B)	Lower	Upper
BMI	−0.890	.449	3.939	1	.047	2.436	1.011	5.869
CA19-9 change	−0.515	.180	8.161	1	.004	.597	.419	.851

BMI = body mass index, CA19-9 = carbohydrate antigen 19-9.

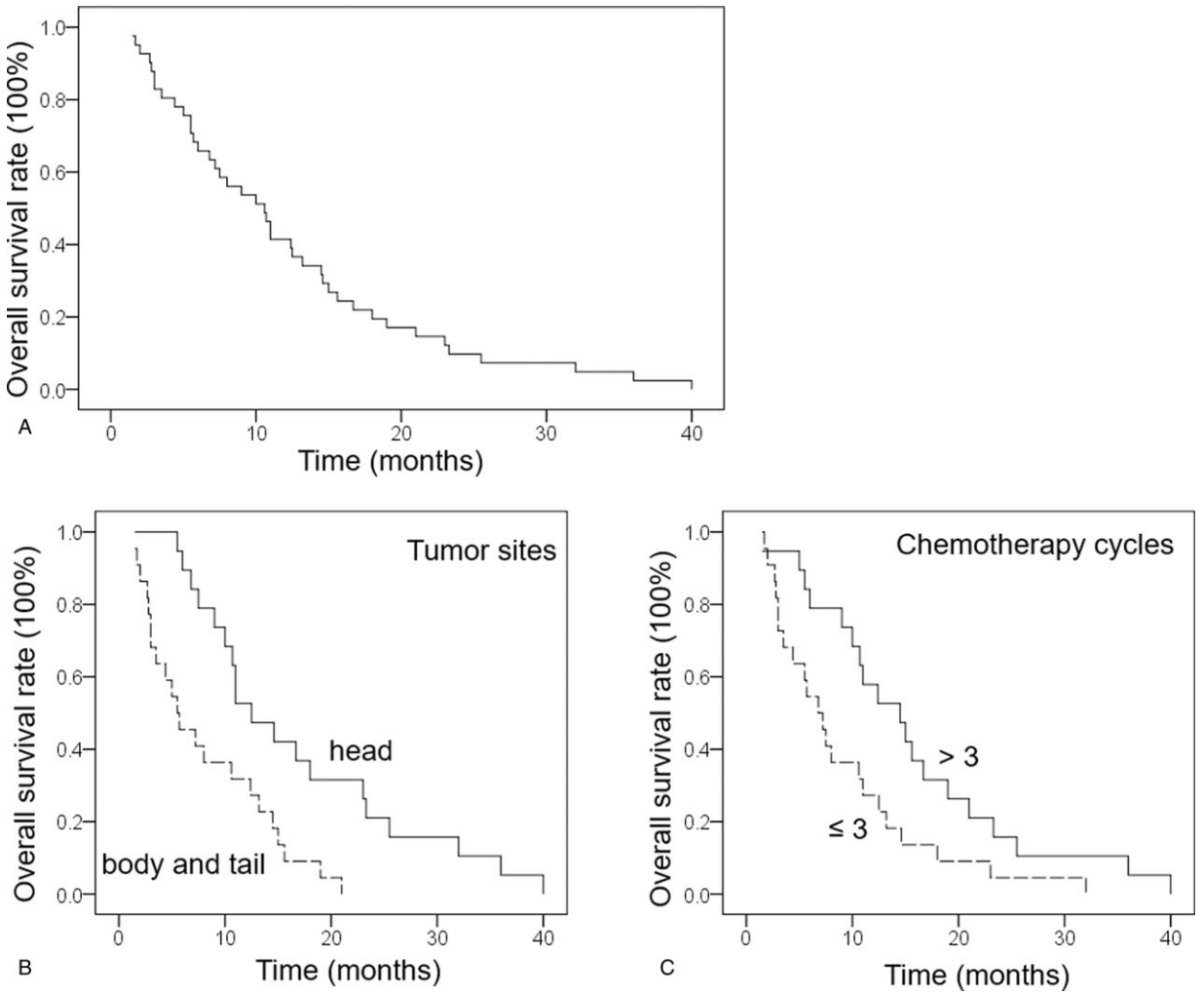

Figure 2. Overall survival of patients with different variables. A. whole group; B. tumor sites; C. chemotherapy cycles.

gastrointestinal reaction was observed in 1 patient. In addition, 12 patients developed grade 1/2 rash mainly on the cheek and neck during treatment. Seventeen patients reduced drug administration as needed and 1 patient stopped treatment because of the severe gastrointestinal reaction. However, no patient stopped treatment for hematological adverse effects.

4. Discussion

Pancreatic cancer accounts for approximately 232,300 cases and 227,000 deaths in 2002 worldwide.[21] Approximately 80% of patients are ineligible for surgery at diagnosis and more than half have metastatic disease.[8] The use of palliative chemotherapy has been shown to improve survival and quality of life compared to best supportive care in patients with good performance status.[16,22] However, the 5-year survival rate is still poor, at less than 10%, and is linked to the high incidence of distant metastasis even at initial diagnosis, as well as the tumor's resistance to anticancer agents.[22,23] Innovation in systemic chemotherapy is thus urgently needed to improve the survival of patients with pancreatic cancer. Both gemcitabine and S-1 are valuable treatments for advanced pancreatic cancer.[23] It is of interest to explore the treatment effects of GS regimens for metastatic pancreatic cancer patients in our institution.

In this study, 9 patients experienced PR during the treatment and 18 patients experienced SD during treatment. The ORR was

Table 3

Multivariate analysis of overall survival (Cox Regression method).

							95.0% CI for Exp (B)	
factor	B	SE	Wald	df	Sig.	Exp (B)	Lower	Upper
Tumor sites	.986	.348	8.037	1	.005	2.681	1.356	5.303
Chemotherapy cycles	−1.276	.375	11.596	1	.001	.279	.134	.582

CI = confidence interval.

22.0% (9/41) and the DCR was 65.9% (27/41), which were similar to those in other studies. Ueno et al[23] reported on 275 locally advanced or metastatic pancreatic cancer patients treated with GS regimens, with an ORR of 29.3% and DCR of 71.5%. Sudo et al[22] reported on 51 unresectable pancreatic cancer patients treated with a GS regimen, in whom the ORR and DCR were 21.6% and 68.6%, respectively. Nakamura et al[6] reported on 33 metastatic pancreatic cancer patients treated with GS regimen, with an ORR of 48.5% and DCR of 75.8%.

At the last follow-up, all patients in the present study had progressed after beginning the GS regimen. The median PFS time was 5.1 months (range, 1.5–21 months). After progression, several patients received second or third-line chemotherapy. However, the response rates of these treatments after first-line treatment were limited. In addition, second or third-line chemotherapy had no significant influence on the PFS or OS in both univariate and multivariate analyses. BMI, chemotherapy cycles, and CA199 change significantly impacted the PFS but only BMI and CA199 change significantly influenced the PFS in multivariate analysis.

The median OS duration overall was 10.6 months (range, 1.5–40 months). The 0.5-, 1-, and 2-year rates of OS overall were 65.9%, 41.5%, and 9.8%, respectively. These results were close to those of other studies. Ueno et al[23] reported on 275 locally advanced or metastatic pancreatic cancer patients treated with GS regimens, with an OS of 10.1 months. Sudo et al[22] reported on 51 unresectable pancreatic cancer patients treated with GS regimen, with a median OS of 8.6 months. Nakamura et al[6] reported on 33 metastatic pancreatic cancer patients treated with GS regimen, with an OS of 12.5 months and 1-year survival rate of 54%.

Univariate analysis showed that sex, tumor sites, chemotherapy cycles, and CA199 change had significant impacts on the OS. However, in multivariate analysis, only tumor sites, and chemotherapy cycles significantly influenced the OS. As shown in Figure 2B, pancreatic cancer originating from the pancreatic head in this study showed a better OS (median: 14.5 months; range, 1.5–40 months) than those originating from the pancreatic body and tail (median: 6.8 months; range, 1.7– 32 months). This finding is hard to explain. Some observational studies analyzing outcome according to tumor stage at diagnosis showed superior survival in patients with cancer located in the pancreatic body and tail compared to that in those with cancer located in the pancreatic head in the case of localized and resectable disease.[21,24] However, a recent analysis based on Surveillance, Epidemiology and End Results Program data (SEER by the NCI) revealed a significant difference in the 3-year survival rates of 3.9% (body/tail) versus 6.2% (head), in which the mortality is worse when the tumor is located in the pancreatic body and tail.[21,25] The number of chemotherapy cycles was another significant influencing factor of OS in this study. Patients who received more than 3 cycles of GS chemotherapy had a better OS (median: 12.5 months; range, 5.5–40 months) than that in patients who did not (median: 5.5 months; range, 1.5–21 months) (Fig. 2C). Therefore, the more cycles of GS chemotherapy patients receive, the better the OS. We encourage unresectable metastatic pancreatic cancer patients to receive as many cycles as they can tolerate.

Twenty patients decreased CA19-9 levels during or after the treatment, 16 (39.0%) with a decrease larger than 50%. For PFS, CA19-9 change showed a significant impact in both univariate and multivariate analysis. A change in CA19-9 level was also a significant influencing factor of OS in univariate analysis. Patients with increased CA19-9 level had a worse prognosis including PFS and OS compared to that in patients with decreased CA19-9 level, especially those with decreases greater than 50%. However, there was no significant difference between patients with CA19-9 decreases of less than 50% and more than 50% (data not shown).

The adverse effects in this study were moderate and tolerable. Grade 3/4 hematological adverse effects occurred in 13 patients, grade 3 liver function damage occurred in 1 patient, and a grade 3 gastrointestinal reaction was observed in 1 patient. The patient stopped treatment because of the severe gastrointestinal reaction. However, no patient stopped treatment for hematological adverse effects.

This study has several limitations. First, the sample size was relatively small. In addition, 9 patients in this study received second- or third-line chemotherapy, which may have influenced the results. However, no significant difference was found. Therefore, we believe that the impacts of second- or third-line chemotherapy were minimal. So, we did not exclude them from this study.

In conclusion, the effects of GS for metastatic pancreatic cancer in our institution were good. BMI and CA19-9 change were significant influence factors of PFS, while tumor sites and chemotherapy cycles were significant influence factors of OS in multivariate analysis. The adverse effects were moderate and tolerable. However, further investigation in future prospective clinical studies is warranted.

Author contributions

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Writing – original draft: Hong Zhu, Cheng Yi, Yaqin Zhao.
Writing – review & editing: Hongfeng Gou.

References

[1] Ueno H, Okusaka T, Furuse J, et al. Multicenter phase II study of gemcitabine and S-1 combination therapy (GS Therapy) in patients with metastatic pancreatic cancer. Jpn J Clin Oncol 2011;41:953–8.
[2] Nakai Y, Isayama H, Sasaki T, et al. A multicentre randomised phase II trial of gemcitabine alone vs gemcitabine and S-1 combination therapy in advanced pancreatic cancer: GEMSAP study. Br J Cancer 2012;106: 1934–9.
[3] Li Y, Sun J, Jiang Z, et al. Gemcitabine and S-1 combination chemotherapy versus gemcitabine alone for locally advanced and metastatic pancreatic cancer: a meta-analysis of randomized controlled trials in Asia. J Chemother (Florence, Italy) 2015;27:227–34.
[4] Li CP, Chao Y, Chi KH, et al. Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study. Int J Radiat Oncol Biol Phys 2003;57: 98–104.
[5] Burris HA3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol Off J Am Soc Clin Oncol 1997;15:2403–13.
[6] Nakamura K, Yamaguchi T, Ishihara T, et al. Phase II trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. Br J Cancer 2006;94:1575–9.
[7] Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. New Engl J Med 2013; 369:1691–703.

[8] Moore MJ, Goldstein D, Hamm J, et al. 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 Off J Am Soc Clin Oncol 2007;25:1960–6.
[9] van Groeningen CJ, Peters GJ, Schornagel JH, et al. Phase I clinical and pharmacokinetic study of oral S-1 in patients with advanced solid tumors. J Clin Oncol Off J Am Soc Clin Oncol 2000;18:2772–9.
[10] Sudo K, Nakamura K, Yamaguchi T. S-1 in the treatment of pancreatic cancer. World J Gastroenterol 2014;20:15110–8.
[11] Okusaka T, Funakoshi A, Furuse J, et al. A late phase II study of S-1 for metastatic pancreatic cancer. Cancer Chemother Pharmacol 2008;61: 615–21.
[12] Shirasaka T. Development history and concept of an oral anticancer agent S-1 (TS-1): its clinical usefulness and future vistas. Jpn J Clin Oncol 2009;39:2–15.
[13] Yoshizawa J, Takizawa A, Takeuchi O, et al. Experimental study of combination therapy with S-1 against pancreatic cancer. Cancer Chemother Pharmacol 2009;64:1211–9.
[14] Morimoto Y, Takeuchi O, Takizawa A, et al. Effect of a combination of S-1 and gemcitabine on cell cycle regulation in pancreatic cancer cell lines. Anti-Cancer Drugs 2012;23:505–14.
[15] Nakahira S, Nakamori S, Tsujie M, et al. Pretreatment with S-1, an oral derivative of 5-fluorouracil, enhances gemcitabine effects in pancreatic cancer xenografts. Anticancer Res 2008;28:179–86.
[16] Ueno H, Okusaka T, Ikeda M, et al. A phase I study of combination chemotherapy with gemcitabine and oral S-1 for advanced pancreatic cancer. Oncology 2005;69:421–7.
[17] Nakai Y, Isayama H, Sasaki T, et al. A pilot study for combination chemotherapy using gemcitabine and S-1 for advanced pancreatic cancer. Oncology 2009;77:300–3.
[18] Wu D, Zhu H, Tang H, et al. Clinical analysis of stereotactic body radiation therapy using extracranial gamma knife for patients with mainly bulky inoperable early stage non-small cell lung carcinoma. Radiat Oncol (Lond, Engl) 2011;6:84.
[19] Xu J, Zhu H, Zhao Y, et al. Factors associated with hepatic dysfunction in hepatitis B-positive patients with postgastrectomy adenocarcinoma. Oncol Lett 2012;4:471–6.
[20] Huang M, Zhu H, Liu T, et al. Comparison of external radiotherapy and percutaneous vertebroplasty for spinal metastasis. Asia Pac J Clin Oncol 2016;12:e201–208.
[21] Lau MK, Davila JA, Shaib YH. Incidence and survival of pancreatic head and body and tail cancers: a population-based study in the United States. Pancreas 2010;39:458–62.
[22] Sudo K, Ishihara T, Hirata N, et al. Randomized controlled study of gemcitabine plus S-1 combination chemotherapy versus gemcitabine for unresectable pancreatic cancer. Cancer Chemother Pharmacol 2014;73:389–96.
[23] Ueno H, Ioka T, Ikeda M, et al. 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 Off J Am Soc Clin Oncol 2013; 31:1640–8.
[24] Sener SF, Fremgen A, Menck HR, et al. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985–1995, using the National Cancer Database. J Am Coll Surg 1999;189:1–7.
[25] Ruess DA, Makowiec F, Chikhladze S, et al. The prognostic influence of intrapancreatic tumor location on survival after resection of pancreatic ductal adenocarcinoma. BMC Surg 2015; 15:123.